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Naphthalene ‘proton sponges’

A F Pozharskii

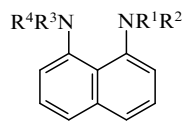
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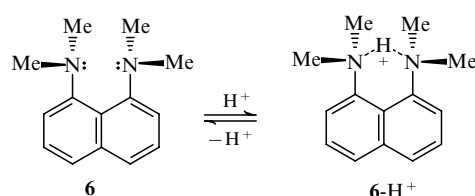
Abstract. Methods of synthesis, physicochemical and structural characteristics, and reactivity of 1,8-bis(dialkylamino)naphthalenes and some of their close analogues pertaining to the class of so-called ‘proton sponges’ are considered. The bibliography includes 154 references.

I. Introduction

In 1968, Alder *et al.*¹ reported on a discovery of unusual changes in the variations of basicity in the series of *N*-methylated 1,8-diaminonaphthalenes (Table 1). It has been found that the pK_a values for the unsubstituted diamine **1** and its mono-, di-, and trimethyl derivatives **2–5** fall in the range typical of ordinary aryl amines, while that for 1,8-bis(dimethylamino)naphthalene **6** increases abruptly by nearly six orders. As a result, the basicity of compound **6** exceeds greatly that of both the known aromatic amines and practically all alkylamines. Further studies revealed that this feature is characteristic not only of aqueous solutions of the amine **6**, but also of solutions in non-aqueous solvents (*e.g.* acetonitrile²) and the gas phase.³

	Compound	R ¹	R ²	R ³	R ⁴
1		H	H	H	H
2		Me	H	H	H
3		Me	H	Me	H
4		Me	Me	H	H
5		Me	Me	Me	H
6		Me	Me	Me	Me

It is believed that the abnormally high basicity of the compound **6** is caused by three main factors: (1) destabilisation of the base due to strong repulsion of unshared electron pairs of nitrogen atoms, (2) formation of a strong intramolecular hydrogen bond (IHB) in the protonated form, the cation (**6-H⁺**), and (3) steric strain relief in the molecule upon the transition from a non-planar base to a planar cation.



Another peculiar feature of the compound **6** is the slowness of proton addition–detachment due to the shielding of internitrogen space by four methyl groups. Thus, the high thermodynamic basicity of 1,8-bis(dimethylamino)naphthalene is associated with its rather low kinetic basicity. This circumstance made it possible to establish a similarity in the behaviour of the diamine **6** and genuine sponges, which slowly absorb water and retain it very strongly so that water is difficult to squeeze out. For this particular reason, the compound **6** has been named ‘proton sponge’,⁴ which is generally accepted now and is further extended to all other compounds possessing this type of properties. At present, we can speak about the concept of ‘proton sponges’, which is based on the following principles: (1) the proper structural organisation of their molecule which provides rigid fixation of two nitrogen atoms at a sufficiently close distance from each other; (2) the existence in the molecule of a base of a destabilising repulsion effect of unshared electron pairs of the nitrogen atoms; (3) the occurrence of a strong IHB in the cation, which relieves steric and electronic strains characteristic of a base, and (4) the presence of a hydrophobic environment at the nitrogen atoms, most often in the form of alkyl groups, which actually accounts for the ‘sponge’ effect.

Table 1. Basicity constants, pK_a , of *N*-methyl derivatives of 1,8-diaminonaphthalene (25 °C).

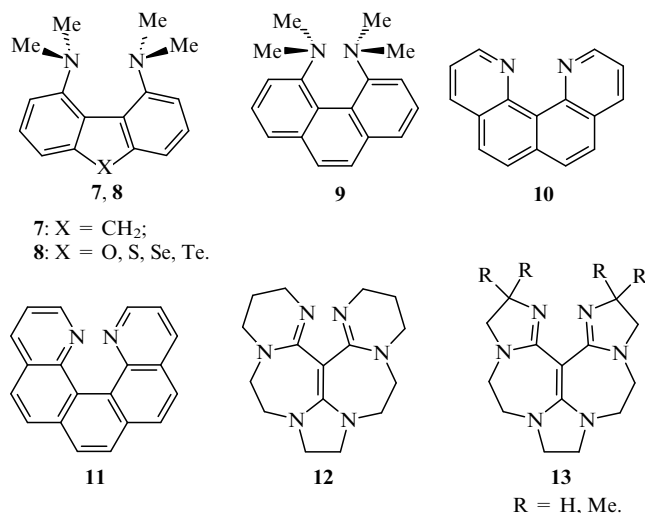
Compound	pK_a	
	in water ¹	in acetonitrile ²
1	4.61	10.99
2	—	11.64
3	5.61	11.95
4	—	12.87
5	6.43	12.91
6	12.34	18.18

A F Pozharskii Rostov State University, ul. Zorge 7,
344090 Rostov-on-Don, Russian Federation. Fax (7-863) 228 56 67.
Tel. (7-863) 222 39 58. E-mail Pozharsk@pozhar.rnd.runnet.ru

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On the basis of this concept, the synthesis of a series of non-naphthalene proton sponges has been carried out since the mid-1980's. Thus, the research group headed by Staab *et al.* synthesised and analysed sponges of the fluorene **7**,⁵ heterofluorene **8**,⁶ and phenanthrene **9**⁷ series and their analogues **10**,^{8,9} and **11**¹⁰ with an sp^2 -hybridised nitrogen heteroatom. The vinamidine sponges **12**, **13** possessing even stronger basicity than compounds **6–11** were synthesised by Schwesinger *et al.*¹¹



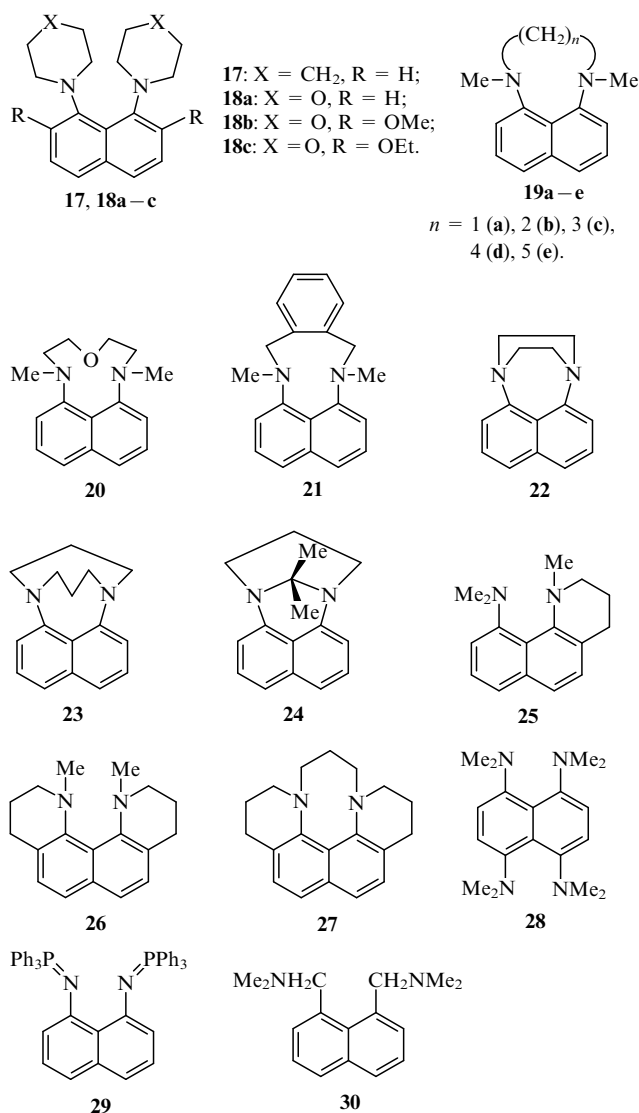
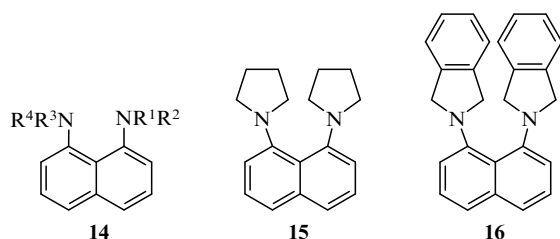
Until now, the main attention in the studies on 'proton sponges' has been given to their structural and physicochemical characteristics and bases and cations were considered from somewhat different points of view. Thus the following aspects have been studied for cations: (1) geometry of the intramolecular hydrogen bond (the distance between the amine nitrogen atoms, the N—H...N angle and, particularly, the position of the proton responsible for the IHB symmetry, (2) the ¹H NMR spectra (primarily, the chemical shift of the NH-proton and the constants of its spin-spin coupling with the NMe₂ groups), (3) kinetic NH-acidity (deprotonation rate).

Bases were analysed as regards: (1) their molecular geometry (the distance between the nitrogen atoms, distortion from the planar structure of the rings, conformational phenomena), (2) basicity, (3) the nature of interactions of unshared electron pairs of the nitrogen atoms with one another and with the π -system of the ring, and (4) reactivity.

Several reviews survey exclusively structural and physicochemical aspects of the 'proton sponges'.^{12–15} At the same time, a vast range of interesting information has been accumulated concerning methods of their synthesis and, especially, their reactivity. This review has been written with the aim of generalising the data on the methods of synthesis, reactivity, and physicochemical characteristics of 'proton sponges' of the naphthalene series. The literature cited herein includes the works published before 1997.

II. The types of naphthalene 'proton sponges'

The types of naphthalene 'proton sponges' known to date are represented by the structures **14–30**.



These include 1,8-bis(dialkylamino)naphthalenes **14** (the substituents R¹–R⁴ can be identical or different), their analogues **15–18** in which the amine nitrogen atoms are incorporated into five- or six-membered rings, compounds **19–24** with bridgehead heteroatoms, compounds **25–27** with the nitrogen atoms incorporated in the fused rings, and the so-called double 'proton sponge' **28**. The properties of 'proton sponges' have also been found in iminophosphoranes **29** and 1,8-bis(dimethylamino-methyl)naphthalene **30**.

III. Synthesis of 1,8-bis(dialkylamino)-naphthalenes and their analogues

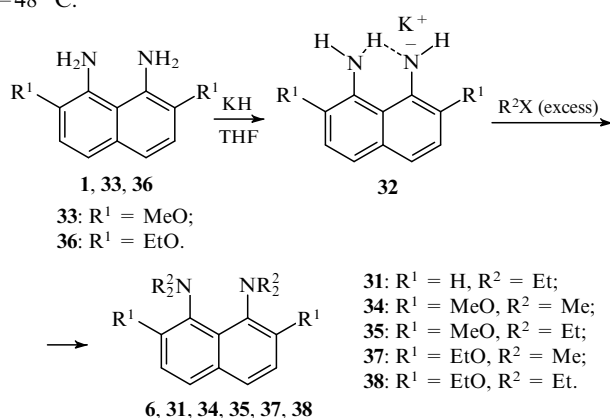
1. 1,8-Bis(dialkylamino)naphthalenes

There are two general approaches to the synthesis of these compounds which successfully complement each other. The first of them is based on the alkylation of 1,8-diaminonaphthalene or its partially alkylated derivatives. In the second, 1,1,3-trialkyl-2,3-dihydroperimidinium salts serve as the starting compounds.

a. Syntheses based on 1,8-diaminonaphthalenes

The first representative of naphthalene 'proton sponges' described in the literature was 1,8-bis(diethylamino)naphthalene **31**, which was obtained by heating the diamine **1** with an excess of ethyl bromide at 135 °C in the presence of alkali¹⁶ (see also Ref. 17). Later, 1,8-bis(dimethylamino)naphthalene **6** was synthesised by treating the diamine **1** with dimethyl sulfate (the yield was not specified).¹⁸ Initially, this compound was characterised as an oil,

although it is now known as a crystalline substance with m.p. 47–48 °C.¹



Two convenient procedures have been elaborated for exhaustive alkylation of the diamine **1**. Both of them entail the use of strong bases (sodium or potassium hydrides in anhydrous tetrahydrofuran¹⁹ or potassium hydroxide in dimethyl sulfoxide) for the ionisation of N–H-bonds.²⁰

Obviously, under these conditions it is the N-anions of the original diamine and intermediate substitution products that undergo alkylation. The ionisation is favoured by the very high (in comparison with ordinary arylamines) NH-acidity of the diamine **1** (pK_a = 24.5, DMSO, 25 °C), which is ascribed to the stabilisation of the N-anion **32** through IHB.²¹ The yields of 'proton sponges' vary from high to satisfactory. Thus in the alkylation of the compound **6** in the presence of KH–THF or KOH–DMSO systems, the yields exceed 90%. To obtain good yields of the compound **31**, it is recommended to use hexametapal as a solvent instead of DMSO.²⁰ However, the alkylation of 1,8-diamino-2,7-dimethoxynaphthalene **33** gives compounds **34** and **35** in low yields (40% and 21%, respectively).²² The yields of the 'proton sponges' **37**, **38** obtained by the alkylation of the diamine **36** are even lower.²³ The yield of the 'double sponge' **28** obtained by methylation of 4,5-diamino-1,8-bis(dimethylamino)naphthalene with dimethyl sulfate in an NaH–THF system was 31%.²⁴

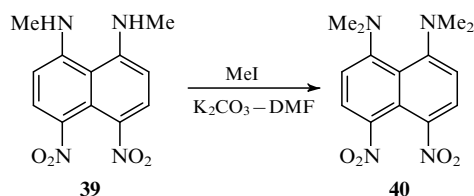
Depending on the length of the methylene chain, alkylation of the diamine **1** with α,ω -dihalogenoalkanes gives various types of 'proton sponges' (Table 2). If the halogens are separated by 4 or 5 atoms, compounds **15**–**18** are formed in which the amine nitrogen atoms are incorporated into five- or six-membered rings. With a closer arrangement of the halogen atoms, bridged sponges **22**–**24** are formed. Interestingly, the alkylation with 1,3-dibromopropane gives, along with compound **23**, a low yield of the pentacyclic compound **27**. Apparently, its precursor is naphtho[1,8-*b,c*]-1,5-diazacyclooctane (also isolated in low yield),

Table 2. 'Proton sponges' obtained by treatment of 1,8-diaminonaphthalene with α,ω -dihalogenoalkanes and their analogues.²²

'Proton sponge'	α,ω -Dihalide	Reaction conditions	Yield (%)
15	Br(CH ₂) ₄ Br	Na ₂ CO ₃ , reflux	60
16	α,α' -Dibromo- <i>o</i> -xylene	Na ₂ CO ₃ –DMF, reflux	5
17	Br(CH ₂) ₅ Br	Na ₂ CO ₃ , reflux	60
18a	O(CH ₂ CH ₂ Cl) ₂	Na ₂ CO ₃ , 150 °C	10
22	BrCH ₂ CH ₂ Br	Na ₂ CO ₃ –DMF, reflux	42
24	Br(CH ₂) ₃ Br	Na ₂ CO ₃ –acetone, reflux	34
23	Br(CH ₂) ₃ Br	DMF, diglyme	1–5
27	Br(CH ₂) ₃ Br	or sulfolane, 150–200 °C	1–2

which undergoes first *N*-, and then intramolecular *C*-alkylation with 1,3-dibromopropane.

In some cases, 1,8-bis(methylamino)naphthalene and its derivatives served as the starting compounds in the synthesis of 'proton sponges' by alkylation. Thus heating of 1,8-bis(methylamino)-4,5-dinitronaphthalene **39** with methyl iodide in DMF in the presence of potassium carbonate gave the compound **40** (yield 32%).²⁴



Alder *et al.*²² have synthesised a series of 'proton sponges' **19**–**21** by treating 1,8-bis(methylamino)naphthalene **3** with α,ω -dihalogenoalkanes (Table 3).

Table 3. 'Proton sponges' obtained by treatment of 1,8-bis(methylamino)-naphthalene with α,ω -dihalogenoalkanes and their analogues.²²

'Proton sponge'	α,ω -Dihalide	Reaction conditions	Yield (%)
19b	Br(CH ₂) ₂ Br	NaH–THF	80
19b	Br(CH ₂) ₂ Br	NaHCO ₃ –DMF	25
19c	Br(CH ₂) ₃ Br	NaHCO ₃ –MeO(C ₂ H ₄ O) ₂ Me, 190 °C	43
19c	Br(CH ₂) ₃ Br	NaH–THF	1
19d^a	Br(CH ₂) ₄ Br	NaHCO ₃ –MeO(C ₂ H ₄ O) ₂ Me, reflux, 46 h	58
19e	Br(CH ₂) ₅ Br	Na ₂ CO ₃ –MeO(C ₂ H ₄ O) ₂ Me	25
20	O(CH ₂ CH ₂ Cl) ₂	Na ₂ CO ₃ –MeO(C ₂ H ₄ O) ₂ Me, reflux	77
21	α,α' -Dibromo- <i>o</i> -xylene	Na ₂ CO ₃ –DMF, reflux	13

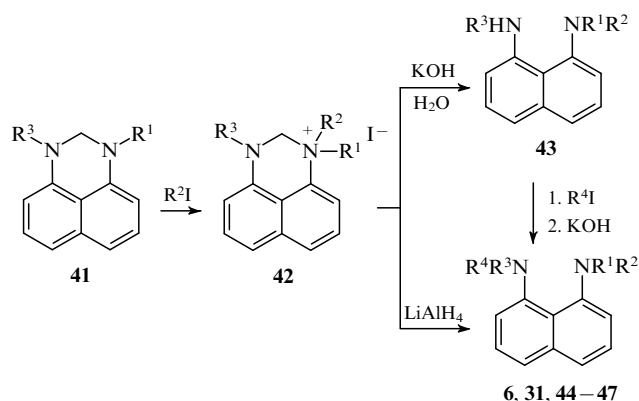
^a The compound was isolated and purified as a salt with the BF₄[–] anion.

The alkylation of *N,N,N'*-trialkyl-substituted 1,8-diaminonaphthalenes proceeds very smoothly. The reaction is usually performed by heating the latter compounds with an excess of alkyl halide in an appropriate solvent or without any solvent. The proton sponge salt formed is converted into the base by treatment with an aqueous alkali.^{25, 26}

b. Syntheses based on 1,1,3-trialkyl-2,3-dihydroperimidinium salts

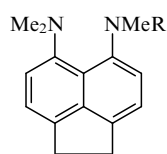
Far from all of the naphthalene 'proton sponges' can be obtained by alkylation of *peri*-diamines or by functionalisation of the unsubstituted compound **6**. Therefore, the author of this review with his coworkers have developed an alternative and practically versatile procedure for the synthesis of 1,8-bis(dialkylamino)-naphthalenes from 1,1,3-trialkyl-2,3-dihydroperimidinium salts. First, quaternisation of readily available 1,3-dialkyl-2,3-dihydroperimidines **41** gives the salts **42**, which are subjected to reductive scission with lithium aluminium hydride, resulting in the corresponding 'proton sponge' (in the ring-opening, the μ -methylene group is converted into the methyl group, *i.e.*, in this case R⁴ = Me). However, sometimes this reaction does not proceed smoothly, *e.g.*, if the molecule of a salt contains halogens or other easily reducible groups. Better results are achieved when the salts **42** are treated with an aqueous alkali, which gives high yields of the corresponding *N,N,N'*-trialkyl-substituted 1,8-diaminonaphthalene **43**. Its alkylation and subsequent treatment of the quaternary salt with alkali give the target 'proton sponge'. This approach was used, in particular, in the synthesis of 1,8-bis(dialkylamino)-

naphthalenes **6**, **31**, and **44–47** with all possible combinations of the methyl and ethyl groups.²⁵

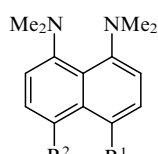


Compound	R ¹	R ²	R ³	R ⁴
44	Me	Me	Me	Et
45	Me	Me	Et	Et
46	Me	Et	Me	Et
47	Et	Et	Et	Me

In a similar way, the acenaphthene ‘sponges’ **48**, **49**,²⁵ 4-halogeno- and 4,5-dihalogeno-1,8-bis(dimethylamino)naphthalenes **50–53**,^{27,28} and partially hydrogenated derivatives of 10-dimethylaminobenzo[*h*]quinoline **25** and quinolino[7,8:7',8']-quinoline **26** were synthesised.²⁹

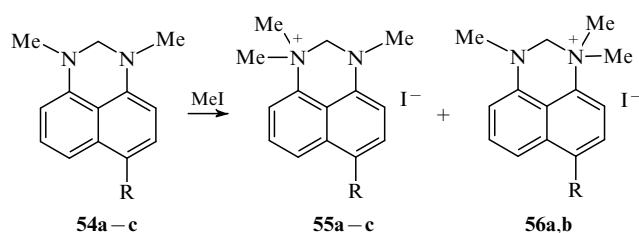


48, 49
48: R = Me;
49: R = Et.



50–53
50: R¹ = Cl, R² = H;
51: R¹ = Br, R² = H;
52: R¹ = R² = Cl;
53: R¹ = R² = Br.

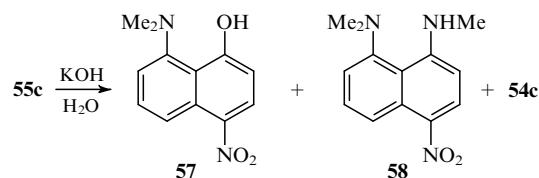
It should be noted that quaternisation of 6-halogeno-1,3-dimethyl-2,3-dihydroperimidines **54a,b** gives a mixture of isomeric salts **55a,b** and **56a,b** in comparable amounts. Separation of this mixture is not required, since methylation of the isomeric *N,N,N'*-trialkyl-substituted 1,8-diaminonaphthalenes formed upon alkaline treatment give the same final product.^{27,28}



R = Br (**a**), Cl (**b**), NO₂ (**c**).

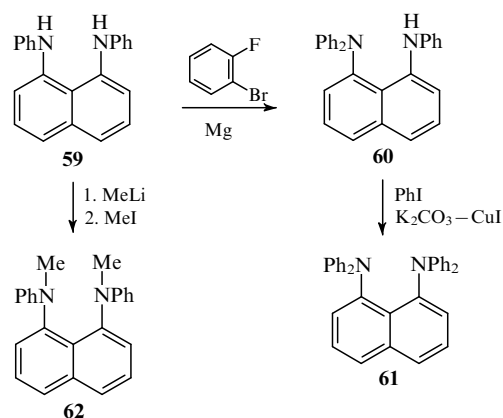
In some cases, however, alkylation of non-symmetrical dihydroperimidines occurs regioselectively. Thus if the nitrogen atoms have different substituents (*e.g.*, Me and Et), quaternisation affects only the nitrogen atom carrying the smallest group.²⁵ Analogously, but owing to electronic (rather than steric) factors, methylation of 1,3-dimethyl-6-nitro-2,3-dihydroperimidine **54c** gives exclusively the salt **55c**.³⁰

The latter manifests an abnormal behaviour upon alkaline treatment. The main product of this reaction is the naphthol **57** formed in 65% yield. Dihydroperimidine **54c** was formed in a small amount (5%), whereas nitronaphthylenediamine **58** was present in only trace amounts.



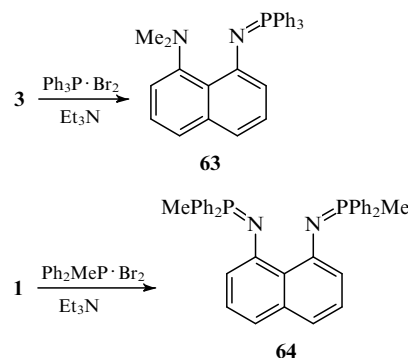
2. Analogues of ‘proton sponges’ with *N*-aryl groups

Two compounds of this type have been described thus far, *viz.*, 1,8-bis(diphenylamino)- and 1,8-bis(methylphenylamino)-naphthalene,³¹ which do not resemble classical ‘proton sponges’ in properties and molecular geometry. Fairly accessible 1,8-bis(phenylamino)naphthalene **59** served as the starting compound for their synthesis. Its sequential arylation (with dehydrobenzene generated from *o*-bromofluorobenzene and then with iodobenzene according to Ullman) has led, *via* the triphenyl-substituted compound **60**, to 1,8-bis(diphenylamino)naphthalene **61**. An attempted exhaustive Ullman arylation of the diamine **1** was unsuccessful. To synthesise 1,8-bis(methylphenylamino)-naphthalene **62**, the diamine **59** was converted into the dilithium salt, which was further subjected to methylation.



3. Iminophosphorane ‘sponges’

In addition to iminophosphorane **29**, its analogues **63** and **64** were synthesised.^{32,33} The general method for the synthesis of these compounds involves the reaction of a bromine–triphenylphosphine (diphenylmethylphosphine) complex with the corresponding amine in the presence of triethylamine. The yields are high, as a rule.



4. 1,8-Bis(dimethylaminomethyl)naphthalene

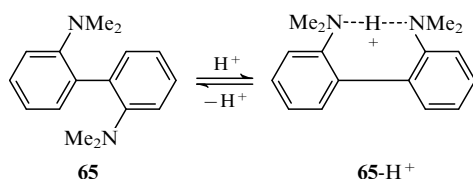
Compound **30** was obtained in 90% yield by reduction of 1,8-bis(dimethylcarbamoyl)naphthalene with lithium aluminium hydride.³⁴ In some features (see below), this can also be referred to as a ‘proton sponge’.

IV. Physicochemical properties of naphthalene 'proton sponges'

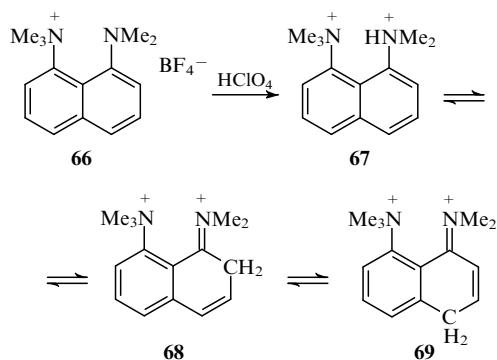
1. Basicity

Unquestionably, high basicity is the main distinctive property of all the 'proton sponges'. The analysis of factors influencing this parameter sheds more light on both structural peculiarities of these compounds and their reactivity. We have already mentioned the three main reasons for the high basicity of 'sponges', namely, destabilisation of the base as a result of repulsion of unshared electron pairs of the proximal nitrogen atoms, steric strain relief upon the transition to the cation, and the formation of a strong IHB in the cation. The greatest importance is given to the latter factor, therefore the stability and geometry of IHB in cations of the 'proton sponges' have become objects of intense studies using ^1H NMR, IR spectroscopy, X-ray analysis, and other methods (see below).¹³

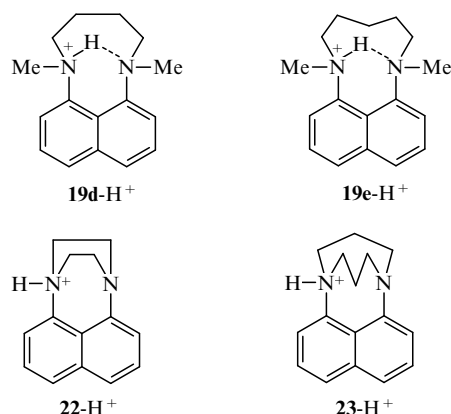
The contribution of IHB to the general increase in the basicity of a 'proton sponge' can be roughly estimated from the $\text{p}K_{\text{a}}$ value of 2,2'-bis(dimethylamino)diphenyl **65**. This value is equal to 7.9, *i.e.*, the basicity of this compound is nearly three orders of magnitude higher than that of *N,N*-dimethylaniline.³⁵ Since the benzene rings in the compound **65** are turned at an angle of 135° relative to one another, this is free from both noticeable repulsion of unshared electron pairs of the nitrogen atoms and steric strain due to this repulsion. Thus this difference in basicity can be ascribed, with a fair degree of confidence, to the stabilising effect of the IBH in the cation **65-H**⁺. Apparently, the energy contribution of the IBH in case of the 'proton sponge' is even higher, since the cation **6-H**⁺ contains a six-membered ring, which is more stable than the seven-membered ring in the cation **65-H**⁺.



Of special note is the fact that the second ionisation constant of the 'proton sponge' measured in water ($\text{p}K_{\text{a}}^2 = -9.0$)³⁶ is much lower than the first one ($\text{p}K_{\text{a}}^1 = 12.1$). It is not surprising that in contrast to 1,8-diaminonaphthalene, which gives a stable crystalline dihydrochloride, the corresponding salts of the 'proton sponge' cannot be obtained. The reason is that the rupture of the IBH needed for the second *N*-protonation is energetically unfavourable even under the action of strong acids. Cations of other 1,8-bis(dialkylamino)naphthalenes behave in a similar way. At the same time, under the action of HClO_4 or $\text{CF}_3\text{SO}_3\text{H}$, the *N*-methylated cation of the 'proton sponge' **66** devoid of the IHB forms the dication **67**, which is partly isomerised into the *C*-protonated forms **68** and **69**.^{37, 38}



For the same reason, the chelated cations **19d-H**⁺ and **19e-H**⁺ do not undergo second *N*-protonation under analogous conditions, whereas the non-chelated cations **22-H**⁺ and **23-H**⁺ do form the *N*(1),*N*(8)-dication.³⁷



Tables 4 and 5 present the values of the basicity constants, $\text{p}K_{\text{a}}$, of the naphthalene 'proton sponges' both without additional substituents in the naphthalene nucleus (**6**, **31**, **44–47**), and with substituents at *ortho*- (**25**, **26**, **70–73**) and *para*- (**48–53**, **74–86**) positions, as well as for one 2,4-disubstituted **87** and polynuclear compounds **88–93**. Only a few of the $\text{p}K_{\text{a}}$ values have been measured in water or in mixtures of water with other solvents. Most of the data were obtained for acetonitrile; in some cases the measurements were performed in DMSO. The $\text{p}K_{\text{a}}$ values of the compound **6** in acetonitrile (18.2), water (12.1, 12.3), and DMSO (7.5) indicate that the basicity of the 'sponge' drops by more than ten orders of magnitude as the proton-acceptor properties of a solvent increase.

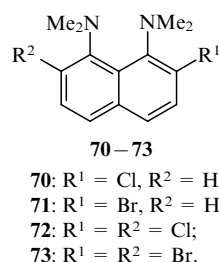


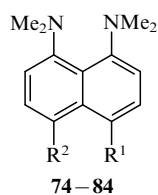
Table 4. Basicity constants, $\text{p}K_{\text{a}}$, of naphthalene 'proton sponges' and some of their analogues in aqueous solvents.

Compound	Solvent ^a	$\text{p}K_{\text{a}}$	Ref.
6	H_2O	12.3; 12.1	1, 17
6	$\text{C}_6\text{H}_{10}\text{O}_2 - \text{H}_2\text{O}$ (1 : 4)	11.5	17
31	$\text{DMSO} - \text{H}_2\text{O}$ (3 : 7)	13.0	39
31	$\text{C}_6\text{H}_{10}\text{O}_2 - \text{H}_2\text{O}$ (1 : 4)	12.7	17
15	H_2O	10.0	40
18a	H_2O	7.5	23
34	$\text{DMSO} - \text{H}_2\text{O}$ (3.5 : 6.5)	16.1	41
35	$\text{DMSO} - \text{H}_2\text{O}$ (3.5 : 6.5)	16.3	41
37	$\text{DMSO} - \text{H}_2\text{O}$ (3.5 : 6.5)	16.1	23
38	$\text{DMSO} - \text{H}_2\text{O}$ (3.5 : 6.5)	16.1	23
18b	H_2O	13.0	23
18c	H_2O	12.5	23
19a	$\text{EtOH} - \text{H}_2\text{O}$ (1 : 1)	3.8	42
19b	H_2O	4.6	40
19c	H_2O	10.3	40
19d	$\text{DMSO} - \text{H}_2\text{O}$ (3 : 7)	13.6	40
19e	$\text{DMSO} - \text{H}_2\text{O}$ (3 : 7)	13.0	40
20	$\text{DMSO} - \text{H}_2\text{O}$ (3 : 7)	12.9	43

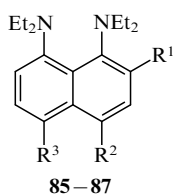
^a Ratio of components is given in brackets (*v/v*).

Table 5. Basicity constants, pK_a , of naphthalene 'proton sponges' in acetonitrile.

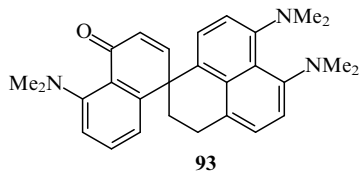
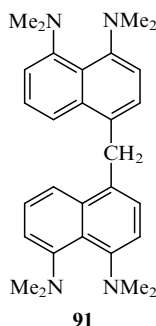
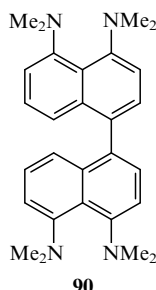
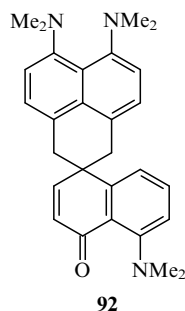
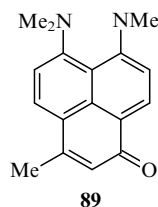
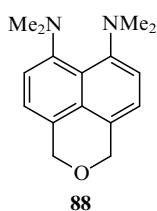
Compound	pK_a^a	Ref.	Compound	pK_a^a	Ref.
6	18.2; 18.5	2, 44	79	8.0 ^b	45
6	7.5 ^b	36	28	9.8 (4.9) ^b	24
31	18.95	25	50	17.4	44
44	18.5	25	51	17.3	44
45	18.7	25	52	16.1	44
46	18.7	25	53	16.4	44
47	18.9	25	80	14.9	44
48	18.3	25	81	12.3	44
49	18.6	25	82	16.8	44
25	17.5	29	83	14.9	44
26	17.6	29	84	14.1	46
70	18.35	44	85	15.3	46
71	18.20	44	86	11.8	46
72	17.8	44	87	15.5	46
73	17.45	44	88	18.6	44
74	17.8	44	89	14.6	44
75	14.45	44	90	18.1 (18.1)	44
76	9.8 ^b	45	91	18.3 (18.3)	44
77	18.35	44	92	18.4 (13.6)	44
78	10.1 ^b	45	93	18.5 (14.5)	44
79	19.15 (7.6)	44			

^a The values in brackets relate to the second ionisation constant, pK_a^2 .^b The pK_a values were measured in DMSO solution.

- 74:** $R^1 = CH=CH_2$, $R^2 = H$;
75: $R^1 = CH=C(CN)_2$, $R^2 = H$;
76: $R^1 = NH_2$, $R^2 = H$;
77: $R^1 = NHCOMe$, $R^2 = H$;
78: $R^1 = NHMe$, $R^2 = H$;
79: $R^1 = NMe_2$, $R^2 = H$;
80: $R^1 = CHO$, $R^2 = H$;
81: $R^1 = R^2 = CHO$;
82: $R^1 = COMe$, $R^2 = H$;
83: $R^1 = COCF_3$, $R^2 = H$;
84: $R^1 = NO_2$, $R^2 = H$.



- 85:** $R^2 = NO_2$, $R^1 = R^3 = H$;
86: $R^1 = H$, $R^2 = R^3 = NO_2$;
87: $R^1 = R^2 = NO_2$, $R^3 = H$.



Measurements of the gas-phase basicity (that is the proton affinity) of the 'proton sponge' and other 1,8-diaminonaphthalenes have been carried out.³ The corresponding values are given in Table 6 in comparison with analogous values for methylated derivatives of aniline and ammonia. The abrupt jump in basicity in both the gas phase and water is observed only for the transition from 1-dimethylamino-8-methylaminonaphthalene **5** to 1,8-bis-(dimethylamino)naphthalene **6**. This indicates that the abnormally high basicity of the 'proton sponge' in vapour and in water is due to the same factors. It is interesting to note that in the gas phase, all 1,8-diaminonaphthalenes are protonated at the nitrogen atom, whereas 1-aminonaphthalene and 1,3-diaminobenzene are protonated in the ring. It is believed that the stability of 1,8-diaminonaphthalene *N*-cations in the vapour is accounted for by the stabilising effect of the IHB.

Table 6. Effect of *N*-methylation on the gas-phase proton affinity (PA) and changes in free energy (ΔG_0^1) of protonation of the succeeding base in comparison with the preceding base in the gas phase and in water.^{3, 47}

Base	PA /kJ mol ⁻¹	ΔG_0^1 /kJ mol ⁻¹	
		gas phase	water
1	954.4	—	—
3	982.8	−28.5	−5.9
5	1000.8	−18.0	−4.6
6	1030.1	−29.3	−33.9
PhNH ₂	895.0	—	—
PhNHMe	925.9	−31.0	−1.26
PhNMe ₂	953.5	−27.6	−1.7
NH ₃	866.1	—	—
MeNH ₂	907.9	−4.2	−7.9
Me ₂ NH	939.3	−31.4	0
Me ₃ N	960.2	−20.9	+4.6

The dependence of gas-phase basicities of amines (including 1,8-diaminonaphthalenes) and core-bond energies of the σ -back-bone has been studied.⁴⁷ It is linear for the bases the geometry of which is not changed significantly upon protonation. However, such a correlation was not found for compounds **3**, **5**, and **6**. It was suggested that for these compounds the degree of deviation from linearity can serve as a measure of steric strain relief upon the transition from the base to the cation. For the 'proton sponge' **6**, this value was estimated to be 62.8 kJ mol⁻¹, and for the amines **3** and **5**, 37.7 and 33.5 kJ mol⁻¹, respectively.

Let us now consider the effect of structural changes at the nitrogen atoms and in the ring on the basicity of 'sponges'. Successive substitution of the *N*-methyl groups by ethyl groups slightly increases the basicity, as a result of which the pK_a value of the 'tetraethyl sponge' **31** is 0.8–1.2 units higher than that of its tetramethyl analogue **6** (*cf.* Tables 4 and 5). More substantial changes in basicity are observed in those cases where the amine nitrogen atoms are incorporated into the rings. Thus, the basicity of 1,8-dipyrrolidino- and 1,8-dimorpholinonaphthalenes **15** and **18** is lower by 2.5 and 4.5 orders of magnitude, respectively, than that of the 'proton sponge' **6** (Table 4). The same tendency, although less pronounced, is manifested in compounds **25** and **26** (Table 5) the nitrogen atoms of which are incorporated into fused ring systems. It may be assumed that their structure is not optimum for the formation of a sufficiently strong IHB in the cation, *e.g.*, because the axes of unshared electron pairs of the nitrogen atoms can hardly be coplanar with the ring. This phenomenon was also noted for some non-naphthalene 'proton sponges'. Thus the basicity of benzo[1,2-*h*:4,3-*h'*]diquinoline **11** with a helicene structure is 2.5 orders of magnitude less¹⁰ than that of the planar quino[7,8-*h*]quinoline **10** (Ref. 8) ($pK_a = 10.3$ and 12.8, respectively).

As can be inferred from Table 4, of a set of diamines **19**, only compounds **19c–e** can be regarded as 'proton sponges'. The basicity of the first two representatives of this series lies at a level characteristic of ordinary arylamines. It is understandable that the methylene and ethylene bridges in the molecules **19a,b** provide rigid fixation of the nitrogen atoms in the configuration where unshared electron pairs largely acquire *p*-character without any noticeable reciprocal repulsion; in addition, the IHB cannot be formed in their cations. Apparently, for this reason the bridged diamines **22–24**, which form the non-chelated cations **22-H⁺** and **23-H⁺**, are not 'proton sponges'.

The effect of substituents in the nucleus on the basicity of 'proton sponges' is roughly as expected (Tables 4 and 5) for 2,7-dialkoxy derivatives **34**, **35**, **37**, and **38** the basicity of which is four orders of magnitude higher than that of the non-substituted 'sponges' (Table 4), and their salts are not significantly deprotonated by strong aqueous alkalis. Formerly, these compounds were considered to be the strongest of the known neutral bases. It is believed that the molecules of compounds **34**, **35**, **37**, and **38** manifest the so-called 'supporting effect' [Buttress effect. Ed.], in which *ortho*-substituents favour closer approach of unshared electron pairs of both dialkylamino groups to each other, enhancing electrostatic repulsion and, presumably, steric strain in the base. The 'supporting effect' was also observed in 2,7-dichloro- and 2,7-dibromo-1,8-bis(dimethylamino)naphthalenes **72** and **73**.^{44,48}

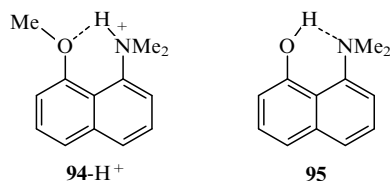
The attempts to separate the first and second ionisation constants for the binaphthyl **90** and binaphthylmethane **91** 'sponges' were unsuccessful.⁴⁴ Apparently, both their basic centers have little influence on each other.

The basicity of compounds **29**, **63**, and **64** could not be determined experimentally due to their poor solubility, slow rates of protonation, and hydrolysis of the iminophosphorane group. However, using complex extrapolations, the pK_a value for compound **29** in water was estimated to be equal to 15.6, which markedly exceeds the basicity of the classical 'proton sponges'.⁴⁹

The basicity of 1,8-bis(dimethylaminomethyl)naphthalene **30** ($pK_a^1 = 18.3$, $pK_a^2 = 11.4$ in acetonitrile) is at a level typical of the 'naphthalene sponges'.⁵⁰ However, the fact that this compound binds two protons instead of one (as is the case with the classical 'proton sponges') testifies to the insufficiently strong IHB in the monocation; the latter finding was confirmed by ¹H NMR spectroscopic data.

2. The mechanism and rates of deprotonation of cations

As has already been mentioned, the high basicity of 'proton sponges' is combined with low rates of their protonation–deprotonation. The deprotonation rate constants for several 'sponges' are given in Table 7, which also contains data for the 1-dimethylamino-8-methoxynaphthalene cation **94-H⁺** and 8-dimethylaminonaphthol **95** for comparison.



Whereas the deprotonation rate for ordinary ammonium salts is limited by diffusion ($k \approx 3 \times 10^{10}$ litre mol^{−1} s^{−1}),⁵¹ in the case of 'sponge' cations this process is much slower. Thus for the cation **6-H⁺** $k = 1.9 \times 10^5$ litre mol^{−1} s^{−1}, and for its tetraethyl analogue **31-H⁺** k is even one order of magnitude lower. Deprotonation of their 2,7-dimethoxy derivatives, **34-H⁺** and **35-H⁺**, is especially slow, and in the latter case the reaction can even be followed spectrophotometrically. It is noteworthy that because of the high basicity of compounds **34** and **35**, the deprotonation of their cations is observed only in alkaline solutions of DMSO.

Table 7. Rate constants for the reaction of deprotonation of some 'proton sponge' cations.

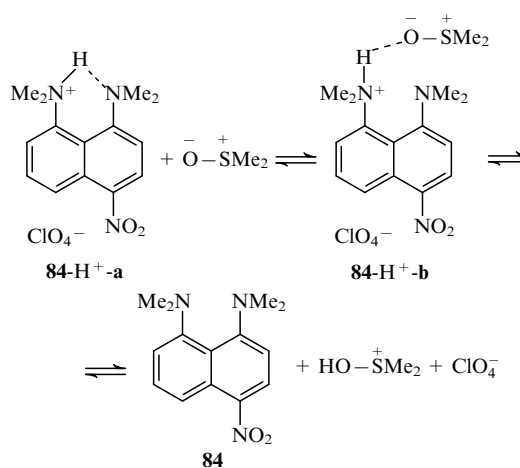
$BH^+ + OH^- \xrightleftharpoons{k} B + H_2O$			
Cation BH ⁺	Solvent ^a	k / litre mol ^{−1} s ^{−1}	Ref.
6-H⁺	H ₂ O	1.9×10^5	17, 52
6-H⁺	Dioxane–H ₂ O (1 : 4)	4.6×10^5	17
6-H⁺	DMSO–H ₂ O (3 : 7)	6.1×10^5	14
31-H⁺	Dioxane–H ₂ O (1 : 4)	1.6×10^4	17
31-H⁺	DMSO–H ₂ O (3 : 7)	1.6×10^4	14
34-H⁺	DMSO–H ₂ O (3 : 2)	4.4×10^2	41
35-H⁺	DMSO–H ₂ O (3 : 2)	3.3	41
18a-H⁺ (see ^b)	H ₂ O	1.2×10^3	43, 53
20-H⁺	DMSO–H ₂ O (3 : 7)	6.2×10^3	43
94-H⁺ (see ^b)	H ₂ O	0.4×10^7	54
95	DMSO–H ₂ O (4 : 1)	3.0×10^6	54

Note For more detailed information see Refs 23 and 40.

^a Ratio of components is given in brackets (*v/v*). ^b HPO₄^{2−} was used as the base instead of OH[−].

It is reasoned that the low rates of cation deprotonation are mainly caused by the necessity of cleavage of a very strong IHB. Presumably, a certain role is played by steric factors: in the cation, the proton resides in a sort of hydrophobic 'pocket', therefore, access to a base must be hindered (especially in the case of tetraethyl 'sponges'). Compounds **94-H⁺** and **95** are also deprotonated very slowly, but still faster than the 'sponge' cations. It may be inferred from these data (Table 7) that the strength of the IHB decreases in the following order: **6-H⁺** > **95** > **94-H⁺**.

Vivid debates in the current literature concern the mechanism of deprotonation of chelated species of 'proton sponge' cations.¹⁴ Virtually all the data indicate that this process occurs in two steps: first, the IHB is cleaved under the influence of a base, and then deprotonation of the unchelated cation takes place. Apparently, the limiting step in this process is its first stage, therefore, the equilibrium concentration of the unchelated cation at each moment of time is low. However, we have recently observed for the first time in our laboratory all the three particles (both cations and the deprotonated base) in equilibrium, with 4-nitro-1,8-bis(dimethylamino)naphthalene **84** as an example.⁵⁵ It was found that the ¹H NMR spectrum of the cation **84-H⁺** in [D₆]-DMSO contained peaks not only of the chelated cation **84-H⁺-a**, but also those of the free base **84** and of a third species the characteristics of which corresponded to those of the non-chelated cation **84-H⁺-b**. At an initial concentration of the dissolved perchlorate **84-H⁺** of 5×10^{-2} mol litre^{−1}, the ratio **84-H⁺-a** : **84-H⁺-b** : **84** is 68 : 19 : 13, *i.e.*, under these conditions the chelated cation is predominant. If the concentration of the



original salt decreases by one order, this ratio changes drastically (26:5:69) and the deprotonated base becomes the predominant form. The cation **84-H⁺-a** does not undergo any noticeable changes in acetonitrile. Similarly, the cation of the 'proton sponge' **6-H⁺** is the only species that is present in [2H₆]-DMSO.

Apparently, there are three reasons for the abnormal behaviour of the cation **84-H⁺**: (1) considerable asymmetry of the IHB [according to X-ray and ¹H NMR data, the proton resides predominantly at the N(8) atom], (2) decreased (four orders of magnitude in comparison with compound **6**) basicity of the nitro-derivative **84**, and (3) the optimum moderate basicity of dimethyl sulfoxide sufficient to induce partial scission of the IHB and subsequent deprotonation, but at the same time insufficient for the complete shift of the equilibrium between the non-chelated cation and the base to the right.

3. Molecular and crystalline structure

a. Bases

The most important peculiarity of 'proton sponge' bases is a considerable distortion of the planar structure of their molecules due to the trend of the dialkylamino groups to maximally separate from one another. According to X-ray data, for compound **6**,⁵⁶ (1) the angle C(1)–C(9)–C(8) increases to 125.8°; (2) the distance C(1)–C(8) increases to 2.56 Å against 2.45 Å in naphthalene; (3) the distance N···N is rather large (2.79 Å) (*cf.* 2.72–2.74 Å in 1,8-diaminonaphthalene).⁵⁷ The mean plane of the naphthalene system is formed by C(2), C(3), C(9), C(10), C(6), and C(7) atoms, whereas the C(1)–C(9)–C(10)–C(4) and C(8)–C(9)–C(10)–C(5) fragments are symmetrically twisted relative to the central bond C(9)–C(10); the torsion angles are equal to 8.9° and 10.5°, respectively. Thus the two benzene rings begin to resemble two chairs put against each other so that the back of one chair is next to the legs of the other chair, and *vice versa*. As a consequence, the C(1) and C(8) atoms and, correspondingly, the nitrogen atoms deviate (the latter, by 0.4 Å) in opposite directions from the mean plane of the fused system (Fig. 1*a*). The orientation of the methyl groups is also different (Fig. 1*b*) as if one pair is directed inward towards the cyclic system, while the other is directed outward, the latter lying nearly in the mean plane of the ring. Obviously, the axes of the unshared electron pairs at the nitrogen atoms are also oriented in opposite directions to form an angle of about 40° with the axes of the aromatic *p*-electrons. The latter circumstance deserves special notice, since with such angles the conjugation of the dimethylamino groups with the π -system of the ring is still considerable.

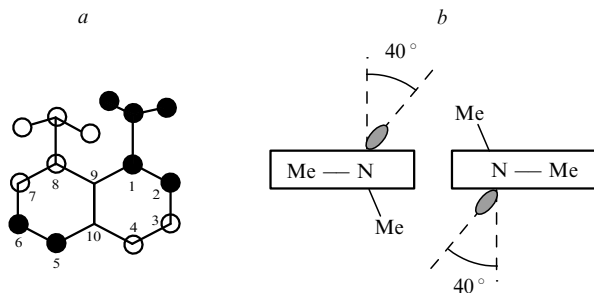
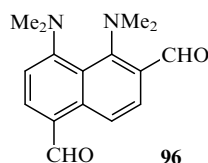


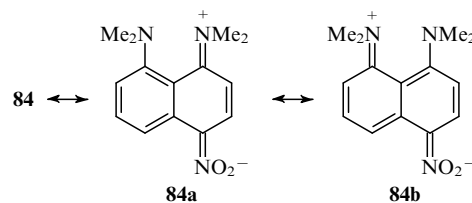
Figure 1. Structure of the 'proton sponge' molecule **6**: view from the top (*a*) and along the mean plane of the ring (*b*) (the empty and full circles belong to the atoms located on different sides of the mean plane).

Table 8. The distance between the nitrogen atoms, $r(\text{N}\cdots\text{N})$, in some 1,8-diaminonaphthalenes.

Compound	$r(\text{N}\cdots\text{N})/\text{\AA}$	Ref.	Compound	$r(\text{N}\cdots\text{N})/\text{\AA}$	Ref.
1	2.72; 2.74 ^a	57	28	2.75	24
6	2.79	56	34	2.76	60
17	2.89	58	84	2.86	55
18a	2.86	58	81	3.03	61
23	2.89	59	96	2.95	61
61	2.86	31			

^a For two independent molecules.

An analogous pattern with some modification is also observed for other 'proton sponges' (Table 8). Thus in the 4-nitro-derivative **84**, as well as in 4,5-**81** and 2,5-dialdehydes **96**, the distance between the nitrogen atoms of the dimethylamino groups shows a tendency to increase, presumably, as a result of conjugation of the latter with π -acceptor substituents. This must be accompanied by flattening of bonds at the amine nitrogen atoms (due to the greater contribution of the structures of the type **84a** and **84b**), so that NMe₂ groups require larger space. Accordingly, the C(1)–N(1) and C(8)–N(2) bonds in compounds **84** (1.37–1.38 Å) and **81**, **96** (1.36 Å) become somewhat shorter than those in the 'proton sponge' **6** itself (1.40 Å).



In compounds with electron-donor groups **28** and **35**, the lengths of C(1)–N(1) and C(8)–N(2) bonds are the same as in compound **6** (1.40 Å). The N···N distance remains virtually unchanged, although the distortions in the naphthalene ring structure become more pronounced. As expected, the N···N distance increases in the 'proton sponges' **61**, **17**, **18a**, and **23** having bulkier or less flexible substituents at the amine nitrogen atoms.

A characteristic feature of the molecular structure of 1,8-bis(dimethylaminomethyl)naphthalene **30** is the practically planar geometry of the naphthalene ring.⁶²

b. Cations

A great number of X-ray studies have been carried out with the salts of the 'proton sponge' **6-H⁺** with various anions (Table 9). All these studies have demonstrated that the transition to the cation brings about drastic changes in the molecular structure. Owing to the formation of the hydrogen bridge, the dialkylamino groups rotate in such a way that the dihedral angle between them and the naphthalene system plane tends to reach 90°. This results in steric strain relief, flattening of the naphthalene fragment, and considerable approach of the nitrogen atoms. The N···N distance varies within the range of 2.55 to 2.65 Å, being, on the average, 2.58 Å. In the majority of salts, the naphthalene ring is virtually flat and both N atoms lie in the same plane. For some salts ($\text{X}^- = \text{C}_6\text{Cl}_5\text{O}^-$, BF_4^- , SCN^-), the twisting (by no more than 4–5°) of the planes of C(1)–C(9)–C(10)–C(4) and C(8)–C(9)–C(10)–C(5) around the central bond C(9)–C(10) still takes place. As a result, the molecule acquires a propeller shape, and the nitrogen atoms diverge in different directions from the mean plane (up to 0.25 Å). However, these deformations are much less than those observed in the 'proton sponge' base. The C(1)–N(1) and C(8)–N(2) distances in the cation **6-H⁺** increase up to 1.45 Å, which testifies to the lack of conjugation between the

Table 9. Geometric parameters of the hydrogen bridge in ‘proton sponge’ salts $6\text{-H}^+ \text{X}^-$.

X^-	T/K	Distances /Å			Angle $\text{N}\cdots\text{H}-\text{N}$ /degree	Ref.
		$\text{N}-\text{H}$	$\text{N}\cdots\text{H}$	$\text{N}\cdots\text{N}$		
$[(\text{hfac})_3\text{Cu}^{2+}]^-$ (see ^a)	298	1.27	1.49	2.65	145	63, 64
$[(\text{hfac})_3\text{Mg}^{2+}]^-$ (see ^a)	298	1.25	1.58	2.60	134	63, 64
$\text{Br}^- \cdot 2\text{H}_2\text{O}$	298	1.30	1.30	2.55	153	65
BF_4^-	298	1.30	1.31	2.56	159	66
SCN^-	298	1.30	1.30	2.57	160	67
SCN^-	188	1.32	1.32	2.58	156	67
Tetrazolide $\cdot \text{H}_2\text{O}$	298	1.31	1.31	2.57	157	68
2,4-Dinitroimidazole	298	1.18	1.47	2.61	160	69
1,8-Bis(tosylamido)-2,4,5,7-tetra-nitronaphthalene (monoanion)	298	1.05	1.63	2.61	152	70
1,8-Bis(trifluoroacetamido)-naphthalene (monoanion)	298	1.22	1.42	2.59	156	71
Pic_2N^- (see ^b)	298	1.05	1.57	2.57	158	72
$[\text{O}(\text{Ph})\text{C}_2\text{B}_{10}\text{H}_{10}]^-$	298	1.22	1.52	2.58	140	73
OTeF_5^- (triclinic form)	167	1.17	1.46	2.57	159	74
OTeF_5^- (orthorhombic form)	143	1.37	1.37	2.58	140	75
Squarate (monoanion)	150	1.08	1.55	2.58	157	76
Squarate (dianion) $\cdot 4\text{H}_2\text{O}$	100	0.94	1.69	2.57	156	77
The same ^c	100	0.97	1.66	2.59	162	77
$\text{C}_6\text{Cl}_5\text{O}^- \cdot 2\text{C}_6\text{Cl}_5\text{OH}$	100	1.11	1.47	2.56	162	78
$\text{C}_6\text{F}_5\text{O}^- \cdot 2\text{C}_6\text{F}_5\text{OH}$	100	1.07	1.56	2.57	154	79
The same ^c	100	0.86	1.84	2.57	141	79
Chloranilic acid dianion	298	1.14	1.51	2.59	155	80
	150	1.07	1.59	2.59	152	80
D-Hydrogen tartrate $\cdot 3\text{H}_2\text{O}$	100	0.91	1.75	2.61	157	81
The same ^c	100	0.84	1.86	2.61	149	81
3,4-Furandicarboxylate (monoanion)	298	1.06	1.62	2.62	155	82
Hemimellitate (monoanion) $\cdot \frac{1}{2}\text{H}_2\text{O}$	100	0.90	1.72	2.60	164	83
The same ^c	100	0.94	1.72	2.60	155	83
Maleate (monoanion)	298	1.17	1.49	2.61	157	84
1,2-Dichloromaleate (monoanion)	100	1.11	1.61	2.64	153	85

^a hfac is hexafluoroacetate. ^b Pic is picryl. ^c Data for two independent molecules obtained by differential Fourier synthesis are given.

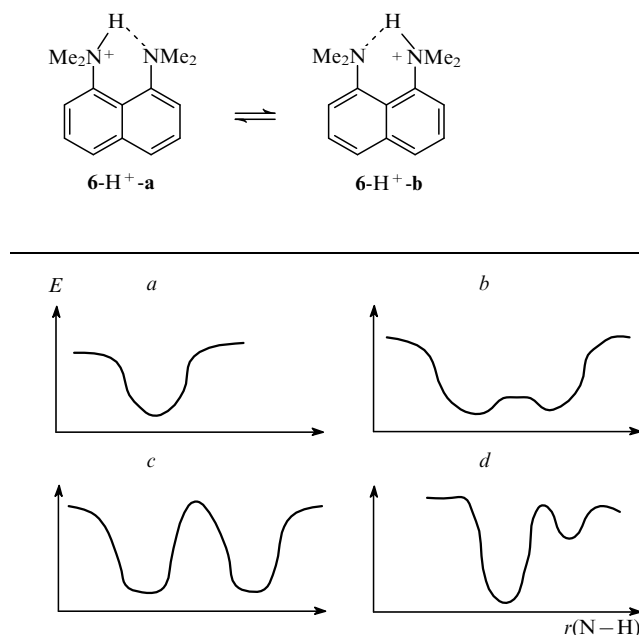
dimethylamino groups and the aromatic π -system. This conclusion is confirmed by a variety of other data.

In contrast to 1,8-bis(dialkylamino)naphthalene cations, the naphthalene ring in cations of the iminophosphorane ‘sponges’ **29**, **63**, and **64**, is strongly distorted, but the distance between the nitrogen atoms is smaller (2.52–2.60 Å).^{32, 33}

The main attention in the studies of ‘proton sponge’ cations has been paid to the symmetry and geometric characteristics of the hydrogen bridge. This problem was comprehensively discussed in a number of reviews,^{13, 86} therefore we shall confine ourselves to a mere statement of the central issues. Theoretically, four types of potential energy curves for the $\text{N}\cdots\text{H}-\text{N}$ system are possible (Fig. 2).

The profile *a* having one minimum corresponds to a completely symmetrical bridge, whereas the profile *b*, which has a low activation barrier, reflects the rapid tautomeric equilibrium between two equivalent asymmetric structures. It is the question as to which of these two profiles is realised in the cation of the ‘proton sponge’ 6-H^+ that has been discussed in most detail.

Theoretical calculations of an $[\text{H}_3\text{N}\cdots\text{H}\cdots\text{NH}_3]^+$ system have shown that when the distance between the nitrogen atoms is 2.75 Å, the potential curve has two minima with a barrier of 10.9 kJ mol⁻¹; with a decrease in the distance down to 2.50 Å, the barrier disappears.¹³ In terms of the data listed in Table 9, these results may indicate that the energy profile for the cation 6-H^+ corresponds to type *b* with a low barrier of transition between the structures $6\text{-H}^+ \text{-a}$ and $6\text{-H}^+ \text{-b}$.

**Figure 2.** Types of potential energy curves for the IHB in ‘proton sponge’ cations; for *a–d*, see text.

Indeed, in some cases it was shown that the proton NH lies in the plane of symmetry of the cation **6-H⁺** not only at room temperature, but even at low temperatures; the length of the N–H bond is averaged (~ 1.3 Å). In those salts (which constitute the majority), where the hydrogen bridge is asymmetrical, the N–H bond is much longer than the standard value (~ 0.9 Å). In the case of the salt **6-H⁺** with the dianion of the chloranilic acid, a decrease in the temperature from 300 to 150 K results in the shortening of this bond from 1.14 to 1.07 Å. This is indirect evidence that the elongation of the N–H bond is due to the disordered position of the NH-proton oscillating between the nitrogen atoms and the plane of symmetry. Obviously, the anion influences the mode of these oscillations and, correspondingly, the geometry of the hydrogen bridge both through the electric field induced by it and due to the changes in the crystal lattice. The formation of a weak bifurcated hydrogen bond involving the anion and the NH-proton was recorded both for the **6-H⁺** salt with hydrosquarate and squarate anions. Thus at present the majority of researchers tend to accept that the cation **6-H⁺** exists in a position of fast tautomerism



An asymmetrical hydrogen bridge was observed in crystals of the ‘double sponge’ dication **28-(2H⁺)** as well as in cations of the bisiminophosphorane **29** and the compound **30**. It is probable that the energy curve profile of the type *c* corresponds to these bridges. As expected, in cations of unsymmetrical bases, e.g., **84-H⁺** or **63-H⁺**, the proton practically completely resides on the more

basic of the two N atoms: on N(8) and the imine nitrogen, respectively (type *d* curve, Fig. 2) (Table 10).

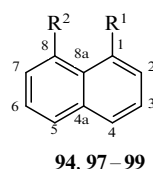
It should be mentioned in conclusion that in cations of all the ‘proton sponges’ the hydrogen bridge is non-linear and the N–H $\cdots$ N angle lies within the range of 150–160° with only few exceptions. The neutronographic method, which is considered to be more precise for establishing the molecular structure than X-ray structural analysis (as was shown with the **6-H⁺** salt with the dichloromaleic acid anion), gives basically the same results.^{85,87}

4. NMR spectra

¹H, ¹³C, and ¹⁵N NMR spectra of the ‘proton sponges’ and their cations were investigated both for solutions and solid state. NMR spectroscopy was used to establish structural characteristics, π -electron distribution, and the ease of proton exchange between the cations and bases.

a. Bases

As expected, the signals for all the aromatic protons in the ¹H NMR spectrum of compound **6** (Table 11) are at higher field than those for naphthalene (δ 7.46 and 7.81 ppm for α - and β -protons, respectively). The greatest shielding is of the protons at positions 2 and 7, then H3(6) and H4(5), the difference in the chemical shifts between *meta*- and *para*-protons being very small.



- 94:** R¹ = OMe, R² = NMe₂;
97: R¹ = R² = OMe;
98: R¹ = NMe₂, R² = H;
99: R¹ = OMe, R² = H.

94, 97–99

If one assumes that the degree of proton shielding is proportional to the +*M*-effect of the substituents, the following conclusion can be made: the electron donor capacity of the NMe₂ groups in the molecule of compound **6** is somewhat lower than that of the *peri*-substituents in 1-dimethylamino-8-methoxy- **94** and 1,8-di-methoxynaphthalenes **97** (Table 12). Even in 1-methoxynaphthalene **99**, the donor effect of the substituent seems to be higher than in 1-dimethylaminonaphthalene **98**. This conclusion is confirmed by analysis of ¹³C NMR spectra (Table 13). Since in benzene derivatives the shielding effects of NMe₂ and MeO groups are opposite and correspond to the Hammett σ -constants, it is reasonable to conclude that the decreased electron donor capacity of the NMe₂ groups in 1-dimethylamino- and 1,8-bis-(dimethylamino)naphthalenes is a

Table 10. Geometric parameters of the hydrogen bridge in cations of some ‘proton sponges’ at 298 K.

Cation	Anion	Distances / Å			Angle N $\cdots$ H–N, /degree	Ref.
		N $\cdots$ N	N–H	H $\cdots$ N		
84-H⁺	ClO ₄ [–]	2.57	0.99	1.64	153	55
28-(2H⁺)	2Br [–]	2.57	1.22	1.39	158	24
29-H⁺	Br [–]	2.58	0.85	1.78	159	32
63-H⁺	Br [–]	2.52	1.20	1.38	154	33
30-H⁺	NO ₃ [–]	2.64	1.28	1.39	164	34
30-H⁺	NO ₃ [–]	2.63 ^a	0.83 ^a	1.83 ^a	161 ^a	88
30-H⁺	NO ₃ [–]	2.63 ^a	1.04 ^a	1.61 ^a	165 ^a	88
30-H⁺	PicO [–]	2.72	1.07	1.68	162	89
30-H⁺	ClO ₄ [–]	2.68	1.18	1.51	167	90

^a At 100 K.

Table 11. ¹H NMR spectra of 1,8-bis(dimethylamino)naphthalene **6** and its cations **6-H⁺**.⁹¹

Compound ^a	Solvent	δ /ppm					<i>J</i> /Hz			
		H(2), H(7)	H(3), H(6)	H(4), H(5)	CH ₃	(NHN) ⁺	<i>J</i> _{H(2)–H(3)}	<i>J</i> _{H(3)–H(4)}	<i>J</i> _{H(2)–H(4)}	<i>J</i> _{NH–CH₃}
6	CDCl ₃ ⁹²	6.96	7.33	7.39	2.82	—	7.3	8.2	1.5	—
6	CD ₂ Cl ₂	6.92	7.27	7.32	2.77	—	7.2	8.1	1.5	—
6	CCl ₄ ¹	6.76	7.09	7.18	2.71	—	7.6	7.9	1.2	—
6	CD ₃ CN	6.90	7.23	7.30	2.70	—	7.2	8.1	1.5	—
6	CD ₃ NO ₂	6.91	7.24	7.30	2.73	—	7.2	8.1	1.5	—
6-H⁺	CF ₃ CO ₂ H ¹	8.04	7.71	7.83	3.21	19.51	8.3	7.6	0.9	2.0
6-H⁺ Cl[–]	CD ₃ CN	8.00	7.70	8.04	3.20	18.58	7.5	8.4	0.9	2.7
6-H⁺ Br[–] · H₂O	CD ₃ CN	7.96	7.71	8.05	3.17	18.66	7.8	8.4	0.9	2.7
6-H⁺ NO₃[–]	CD ₃ CN	7.94	7.70	8.04	3.14	18.92	7.8	8.4	0.9	2.7
6-H⁺ BF₄[–]	CD ₃ CN	7.92	7.71	8.05	3.12	18.67	7.5	8.4	0.9	2.7
6-H⁺ ClO₄[–]	CD ₃ CN	7.91	7.70	8.05	3.11	18.66	7.8	8.4	1.2	2.7
6-H⁺ ClO₄[–]	CD ₃ NO ₂	7.98	7.75	8.08	3.25	19.08	7.8	8.4	0.9	2.7
6-H⁺ ClO₄[–]	(CD ₃) ₂ SO ⁹³	8.08	7.73	8.09	3.12	18.33	7.7	8.2	1.1	2.6

^a The ¹H NMR spectra of ‘proton sponge’ salts with the following anions: I[–], NCS[–], PF₆[–], Ph₄B[–] were also recorded in CD₃CN.⁹⁴ The values of chemical shifts in these salts are very close to those cited above.

Table 12. ^1H NMR spectra of some close analogues of the ‘proton sponge’ in CDCl_3 .⁹²

Compound	δ /ppm							
	H(2)	H(3)	H(4)	H(5)	H(6)	H(7)	H(8)	CH_3
94	6.89	7.45	7.38	7.38	7.45	7.02	—	4.01 (MeO); 2.87 (NMe ₂)
97	6.86	7.36	7.40	7.40	7.36	6.86	—	3.99
98	7.18	7.50	7.60	7.60	7.60	7.94	8.38	3.00
99	6.88	7.47	7.56	7.56	7.56	7.90	8.40	4.06

Table 13. ^{13}C NMR spectra of the ‘proton sponge’ and some of its close analogues.

Com- pound	Solvent	δ /ppm											Ref.
		C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(8a)	C(4a)	CH ₃	
6	CDCl ₃	150.70	112.70	125.40	121.70	121.70	125.40	112.70	150.70	120.60	137.80	44.40	92
6	CDCl ₃	151.26	113.47	126.02	122.49	122.49	126.02	113.47	151.26	121.37	138.66	—	95
6	CD ₃ CN	151.33	113.57	126.30	122.28	122.28	126.30	113.57	151.33	121.13	138.58	44.68	91
6	CD ₃ NO ₂	152.03	113.92	126.78	122.65	122.65	126.78	113.92	152.03	121.65	139.12	44.99	91
6	see ^a	119.80	112.10	124.60	120.90	122.10	123.90	113.30	121.80	149.70	136.50	41.0; 41.8 44.2; 45.1	96
1	CDCl ₃	144.20	111.30	126.00	119.40	119.40	126.00	111.30	144.20	116.80	136.70	—	57
94	CDCl ₃	156.10	106.40	126.00	122.00	121.60	125.60	113.30	150.70	120.30	137.60	56.3; 45.6	92
97	CDCl ₃	157.10	106.30	126.30	120.80	120.80	126.30	106.30	157.10	117.60	137.40	56.40	92
6-H⁺ClO₄[−]	CD ₃ CN	145.12	122.36	127.86	130.04	130.04	127.86	122.36	145.12	120.02	136.19	46.73	91
6-H⁺BF₄[−]	see ^a	117.40	120.70	128.30	126.50	126.50	128.30	120.70	117.40	143.40	134.80	43.6; 46.4	96

^a Spectrum for solid compound.

result of their considerable non-coplanarity with the nucleus caused by *peri*-interactions. It is noteworthy in this respect that the chemical shift of the *N*-methyl groups (δ 2.8 ppm) in the ‘proton sponge’ is lower than that of 1-dimethylaminonaphthalene (δ 3.0 ppm), which testifies to an increased contribution of the *s*-component in the *n*-orbital of the amine nitrogen.

Evidence for the effects of substituents in the nucleus on the parameters of the ^1H NMR spectra can be inferred from Table 14. As can be seen, *ortho*- (Cl, Br) and *−M*-substituents at position 4 (CHO, COCF₃, NO₂) cause a down-field shift of the *N*-methyl signals (by $\sim$ 0.2 ppm). In addition, *−M*-substituents produce a strong deshielding effect on H(5) [to a lesser degree, on H(3)]. This is accompanied by reduction of the spin-spin coupling constant $J_{\text{H}(5)-\text{H}(7)}$ and marked increase in the spin-spin coupling constant $J_{\text{H}(2)-\text{H}(3)}$ (presumably, due to an increased contribution of structures of the type **84a,b**).

Recent measurements of MAS ^1H NMR and ^{13}C NMR spectra of a solid sample of the ‘proton sponge’ **6** gave quite unexpected results:⁹⁶ they revealed strong asymmetry of its molecule. It was found that all four methyl groups, like all ten ring carbon atoms, resonate as separate peaks, *i.e.*, they are non-equivalent (Table 13). This has been interpreted in terms of electrostatic interactions between the neighbouring molecules in the crystal lattice and has led to partial revision of the previously established⁵⁶ results of X-ray studies of the ‘proton sponge’.

^1H NMR spectra have been used to study the ease of the proton exchange between the bases of the ‘proton sponge’ **6** and its tetraethyl analogue **34**, on the one hand, and the corresponding cations, on the other.⁹⁷ The ^1H , ^{13}C , and ^{15}N NMR spectra of compound **30** have also been recorded.^{34, 98}

Table 14. ^1H NMR spectra of ‘proton sponge’ derivatives in CDCl_3 (300 MHz, 298 K).

Com- pound	δ /ppm								J /Hz					Ref.
	1-NMe ₂	8-NMe ₂	H(2)	H(3)	H(4)	H(5)	H(6)	H(7)	$J_{\text{H}(2)-\text{H}(3)}$	$J_{\text{H}(3)-\text{H}(4)}$	$J_{\text{H}(5)-\text{H}(6)}$	$J_{\text{H}(6)-\text{H}(7)}$	$J_{\text{H}(5)-\text{H}(7)}$	
70	3.03	2.78	—	7.32	7.39	7.37	7.29	7.05	—	8.71	7.91	7.62	1.33	28
71	3.02	2.75	—	7.30	7.51	7.37	7.30	7.07	—	8.71	7.99	7.39	1.39	93
72	2.98	2.98	—	7.33	7.45	7.45	7.33	—	—	8.71	8.71	—	—	28
73	2.96	2.96	—	7.35	7.51	7.51	7.35	—	—	8.70	8.70	—	—	93
50	2.78	2.80	6.80	7.38	—	7.80	7.41	6.98	8.21	—	8.35	7.62	1.03	28
51	2.82	2.84	6.79	7.63	—	7.84	7.45	7.02	8.20	—	8.20	7.61	1.17	27
52	2.76	2.76	6.74	7.37	—	—	7.37	6.74	8.28	—	—	8.28	—	28
53^a	2.74	2.74	6.62	7.60	—	—	7.60	6.62	8.35	—	—	8.35	—	27
74^b	2.82	2.80	6.98	7.51	—	7.64	7.35	6.98	7.98	—	8.20	8.20	< 1.0	109
79	2.79	2.79	6.86	6.97	—	7.85	7.30	6.90	8.13	—	8.35	7.62	1.02	45
80	2.97	2.78	6.84	7.72	—	8.89	7.48	6.97	8.20	—	8.21	7.62	0.88	131
83^c	3.00	2.72	6.84	7.90	—	8.64	7.45	6.94	9.08	—	8.43	7.77	0.88	110
84	2.99	2.78	6.70	8.30	—	8.43	7.49	6.95	9.08	—	8.49	7.62	0.88	55

^a At -55°C . ^b In $[\text{D}_6]\text{-acetone}$. ^c In $[\text{D}_6]\text{-DMSO}$.

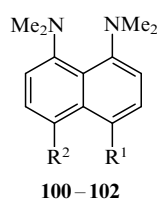
b. Cations

On going from the base **6** to the cation **6-H⁺**, the signals for all the protons are shifted down-field: H[2(7)], by +1.1 ppm, H[3(6)], by +0.4 ppm, H[4(5)], by +0.7 ppm, and CH₃, by +0.3 ppm. Although it would be logical to expect that the signals of *ortho*-protons were at the lowest field, it is not always the case (Table 11). For example, in a solution of the perchlorate **6-H⁺** in [²H₆]-DMSO, the signals of *ortho*- and *para*-protons overlap; however, in CD₃CN and CD₃NO₂, the doublet of doublets of H[4(5)] are at lower field. The signals of the both types of protons can be distinguished by larger values of the *ortho*-constants, $J_{H(3)-H(4)}$ and $J_{H(5)-H(6)}$ in comparison with $J_{H(2)-H(3)}$ and $J_{H(6)-H(7)}$. The nature of the anion in 'proton sponge' salts has practically no effect on their NMR spectra (Table 11).

Yet, the main peculiarity of the ¹H NMR spectra of 'proton sponge' cations is the unusually high chemical shift of the NH-proton (δ 18–20 ppm), which is indicative of strong chelation. For the cations of symmetrical 'proton sponges' including **6-H⁺**, the NH signal in high-resolution spectra has thirteen lines due to spin-spin coupling with the protons of the methyl groups. The signal of the latter is split into a doublet with an intensity of 12 proton units with a spin-spin coupling constant of about 2.5 Hz. Thus the NMR method has permitted recording of a symmetrical IHB for these cations at room temperature, which probably reflects rapid (on the NMR time scale) deviations of the NH-proton relative to the plane of symmetry. The same is observed in the spectra of the symmetrical iminophosphorane 'sponges' **29** and **64**.^{32, 49} Although, as has been shown earlier, the hydrogen bridge has an asymmetrical shape in crystals of their cations, according to NMR data both tautomeric forms are in fast

equilibrium and the NH-proton is shared equally by both nitrogen atoms.

In non-symmetrically substituted cations, the dimethylamino groups are non-equivalent, they are observed as two doublets with different spin-spin coupling constants (Table 15). It has been suggested to use the relationship between the coupling constants for estimating the degree of IHB asymmetry in a particular cation.⁹³ The most asymmetrical is the hydrogen bridge in the cations of 2-halogeno-1,8-bis(dimethylamino)naphthalene **70-H⁺** and **71-H⁺**; in [²H₆]-DMSO, the NH-proton belongs to the N(8) atom by more than 80%. The asymmetry of IHB in the cations of 4-amino- **76-H⁺** and 4-methylamino derivatives **78-H⁺** is very strong [in these cases, the NH-proton is closer to the N(1) atom] and it is somewhat less in the cations having *M*-substituents at position 4: **80-H⁺**, **82-H⁺** – **84-H⁺**, and **100-H⁺**. The least asymmetrical is the IHB in the cations of 4-vinyl- **74-H⁺**, 4-acetamido- **77-H⁺**, and 4-halogeno-derivatives **50-H⁺** and **51-H⁺**. It was established that the transition from [²H₆]-DMSO to a less proton-accepting solvent, acetonitrile, favours the symmetrisation of the hydrogen bridge, which is especially pronounced in the cations of 2-halogeno- and 4-amino-1,8-bis(dimethylamino)-naphthalenes.



- 100:** R¹ = CN, R² = H;
101: R¹ = PhCO, R² = H;
102: R¹ = R² = PhCO.

Table 15. Parameters of ¹H NMR spectra of the groups involved in hydrogen bridge formation in 'proton sponge' cations.⁹³

Cation	Solvent	δ /ppm			J /Hz		Proton localisation (%) ^a	
		1-NMe ₂	8-NMe ₂	NH ⁺	$J_{NH-1-NMe_2}$	$J_{NH-8-NMe_2}$	1-NMe ₂	8-NMe ₂
6-H⁺	[² H ₆]-DMSO	3.12	3.12	18.33	2.63	2.63	50	50
6-H⁺	CD ₃ CN	3.11	3.11	18.69	2.64	2.64	50	50
70-H⁺	[² H ₆]-DMSO	3.18	3.32	18.02	0.77	4.06	16	84
70-H⁺	CD ₃ CN	3.25	3.27	18.80	1.54	3.84	29	71
71-H⁺	[² H ₆]-DMSO	3.21	3.33	18.09	< 1	4.06	16	84
71-H⁺	CD ₃ CN	3.27	3.26	18.87	1.65	3.84	30	70
72-H⁺	[² H ₆]-DMSO	3.37	3.37	19.91	2.41	2.41	50	50
73-H⁺	[² H ₆]-DMSO	3.40	3.40	20.09	2.41	2.41	50	50
73-H⁺	CD ₃ CN	3.41	3.41	20.33	2.64	2.64	50	50
50-H⁺	[² H ₆]-DMSO	3.11	3.14	18.52	2.42	2.64	48	52
51-H⁺	[² H ₆]-DMSO	3.11	3.14	18.56	2.31	2.53	48	52
52-H⁺	[² H ₆]-DMSO	3.10	3.10	19.14	2.52	2.52	50	50
53-H⁺	[² H ₆]-DMSO	3.10	3.10	19.12	2.41	2.41	50	50
74-H⁺	[² H ₆]-DMSO	3.12	3.12	18.64	2.30	2.30	~50	~50
76-H⁺	[² H ₆]-DMSO	3.09	2.99	18.26	3.23	1.21	73	27
76-H⁺	CD ₃ CN	3.10	3.02	18.64	3.41	1.87	65	35
77-H⁺	[² H ₆]-DMSO	3.12	3.11	18.55	2.86	2.24	56	44
77-H⁺	CD ₃ CN	3.12	3.11	18.90	2.75	2.63	51	49
78-H⁺	[² H ₆]-DMSO	3.11	2.98	18.31	3.40	1.21	74	26
79-H⁺	[² H ₆]-DMSO	3.11	3.06	18.48	2.86	2.20	57	43
79-H⁺	CD ₃ CN	3.10	3.07	18.84	2.97	2.31	56	44
80-H⁺	[² H ₆]-DMSO	3.10	3.21	18.43	1.75	3.08	36	64
80-H⁺	CD ₃ CN	3.10	3.20	18.75	1.98	3.30	38	62
82-H⁺	[² H ₆]-DMSO	3.10	3.17	18.58	1.97	2.86	41	59
83-H⁺	[² H ₆]-DMSO	3.09	3.23	18.35	1.44	3.15	31	69
83-H⁺	CD ₃ CN	3.10	3.22	18.67	1.86	3.41	35	65
84-H⁺	[² H ₆]-DMSO	3.17	3.28	18.50	1.72	3.19	35	65
84-H⁺	CD ₃ CN	3.08	3.19	18.72	2.13	3.36	39	61
100-H⁺	[² H ₆]-DMSO	3.09	3.21	18.15	1.88	2.97	39	61

^a Indices of proton localisation at each of the dimethylamino groups (PL) were calculated by the formula:

$$PL = [J_{NH-1(8)-NMe_2} / (J_{NH-1-NMe_2} + J_{NH-8-NMe_2})] \cdot 100\%.$$

For a series of compounds of the same type, there is no apparent correlation between the stability of the IHB and the chemical shift of the NH-proton. It is therefore sufficient to compare the cation **6-H**⁺ and its 4-nitro-derivative **84-H**⁺. Although in the latter case, the signal of the NH-proton is shifted down-field by 0.4 ppm relative to the analogous signal in the spectrum of the cation **6-H**⁺, its hydrogen bridge is partly cleaved by DMSO and other dipolar solvents (see section IV. 2), whereas in the cation **6-H**⁺, no signs of its cleavage were observed. Apparently, the stability of the IHB is largely determined by the basicity of the corresponding 'proton sponge', while the δ_{NH} value depends on the distance between the nitrogen atoms and the degree of NH-proton expulsion from the plane of the ring as a result of which it experiences the effect of the diamagnetic component of the magnetic field of the naphthalene π -system. The unusually high chemical shift of the NH-proton ($\delta \sim 20.0$ ppm) in the spectra of cations of 2,7-dihalogeno-derivatives of the 'proton sponge' is indirect evidence in favour of this explanation. It is unlikely that in these compounds the NH-proton lies in the plane of the ring. More probably, the nitrogen atoms become closer to each other pushed by the halogens, so that this proton is out of the plane and undergoes strong deshielding in the cation **11-H**⁺ (δ_{NH} 24.0 ppm).¹⁰ On the whole, the factors influencing the magnitude of the chemical shift of the NH-proton in 'proton sponge' cations have been studied insufficiently. For example, it is still unclear why the signals of the NH-protons in the cations **25-H**⁺ (δ 16.56 ppm), **26-H**⁺ (δ 14.90 ppm),²⁹ **29-H**⁺, **64-H**⁺ ($\delta \sim 16.5$ ppm),^{32,49} and **30-H**⁺ ($\delta \sim 15.8$ ppm)³⁴ are at much higher fields than those in the cations of 1,8-bis(dialkylamino)naphthalenes.

¹³C and ¹⁵N NMR spectra of salts of **6-H**⁺ (with tetrazolide,⁹⁹ 1-methyltetrazole-5-thiolate, and hydrogen squarate¹⁰⁰ anions) were recorded for solutions in MeCN and in the solid state. As expected, the signals of C(2) and C(4) nuclei are more sensitive to salt formation: they shift 4–5 ppm down-field. However, the largest changes in the chemical shifts (by 6 ppm for solutions in MeCN and by 10 ppm in solid state) are observed in the ¹⁵N NMR spectra upon transition from the base to the cation. It is ¹⁵N NMR spectroscopy that is recognised as being the most appropriate for the study of the structure of cations in solution and in the crystalline state. Recent ¹H and ¹³C NMR spectral data of solid samples of **6-H**⁺ with thiocyanate and tetrafluoroborate revealed two types of *N*-methyl groups, presumably located close to the plane of the ring and remote from it. At the same time, unlike the base, the naphthalene ring of the cation **6-H**⁺ itself did not reveal any signs of asymmetry.⁹⁶

¹³C (Ref. 49) and ³¹P MAS (Ref. 101) NMR spectra of cations of the iminophosphorane 'proton sponges' **29**, **63**, and **64**, and ¹³C and ¹⁵N NMR spectra of the salts **30-H**⁺ have been analysed.⁹⁸

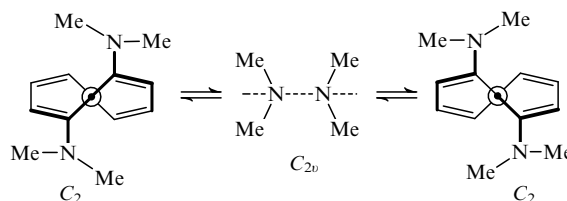
c. NMR spectra and molecular dynamics

The majority of the naphthalene 'proton sponges' are sterically strained, therefore, many of them exist in different conformations due to hindered rotation of dialkylamino groups around the C_{Ar}–N bonds, distorted ring shape, inversion of nitrogen, *etc.* The corresponding transitions can most effectively be followed by NMR spectroscopy. Sometimes, dynamic processes manifest themselves even at room temperature as a widening (sometimes, rather prominent) of peaks of the *N*-alkyl groups and aromatic protons.

Although the solution ¹H and ¹³C NMR spectra of the 'proton sponge' **6** demonstrate the equivalence of all the four *N*-methyl groups at room temperature, this was shown to result from rapid reversible transitions that average the respective conformations on the NMR time-scale.²⁶ It was found that the singlet of the methyl groups in the ¹H NMR spectrum of compound **6** in CF₂Cl₂ splits into a doublet upon cooling down to –120 °C. The free energy of activation ($\Delta G^\ddagger$) for the conformational transition was estimated as 31.4 ± 0.8 kJ mol^{–1}. It

was assumed that the interconversion of the methyl groups is of a 'narcissistic' type and occurs *via* a planar transition state with C_{2v} symmetry (Scheme 1).

Scheme 1



In the case of sterically more hindered 1-benzylmethylamino-8-dimethylaminonaphthalene, the conversion of the NMe₂ group singlet into the doublet occurs at –38 °C; simultaneously, the methylene group singlet splits into a quartet. In this case, the $\Delta G^\ddagger$ value is equal to 57.3 ± 1.7 kJ mol^{–1}.²⁶ Similar dynamic processes were observed in the ¹H NMR spectra of compounds **62**,³¹ **53**,²⁷ and **90**.¹⁰²

5. Nuclear quadrupole resonance spectra

Contrary to the original interpretation of the ¹⁴NQR spectrum, with cross-relaxation, of the base **6**,¹⁰³ recent measurements revealed the presence in this spectrum of four (rather than two) resonance peaks from two nitrogen atoms.¹⁰⁴ This finding unambiguously testifies to their non-equivalence and thus correlates with NMR data on the asymmetry of the 'proton sponge' molecule in crystals.

6. Electron spectroscopy for chemical analysis

According to Hasselbach *et al.*,¹⁰⁵ neither NMR nor X-ray diffraction analysis can give an unequivocal answer to the question about the IHB symmetry in the 'proton sponge' cation. This can be done only with the help of 'faster' methods, such as electron spectroscopy for chemical analysis (ESCA). Here, the ionisation of core electrons takes about 10^{–16} s, therefore the non-equivalent atoms can be distinguished even at fast equilibrium. The ESCA spectrum recorded for the salt **6-H**⁺ BF₄[–] in the N1s energy region revealed two maxima of identical height, which points to the non-equivalence of nitrogen atoms in the cation **6-H**⁺. However, the splitting of the two peaks was relatively low. This points to the fact that the hydrogen bridge in the cation **6-H**⁺ is nevertheless nearly symmetrical. ESCA studies of a number of other 'proton sponge' salts have also been carried out.^{106, 107}

7. Electronic absorption spectra, colour, and solvatochromism

Perhaps the most valuable information about the electron interaction of dialkylamino groups and the naphthalene π -system in 'proton sponges' can be derived from UV spectra. The longwave absorption band in the UV spectra of 1,8-diaminonaphthalene and its *N*-alkyl derivatives including compound **6** lies in the region 340–350 nm (Table 16). As in the case of other aryl amines, it is ascribed to the transfer of electron density from the *n*-orbital of the nitrogen atoms to the π -antibonding orbital of the naphthalene system (*p*– π^* transition). The intensity of this band strongly depends on steric factors influencing the rotation of the amino group around the C_{Ar}–N bond. We used this circumstance² to determine the value of the dihedral angle (φ) between the plane passing through the C_{Ar}–N bond perpendicularly to the aromatic system and the plane passing through the same bond and the symmetry axis of the unshared electron pair of the nitrogen atom. The angle φ was determined from the known ratio, $\varepsilon/\varepsilon_0 = \cos^2\varphi$, where ε is the extinction coefficient at the absorption maximum for the amine under study, and ε_0 is the same for a planar model, in which $\varphi = 0$, *i.e.*, the conjugation is a maximum. 1,3-Dimethyl-2,3-dihydroperimidine **19a** was used as a model for which the longwave absorption band did have the maximum intensity. The experimental values of φ are listed in Table 16. For the 'proton

Table 16. The position of longwave absorption bands ($\lambda_{\max}$, ε) and magnitudes of dihedral angles (φ) in UV spectra of 1,8-diaminonaphthalenes.²

Compound	$\lambda_{\max}$ /nm	$10^{-3} \varepsilon$ /litre mol ⁻¹ cm ⁻¹	φ /deg
1	337	10.40	42
2	339	8.96	46
3	351	6.07	55
4	341	8.72	90; 14
5	351	9.50	81; 0
6	341	12.40	35
19a	344	18.60	0

sponge' **6**, $\varphi = 35^\circ$, which agrees well with the X-ray data ($\varphi = 40^\circ$)⁵⁶ and other estimates.¹ The not very high value of the angle φ points to the possibility of significant conjugation of the dimethylamino groups with the naphthalene system in the base **6**, which is confirmed by all its physicochemical properties and reactivity.

The π -donor effect of the dimethylamino groups is especially prominent in the derivatives of the 'proton sponge' containing $-M$ -substituents at position 4. In contrast to the colourless compound **6**, these compounds give different colours from yellow to violet depending on the electron-acceptor properties of the substituent (Table 17). As expected, the longwave absorption band, which is determined by direct polar conjugation, is very sensitive to the solvent polarity. Thus in the case of the 4-nitro-derivative **84**, the $\lambda_{\max}$ in hexane, benzene, methanol, and DMSO is 411, 444, 463, and 484 nm.⁵⁵ Such a solvatochromism may be due to the different solvation of the excited state, which can be represented by bipolar structures of the type **84a,b**. Evidently, the more polar the solvent, the stronger the solvation, the smaller the electron transfer energy, and the deeper the colour.

Table 17. Position of the longwave absorption band in UV spectra and colour of some 'proton sponge' derivatives (in methanol).

Compound	$\lambda_{\max}$ /nm	lg ε	Colour	Ref.
74	353	3.62	Pale yellow	109
75	516	4.02	Dark violet	110
80	407	3.84	Yellow	61
81	449	3.52	Brown	61
82	389	3.68	Yellow	110
83	431	3.68	Red	110
84	463	4.02	Dark red	55
89	521	4.00	Claret	110
96	403	3.67	Yellow	61
101	405	3.57	"	110
102	413	3.82	"	110

Since chelation of the NH-proton takes the dimethylamino groups completely out of conjugation with the ring, the absorption spectra of 'proton sponge' cations closely resemble the spectra of appropriate naphthalenes devoid of dimethylamino groups. Thus, the $\lambda_{\max}$ of the longwave absorption band for the cations **6-H**⁺ and **84-H**⁺ are equal to 288 nm (lg $\varepsilon = 3.85$)¹⁰⁸ and 334 nm (lg $\varepsilon = 3.50$)⁵⁵ (in 0.1 M HCl), whereas the corresponding values for naphthalene and 1-nitronaphthalene are 297 nm (lg $\varepsilon = 2.82$) and 342 nm (lg $\varepsilon = 3.59$).

An interesting variety of solvatochromism was observed for the cation **84-H**⁺.⁵⁵ When the colourless perchlorate is dissolved in DMSO, DMF, or pyridine, the solution immediately turns deep red or red-orange (for DMF); in the majority of other solvents, colourless, yellowish, or pink solutions are formed. The reason for solvatochromism is the decreased basicity of 1,8-bis(dimethylamino)-4-nitronaphthalene **84** and IHB asymmetry in its cation,

so that the solvents with high proton-acceptor capacity disrupt the IHB, thereby releasing the dimethylamino groups for the conjugation. Practical applications of solvatochromism of the perchlorate **84-H**⁺ are proposed.⁵⁵

8. Infrared spectra

The most important in the IR spectrum of the base **6** are the bands at 2780, 2830, 2870, and 1580 cm⁻¹ (Refs 86, 111). The first three of them, known as Bolman bands, are associated with stretching vibrations of the C—H bonds of the methyl groups *trans*-oriented with respect to the unshared electron pairs of the nitrogen atoms. The band at 1580 cm⁻¹ is associated with stretching vibrations of the ring. Its high intensity is the consequence of the asymmetry of the naphthalene system. Indeed, the intensity of this band sharply decreases upon protonation, and the band slightly shifts towards high frequencies. The Bolman bands also practically disappear upon transition to the cation or, in the case of partial protonation, decrease in intensity. These changes can be used for the quantitative estimation of the degree of protonation of the base **6** by different acids including phenols. However, the most interesting feature is the appearance of stretching vibration bands of the hydrogen bridge $\nu_s(\text{NHN})$ in the IR spectra of **6-H**⁺ salts. The dependence of the position of this band on pressure,¹¹² counterion structure,¹¹³ deuteration [the isotope ratio, $\nu(\text{NHN})/\nu(\text{NDN})$ was determined],¹¹⁴ and the change in the aggregate state¹¹⁵ was studied. In solution (the measurements were performed in acetonitrile, dichloromethane, and dichloroethane), the band manifests itself as a very broad 'continuum' at the background level extending from 3000 to about 300 cm⁻¹. In the crystalline state, the type of absorption changes drastically; the band shifts towards 800–250 cm⁻¹ and acquires fine structure. This phenomenon is typical of very stable hydrogen bridges having a short N...N distance (~ 2.55 – 2.65 Å). It is assumed that the band structure can be explained in detail only by taking into account the superposition of δ - and γ -deformation oscillation, their overtones, and internal oscillations causing modulation of the hydrogen bridge geometry.¹¹¹ These data are consistent with the abnormally high isotope ratio, which in some cases reaches 1.8–2.05 (in the case of weak IHBs, it is less than 1.45).¹¹⁴ There is a tendency to broadening of the $\nu_s(\text{NHN})$ band, and its shift towards higher frequencies with an increase in the proton-acceptor capacity of the anion.^{113, 114} Thus, in the case of the anions Ph₄B⁻ and F⁻, the centre of the band is at 463 and 583 cm⁻¹, respectively. The effect of the anion was explained by its bifurcation interaction with the NH-proton of the cation. It should be recalled, however, that X-ray studies of numerous salts of the 'proton sponge' allowed one to reveal reliably the bifurcation effect only in two cases (Section IV. 3. b).

On the basis of the IR spectral data of proton sponge salts, most authors concluded that the potential energy curve for the hydrogen bridge corresponded either to a potential with two minima and a very low barrier, or to a potential with one minimum and a flat bottom (Fig. 2a, b).

Because of the nearly planar structure of the naphthalene system in compound **30**, its IR spectrum differs substantially from that of the 'proton sponge' **6**.⁶²

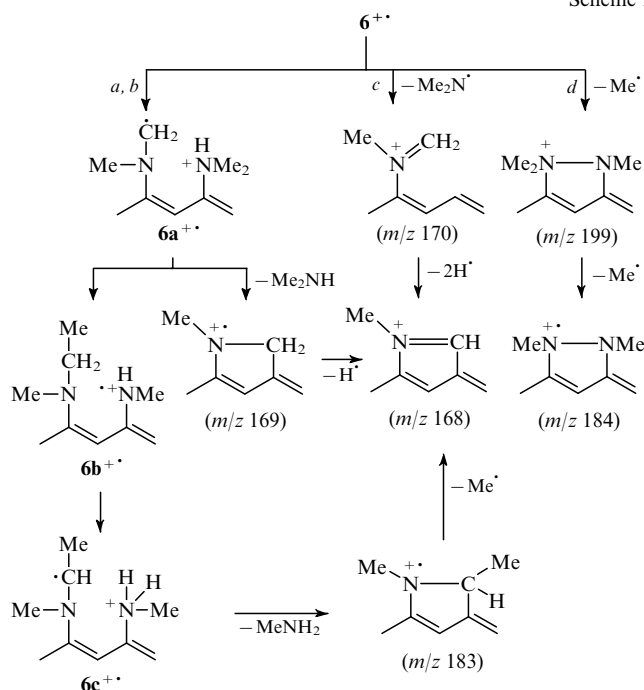
9. Mass spectra

Mass spectra of sterically hindered bis(dimethylamino)arenes including various types of 'proton sponges' were studied in most detail.^{116, 117} In all cases, the fragmentation of the molecular ion which is the most intense, as a rule, is determined by the proximity of dimethylamino groups (the so-called 'proximity effect') and at early stages involves practically only these groups. The fragmentation processes include isomerisation and elimination of the MeNH₂, Me₂NH, and H⁺ fragments giving rise to stable heterocyclic ions.

Four main pathways of fragmentation of the molecular ion of the base **6** under electron impact are shown in Scheme 2.¹¹⁶ The first pathway (a) is a stepwise counterflow intramolecular transfer

of H^+ and Me^+ species from one nitrogen atom to another resulting in the ions $6\text{a}^{+\bullet}$, $6\text{b}^{+\bullet}$, and $6\text{c}^{+\bullet}$, respectively.

Scheme 2



The latter eliminates MeNH_2 , which accounts for the presence in the spectrum of an intense peak with m/z 183; this peak was assigned to the 1,2-dimethyl-1,2-dihydrobenzo[*c,d*]indolium ion. Its subsequent aromatisation gives the 1-methylbenzo[*c,d*]indolium ion (m/z 168). The peak of this ion is second in intensity after the peak of $\text{M}^{+\bullet}$ and in some 'proton sponge' derivatives it is the most abundant. The second pathway of fragmentation (*b*), which also gives the 1-methylbenzo[*c,d*]indolium ion, consists in the elimination of Me_2NH from the $6\text{a}^{+\bullet}$ ion. The third (*c*) and the fourth (*d*) pathways represent direct fragmentation of the molecular ion $6^{+\bullet}$ consisting in the loss of Me_2N^+ or Me^+ species. In the latter case, methyl derivatives of the benzo[*c,d*]indazolium ion with m/z 199 and 184 are formed.

The above fragmentation features are observed in the mass spectra of other derivatives of the 'proton sponge' and, which is the most interesting, in the spectrum of 1,8-bis(diphenyl-amino)-naphthalene **61**.¹¹⁷

10. Dipole moments

Dipole moments in benzene were measured for three compounds of the given series: the 'proton sponge' **6**, its 4-formyl- **80**, and 4,5-diformyl derivatives **81**.⁶¹ The dipole moment of compound **6** ($\mu = 1.19$ D) is precisely equal to that of 1-dimethylaminonaphthalene. This is lower than the expected value, since the π -conjugation of both dimethylamino groups with the ring would result in the summation of the vectors of the corresponding dipole moments. Apparently, due to the high non-coplanarity of the molecule **6**, both vectors are directed at a considerable angle to each other. In contrast, the dipole moments of the aldehyde **80** ($\mu = 5.44$ D) and the dialdehyde **81** ($\mu = 9.21$ D) appeared to be unexpectedly high. This suggests that the conjugation of the aldehyde and the NMe_2 groups in them is very efficient. The additional moment of the π -interaction, μ^π , in compounds **80** and **81** is equal to ~ 1.4 and 2.3 D, which is higher than in 4-dimethylaminonaphthalene-1-carbaldehyde ($\mu^\pi = 0.35$ D) and even in *p*-dimethylaminobenzaldehyde ($\mu^\pi \approx 1$ D). These data are in good agreement with the X-ray data for compound **81**. The high dipole moment makes this compound closer to ionic substances; it is therefore not incidental that in contrast to many

other derivatives of the 'proton sponge', the dialdehyde **81** is rather soluble in water and has a high melting point ($162\text{--}164^\circ\text{C}$).

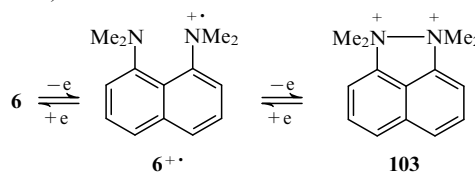
11. Donor-acceptor properties

a. Gas-phase ionisation potentials

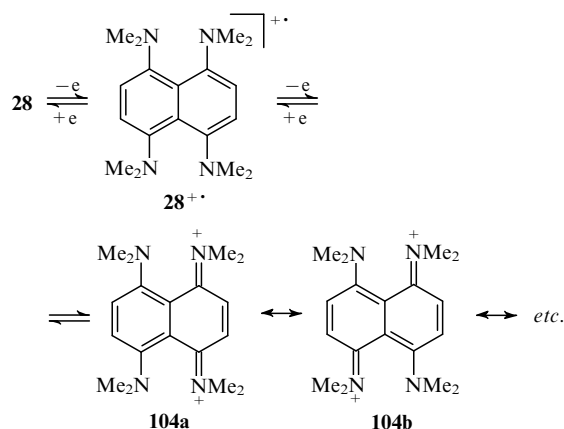
The gas-phase ionisation potentials, IP_1 , of the 'proton sponge' **6** and its partially *N*-methylated precursors **1–5** measured by electron impact were strikingly similar, from 7.38 to 7.47 eV (see Table 18).² This could indicate that the first electron is ejected from the π -orbital of compounds **1–6**. Indeed, if these values characterised the ejection of an *n*-electron, then, taking into account significant differences in the basicity of these compounds, the ionisation potential of the 'proton sponge' would be much lower in comparison with that of the diamines **1–5**. However, Maier,¹¹⁸ who used photoelectron spectroscopy to measure the ionisation potentials of compounds **1** and **6**, came to a somewhat different conclusion. The IP_1 value for the diamine **1** (7.10 eV) was also assigned to the π -ionisation potential, while for the 'proton sponge' **6** ($\text{IP}_1 = 7.05$ eV) it was ascribed to electron ejection from the *n*-orbital. This conclusion was made on the basis of calculations using perturbation theory, which revealed that the highest occupied π -MO for compound **6** correlated better with the second ionisation potential, $\text{IP}_2 = 7.47$ eV. It is hardly probable that this argument is self-explanatory. It will be recalled once again that according to UV spectroscopy data, the conjugation of the nitrogen atoms with the naphthalene ring and, correspondingly, the π -donor capacity of compound **6** is at least no less than that of 1,8-diaminonaphthalene.

b. Anodic oxidation potentials. Radical cations

Electrochemical oxidation of the 'proton sponge' **6** on a platinum disc electrode in MeCN gives two reversible one-electron waves with $E_{\text{ox}}^{1/2} = 0.36$ and 1.02 V.¹¹⁹ Presumably, the radical cation $6^{+\bullet}$ is formed at the first step, and the dication **103**, at the second; the structure with a σ -bond between the nitrogen atoms was ascribed to the latter. The radical cation $6^{+\bullet}$ was also generated by oxidation of compound **6** with PbO_2 . Its EPR spectrum represents an unresolved singlet with a width ΔH of 23 G ($g = 2.0043$). On the basis of these data, it was concluded that the conjugation of the dimethylamino groups with the naphthalene ring in compound **6** is significant and according to its electron-donor properties it occupies a position between *N,N*-dimethylaniline ($E_{\text{ox}}^{1/2} = 0.68$ V) and *N,N,N',N'*-tetramethyl-*p*-phenylenediamine ($E_{\text{ox}}^{1/2} = 0.015$ V).



The oxidation of compound **23** occurs in an analogous way, but more easily.¹²⁰ Its radical cation can be conserved unchanged in acetonitrile over a period of many months. The UV spectrum of this radical cation ($\lambda_{\text{max}} = 480$ nm, $\lg \epsilon = 3.1$) is very similar to that of compound **23** itself, which has led to a conclusion that the naphthalene fragment of the molecule does not take part in the oxidation. In contrast to compounds **6** and **23**, the 'double proton sponge' **28** is oxidised in one two-electron wave with $E_{\text{ox}}^{1/2} = -0.50$ V (relative to $\text{Fc}/\text{Fc}^+ = 0.0$ V, Fc is ferrocene).²⁴ Apparently, the driving force of this process is the formation of the resonance-stabilised dication **104**, which was isolated in the form of black crystals and thoroughly characterised.^{24, 121} The radical cation $28^{+\bullet}$ giving the EPR spectrum with hyperfine structure can be obtained by chemical oxidation of compound **28**.²⁴



c. The formation of π -complexes

All 1,8-diaminonaphthalenes, including the 'proton sponge' **6** can easily form molecular complexes (MC) in which they act as donors. An attempt has been made to use the complexes with 1,3,5-trinitrobenzene (1 : 1, the complex formation constants K_c lie in the range 2.0–3.4 litre mol⁻¹) for estimating their electron-donor capacity.² Presumably, stronger donors would produce MC with an absorption maximum of the charge transfer band shifted to longer wavelengths. However, measurements revealed (Table 18) the lack of correlation between the basicity of 1,8-diaminonaphthalenes and the ease of formation of MC by these compounds. Moreover, the most basic compound (the 'proton sponge' itself) gives a MC having the lowest value of $\lambda_{\max}$ (500 nm). It was therefore concluded that compounds **1–6** behave as π -donors in the formation of MC, whereas the differences in the ease of formation and stability of MC are determined predominantly by steric factors and inductive effects of the methyl groups.

Table 18. Ionisation potentials, IP₁, and electrochemical oxidation potentials ($E_{\text{ox}}^{1/2}$) of 1,8-diaminonaphthalenes and the long-wave absorption maximum (UV spectra) of their molecular complexes with 1,3,5-trinitrobenzene.

Compound	IP ₁ / eV		$E_{\text{ox}}^{1/2}$ / V (in MeCN)	$\lambda_{\max}$ / nm (in CHCl ₃) ²
	EI ²	PS ¹¹⁸		
1	7.47	7.10	—	530
2	7.40	—	—	560
3	7.43	—	—	575
4	7.38	—	—	540
5	7.40	—	—	580
6	7.38	7.05	0.36, 1.02 ¹¹⁹	500
23	—	—	0.11, 0.72 ¹²⁰	—

d. The formation of H-complexes

In some cases, IR and NMR methods were used to investigate the interaction of compound **6** with phenols,^{113, 122–124} carboxylic acids,¹²³ and SH-acids.¹²⁵ An unexpected finding was that phenol ($\text{p}K_a = 9.99$) hardly protonated the 'proton sponge', although its basicity exceeded that of the phenolate anion by more than two orders of magnitude. Distinct protonation is observed only with phenols having $\text{p}K_a < 8.4$. This reaction gives two types of salts having the composition of 1 : 1 and 1 : 2, the latter being much more stable. This is rationalised by formation of homoconjugated anions, $\text{ArOH} \cdots \text{OAr}$. Evidence for their stability can be derived from the fact that the salt of the base **6** with pentachlorophenol (1 : 1) disproportionates in acetonitrile to give a 1 : 2 salt and a non-protonated 'proton sponge':¹¹³



e. Electron acceptor properties. Radical anions

There is only one study concerned with the ability of 'proton sponges' to undergo one-electron reduction.¹²⁶ It has been shown that treatment of compound **6** with sodium in 1,2-dimethoxyethane gives a stable radical anion; its EPR spectrum was recorded at -20°C . The hyperfine splitting constants (HFS) for the unpaired electron with cyclic protons are: $a_{\text{H}(4),\text{H}(5)} = 4.46$, $a_{\text{H}(3),\text{H}(6)} = 1.77$, and $a_{\text{H}(2),\text{H}(7)} = 1.39$ Gs, *i.e.*, they are somewhat smaller than the corresponding values for the naphthalene radical anion. At the same time, the HFS constants with the protons of the methyl groups and ¹⁴N nuclei are very small. This was interpreted as a result of non-coplanarity of the dimethylamino groups and the naphthalene ring. The magnitude of the dihedral angle between the axes of unshared electron pairs of the nitrogen and the $2p_\pi$ -orbitals of cyclic C-atoms in the radical anion **6^{•-}** was estimated to be $60-70^\circ$.

12. Quantum-mechanical calculations

Using the *ab initio* method with optimisation of geometry, the optimum structures of the 'proton sponge' **6** and its protonated form **6-H⁺** were calculated.¹²⁷ The following main conclusions were made: (1) in the gas phase, the molecule of compound **6** has C_2 symmetry and the fragment $\text{N}(\text{C}_{10}\text{H}_6)\text{N}$ is essentially non-planar; (2) the degree of non-planarity in the isolated molecule of the base is lower than in the crystals; (3) increased orders of the $\text{N}-\text{C}_{\text{Ar}}$ bonds attest to a significant conjugation of the nitrogen atoms with the π -system of the ring; (4) in protonation, the molecule becomes practically planar and its symmetry approximates the C_{2v} type; (5) the hydrogen bridge in the isolated cation **6-H⁺** is symmetrical; its optimum parameters are as follows: $r[\text{N}(1)-\text{H}] = 1.05 \text{ \AA}$, $r[\text{N}(2) \cdots \text{H}] = 1.64 \text{ \AA}$, the angle $\text{N}(1)-\text{H}-\text{N}(2) = 156.8^\circ$.

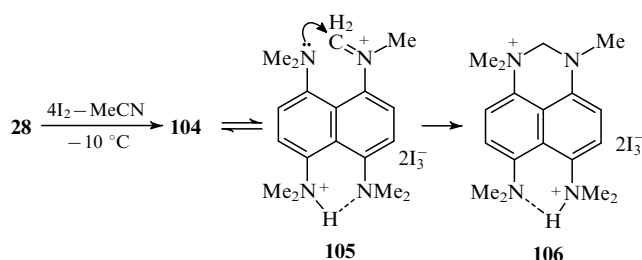
Semi-empirical simulations of the optimum structures of the base **6** and the cation **6-H⁺** were made^{13, 84} using the AM1 and PM3 methods; the enthalpies of protonation for compounds **1**, **3**, **5**, and **6** and some hypothetical aza-derivatives of the 'proton sponge' were also estimated.¹²⁸

V. Reactivity of naphthalene 'proton sponges'

Naphthalene 'proton sponges' are typical electron-rich compounds. In addition to high basicity, they are characterised by significant π -donor capacity and the presence of a negative π -charge on the cyclic carbon atoms. It is not surprising that electrophilic substitution and oxidative conversions are the most typical reactions for these compounds. A few examples of nucleophilic substitution are reported, only for compounds with electron-acceptor groups in the ring. It is probable that some reactions of the 'proton sponge', *e.g.*, chlorination with *N*-chlorobenzotriazole (CBT) or bromination with *N*-bromosuccinimide (NBS) occur through a radical mechanism, as can be judged from their unusual orientation. However, convincing evidence for this mechanism is absent, and the corresponding transformations are discussed in Section V. 2 dealing with reactions with electrophiles.

1. Oxidation

As has been mentioned above, electrochemical or chemical oxidation of 'proton sponges' results first in the formation of radical cations and then of dication. Thus treatment of the 'double sponge' **28** with an excess of iodine at -10°C gave black needles of the salt **104** (with the I_3^- anion), which could be studied by the X-ray method.¹²¹ It is noteworthy that increase in temperature to 25°C or heating of the salt **104** results in its isomerisation, presumably *via* the immonium cation **105**, into the dication **106**.¹²¹ The 'proton sponge' undergoes similar conversions under the action of certain complexes of Rh^{3+} , Ru^{3+} , and Ru^{2+} , which result in the formation of the 1,1,3-trimethyl-2,3-dihydroperimidinium cation **42** ($\text{R}^1 - \text{R}^3 = \text{Me}$).¹²⁹



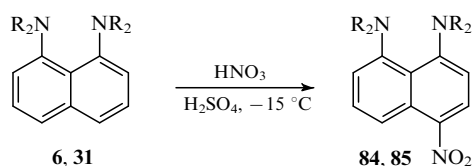
Oxidation of compound **6** with thallium triacetate or lead tetraacetate in dichloromethane at low temperature¹⁰² or, which is better, with iodine in boiling acetonitrile¹³⁰ gives the 1,1'-binaphthyl 'sponge' **90** in moderate yields. The latter is also formed as a by-product (yield 10%) in the nitration of compound **6**.¹³⁰ Apparently, in all these cases it is the intermediate radical cation **6**^{•+} that undergoes dimerisation.

2. Electrophilic substitution reactions

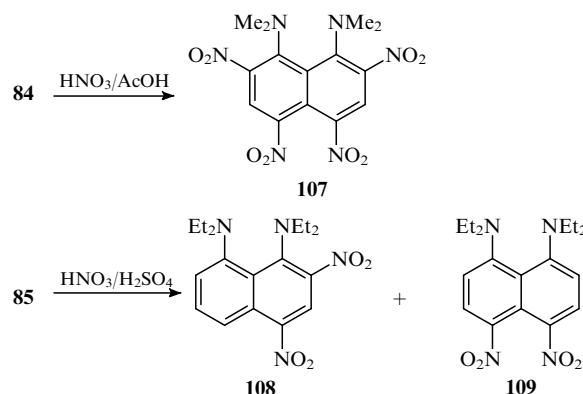
'Proton sponges' manifest unusually high activity in reactions of electrophilic substitution. To avoid resinification and to ensure desired regioselectivity, the syntheses are usually carried out at low temperatures (< 0 °C). In some cases (the Friedel–Crafts acylation), the substrate should be passivated by being converted into a salt. It should be noted that such catalysts as AlCl₃ or BF₃ do not give *n*-complexes with 'proton sponges'. As a rule, the first substituent enters only at positions 4 and 5 (for exceptions see Section V.2.b). The second and subsequent substituents can occupy both the *para*- and *ortho*-positions. The specific orientation is determined by the nature of the substituent already present and, consequently, by the p*K*_a of the substrate and the degree of symmetry of the IHB in the corresponding cation. There is good reason to believe that some reactions of naphthalene 'proton sponges' with electrophiles occur through a radical cation mechanism, where the radical cation generated first undergoes further nucleophilic attack by the anion present in the reaction mixture (see Section V.2.b).

a. Nitration

Nitration of the 'proton sponges' **6** and **31** in acetic acid gives directly the 2,4,5,7-tetranitro-derivative of the type **107** irrespective of the amount of nitric acid.⁴⁶ This was explained by the fact that due to the decrease in basicity of each subsequent substitution product and the increase in the concentration of the corresponding free base the rate of each successive nitration increases. Mononitration, which gives the 4-nitro-derivatives **84** and **85** in 50%–70% yields, can be carried out only in concentrated sulfuric acid with one equivalent of HNO₃^{46,55} (as mentioned above, the binaphthyl 'sponge' **90** is also formed as a by-product). Obviously, in strongly acidic media, compounds **84** and **85** are present exclusively in the form of cations, and the reaction does not proceed further. However, an attempt at subsequent nitration of compound **84** gave only the tetranitro-derivative **107**. In the case of the ethyl analogue **85**, dinitration could be accomplished with one equivalent of HNO₃ to give the 2,4- and 4,5-dinitro-derivatives **108** and **109** in yields 32% and 28%, respectively.⁴⁶ The nitration of compound **6** can be controlled to a greater extent when nitrogen dioxide is used as a nitrating agent.¹³⁰



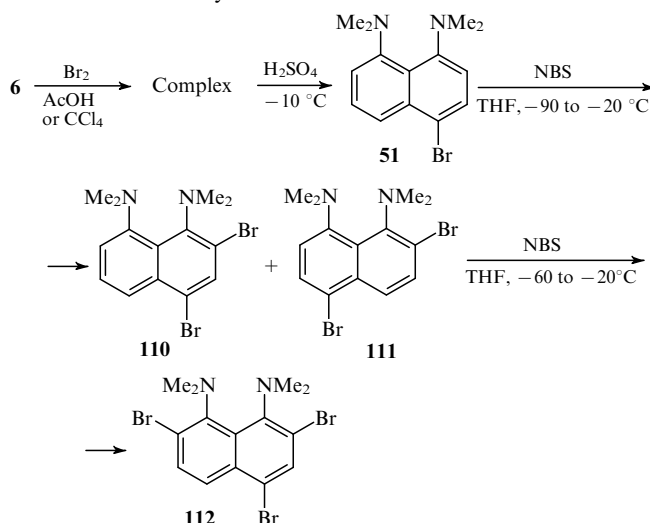
R = Me (**6**, **84**), Et (**31**, **85**).



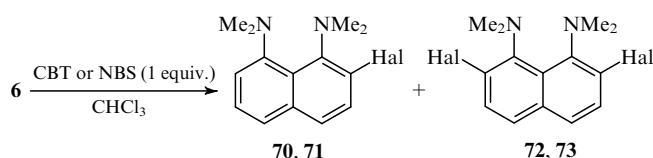
Nitration of 4-bromo-1,8-bis(dimethylamino)naphthalene **51** with one equivalent of HNO₃ in concentrated H₂SO₄ gave 4-bromo-5-nitro- and 4-bromo-2-nitro-derivatives (yields 27% and 15%, respectively).²⁷

b. Halogenation

On treatment of the 'proton sponge' **6** with one equivalent of bromine in acetic acid or CCl₄, a crimson-coloured complex of an unknown structure precipitates, and gradually resinifies. Treatment of the complex with concentrated H₂SO₄ converts it into 4-bromo-1,8-bis(dimethylamino)naphthalene **51** in good yield. Subsequent bromination could be achieved only with NBS.²⁷ First, with 1 equiv. of NBS, a mixture of 2,4- and 2,5-dibromo-derivatives **110** and **111** is formed in a 54:46 ratio. Further bromination of this mixture (1 equiv. of NBS) gives 2,4,7-tribromo-1,8-bis(dimethylamino)naphthalene **112** as the only product. An attempt to convert it into a tetrabromo-derivative was unsuccessful. Thus unlike nitration, acylation, and formylation (see below), *peri*-dibromination in naphthalene 'proton sponges' does not take place, presumably due to larger steric hindrances exerted by bromine atoms.

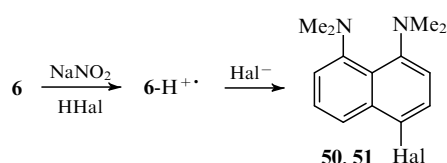


It is noteworthy that bromination of the 'proton sponge' **6** with NBS (1 equiv.) in chloroform occurs in quite a different way.⁹³ In this case, 2-bromo-**71** and 2,7-dibromo-derivatives **73** are formed in 36% and 52% yields, respectively. *ortho*-Substitution occurs nearly quantitatively in the chlorination of compound **6** with *N*-chlorobenzotriazole (CBT) to give 2-chloro-**70** and 2,7-dichloro-derivatives **72**.²⁸ Probably, these reactions proceed with the participation of the 'sponge' base (rather than the cation) in which the π -electron density at positions 2 and 7 is greater than at positions 4 and 5. At the same time, one should not rule out the radical mechanism of substitution.



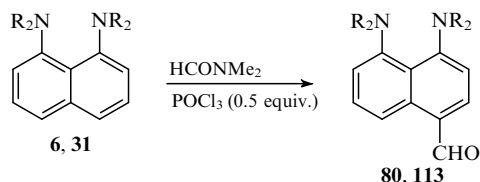
Hal = Cl (70, 72), Br (71, 73).

Recently, in our laboratory we have established that treatment of compound **6** with sodium nitrite in hydrochloric acid gives 4-chloro-1,8-bis(dimethylamino)naphthalene **50** in a nearly quantitative yield. If hydrobromic acid is used instead of hydrochloric acid, the yield of the 4-bromo-derivative **51** is much lower (~20%).¹³⁰ The formation of these somewhat unusual products is a convincing proof of the radical-cation mechanism of halogenation. Obviously, at the first stage the 'proton sponge' is oxidised with nitrous acid to the radical cation, which is subjected to nucleophilic attack by the halide anion at position 4, where the highest positive charge is accumulated.

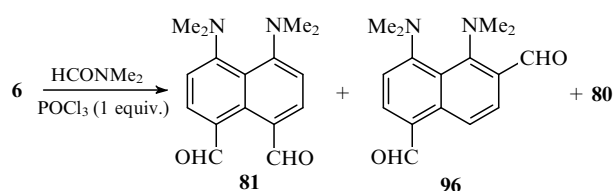


c. Formylation and acylation

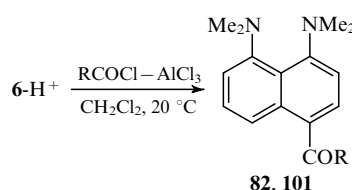
Formylation of the 'proton sponges' **6**¹³¹ and **31**¹³² under conditions of the Vilsmeier reaction in a deficiency of POCl₃ (0.5 equiv.) gives the corresponding 4-formyl-derivative **80** and **113** in moderate yields. When an equimolar amount of POCl₃ is used, compound **6** gives the 4,5-dialdehyde **81** and small amounts of the 2,5-dialdehyde **96** along with the monoaldehyde **80**.¹³¹



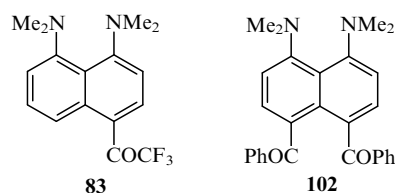
R = Me (**80**), Et (**113**).



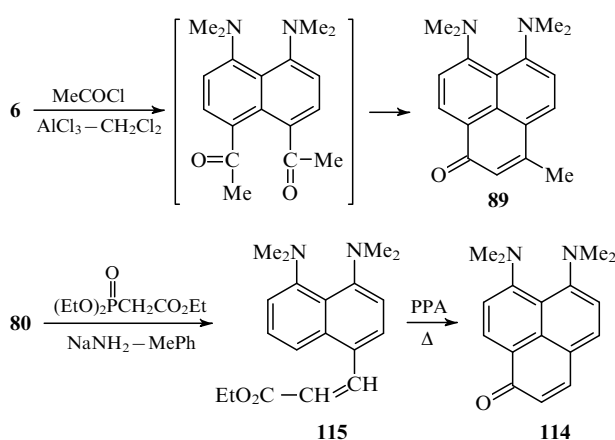
1,8-Bis(dimethylamino)naphthalene **6** does not undergo the Vilsmeier-Haack acylation or acylation with carboxylic acids in polyphosphoric acid (as takes place in the series of perimidones, 2,3-dihydroperimidines, and perimidines).¹³³ At the same time, under conditions of the Friedel-Crafts reaction in the presence of AlCl₃ or AlBr₃, acyl chlorides acylate the 'sponge' base even at -90 °C.¹¹⁰ The reaction is not very smooth, therefore it is more convenient to perform it with the salt 6-H⁺. The yields of the ketones **82** and **101** are virtually quantitative.



The reaction of the base **6** with trifluoroacetic anhydride does not require a catalyst and proceeds at -30 °C. This results in the formation of the 4-trifluoroacetyl derivative **83** in moderate yield.

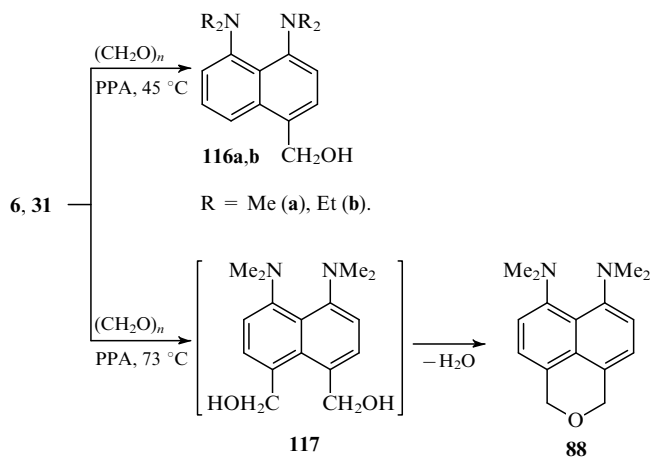


Treatment of the base **6** with an excess of benzoyl chloride gave the 4,5-benzoyl derivative **102** (yield 7%). Under the same conditions, the reaction with excess acetyl chloride gives phenalene-9-one **89** (yield 27%), presumably as a result of intramolecular aldol condensation of the intermediate, the 4,5-diacetyl derivative. The progenitor of this phenalene series (**114**) was synthesised (yield 15%) by intramolecular acylation of ethyl acrylate **115** upon heating in polyphosphoric acid (PPA).¹¹⁰



d. Hydroxymethylation

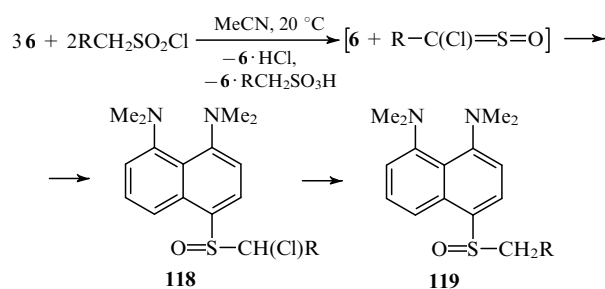
'Proton sponges' undergo hydroxymethylation with paraformaldehyde in polyphosphoric acid at 45 °C to give the alcohols **116a,b**.^{132, 134} At higher temperatures, compound **6** is converted into naphthopyran **88** in good yield, apparently as a result of dehydration of the intermediate 4,5-bishydroxymethyl derivative **117**. The alcohols **116** were also obtained by reduction of the aldehydes **80** and **113** with LiAlH₄.¹³²



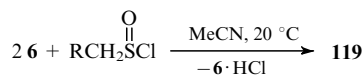
e. Miscellaneous reactions

The 'proton sponge' **6** reacts with alkanesulfonyl chlorides to give the 4-alkylsulfonyl derivatives **118** and **119**.¹³⁵ It was established that the active species, which directly interacts with compound **6**, is the corresponding chlorosulfine generated *in situ*. Compounds

119 can be also obtained by the reaction of the 'proton sponge' **6** with alkanesulfinyl chlorides.

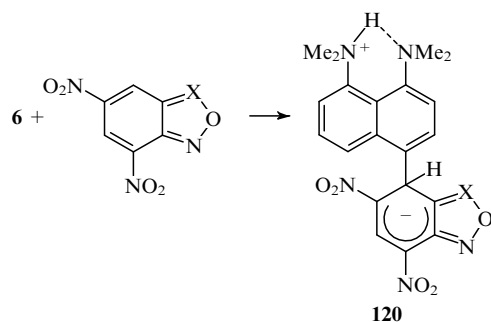


R = H, Me, PhCH₂.



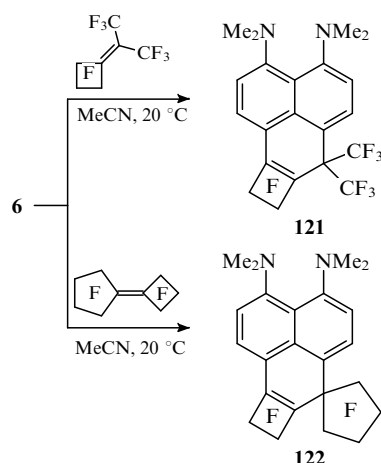
R = H, Me, CF₃, F, Cl.

Compound **6** behaves as a strong CH-nucleophile with respect to 4,6-dinitro-derivatives of benzofuroxan and benzofurazan to give the corresponding adducts **120**.¹³⁶



X = N, N→O.

The 'proton sponge' easily adds to perfluorocycloalkanes with exocyclic double bonds. This reaction involves both *peri*-positions and the phenylene derivatives are formed **121,122**.¹³⁷

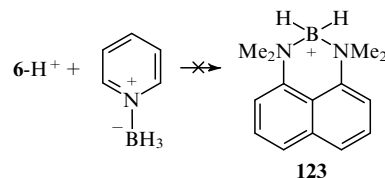


3. Reactions involving dialkylamino groups

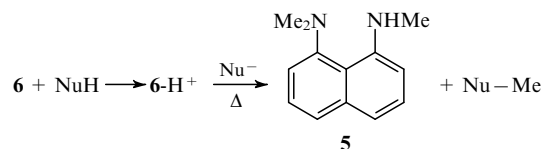
The following four types of these reactions are known: (1) quaternisation, (2) dealkylation, (3) substitution of the dialkylamino groups, and (4) oxidative conversions. The latter have already been described in Section V. 1. Here, only the first three types will be considered. Practically all these reactions have been performed with compound **6**.

Only one example of quaternisation of the 'proton sponge' is known. Contrary to the original report,¹ it was established that its treatment with methyl fluorosulfate gives the non-crystalline salt **68** (as the SO₃F⁻ anion), which is converted into the crystalline

tetrafluoroborate **67** under the action of NaBF₄.³⁷ An attempt to synthesise the borate complex **123** by treating the cation **6-H**⁺ with pyridine-borane was unsuccessful.¹³⁸ At the same time, complexes of this type are easily formed with tetramethyl-*o*-phenylenediamine and 2,2'-bipyridyl. This circumstance can be regarded as additional proof of the extremely low nucleophilicity of the 'proton sponge'.

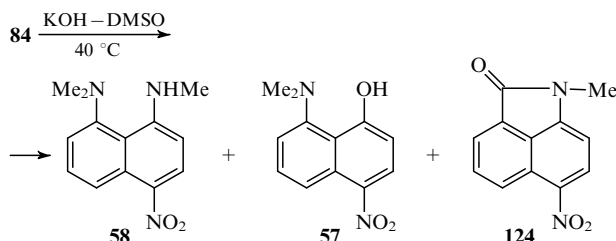


Heating of 'proton sponge' salts containing mild nucleophiles, such as thiocyanate,²⁶ phenylmercaptide, and phenylselenide¹³⁹ leads to demethylation and the formation of 1-dimethylamino-8-methylaminonaphthalene **5**. This reaction proceeds especially smoothly with selenophenol; the yield of the amine **5** is close to quantitative. It is of note that if the 'sponge' **6** is heated with thiophenol and selenophenol, the formation of the cation **6-H**⁺ proceeds at a very low rate (> 1 h).

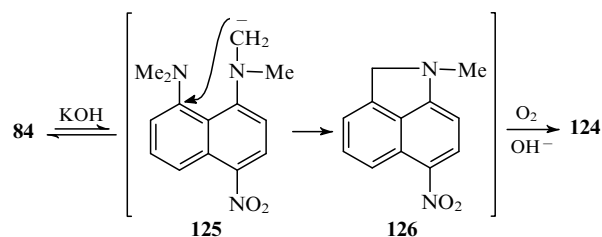


Nu⁻ = SCN⁻, PhS⁻, PhSe⁻.

Demethylation of 'proton sponge' bases occurs only if the ring contains strong electron-acceptor groups and if the reaction is carried out in a superbasic medium.³⁰ Thus, treatment of the 'nitro sponge' **84** with a solution of KOH in DMSO (40 °C, 24 h) gave the trimethyl-substituted compound **58** (yield 40%). The two other reaction products were naphthol **57** (yield 7%) and, which is especially unexpected, lactam **124** (yield 11%).



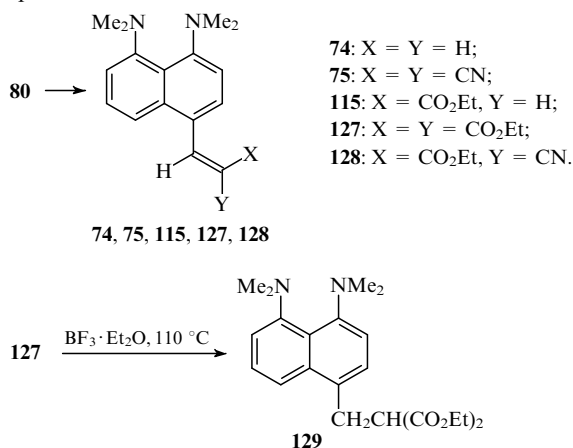
The formation of naphthol **57** seems to be a result of nucleophilic substitution of the dimethylamino group in the more activated position 1. Some complex reactions also entail hydrolytic substitution of the dimethylamino group by the carbonyl group (see Section V. 5). The mechanism of formation of the lactam **124** is not known with certainty. Presumably, this reaction begins with the generation of an equilibrium amount of the carbanion **125** in which intramolecular nucleophilic substitution of the 8-NMe₂ group takes place. The 1-methyl-6-nitro-1,2-dihydrobenzo[*c,d*]indole **126** formed undergoes further autooxidation, which is also characteristic of other compounds of this kind.



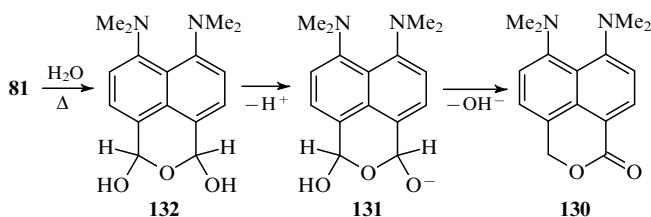
It is known that the 8-NMe₂ group can be substituted by hydrogen in the catalytic hydrogenation of the 'nitro sponge' **84** (see Section V. 4).

4. Reactions of functional groups

The greatest number of 'proton sponge' derivatives (azomethines, hydrazones, oxime, nitrile, *etc.*) were synthesised from the 4-aldehyde **80**.¹²⁹ The latter was also converted by the Wittig reaction into 4-vinyl-1,8-bis(dimethylamino)naphthalene **74**¹⁰⁹ and compound **115**.¹³¹ A number of other 4-vinyl derivatives (**75**, **127**, **128**) were synthesised by condensation of the aldehyde **91** with the corresponding CH-acids. The conditions for polymerisation of the vinyl 'sponge' were investigated.¹⁰⁹ It was found that heating of compound **127** with boron trifluoride etherate results in the reduction of the exocyclic C=C bond and the concomitant formation of the naphthylmethyl derivative of diethyl malonate **129** instead of the expected intramolecular cyclisation into the corresponding phenalenone.¹³¹ It was assumed that the ethyl groups of the etherate play the role of a hydride donor, and the reaction can be realised due to polarisation of the C=C bond, which is enhanced by the donor effect of the dimethylamino groups.

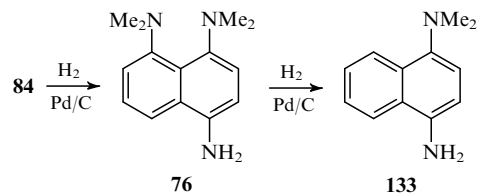


Upon boiling in water, the dialdehyde **81** undergoes the intramolecular Cannizzaro reaction to give the naphtho[1,8-*c,d*]pyranone derivative **130** in 36% yield.¹³¹ The unusual feature of this reaction is that it does not require any alkali. Apparently, the alkalinity of the medium sufficient for the formation of the anion **131** is created by the 'proton sponge' itself. It should be noted that unlike the naphthalene-1,8-dicarbaldehyde, which exists under ordinary conditions only in the form of a cyclic hydrate, the dialdehyde **81** is stable. This may be ascribed to the stabilising effect of the dimethylamino groups, which, when entering into conjugation, reduce the partial positive charge on the carbonyl carbon atoms and thus hamper the hydration. However, the formation of the hydrate **132** which is needed for the Cannizzaro reaction, does take place upon boiling of the dialdehyde **81** in water.



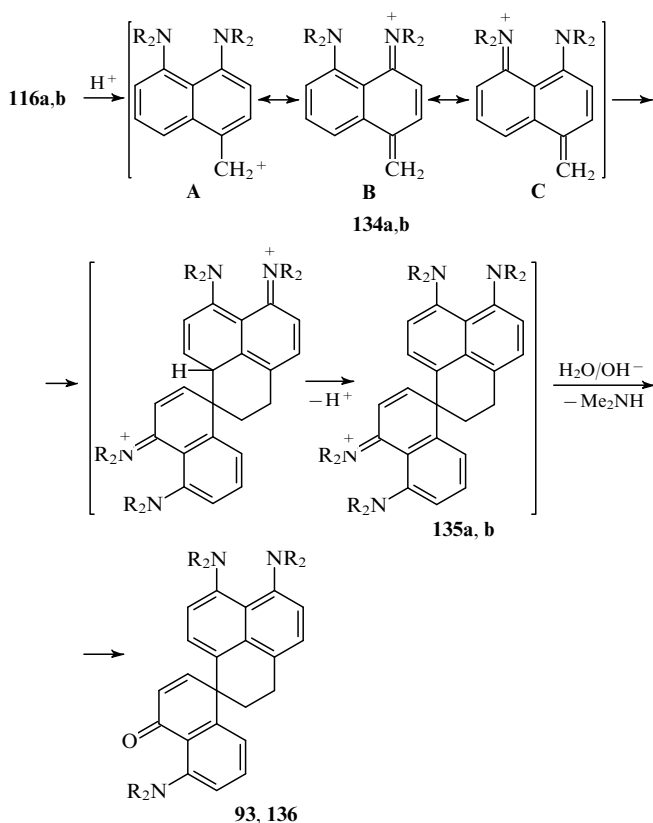
Catalytic hydrogenation of the 'sponge' **84** gave the amine **76**,⁴⁵ which is extremely unstable and oxidisable in air. 4,5-Diamino-1,8-bis(dimethylamino)naphthalene was obtained by hydrogenation of the dinitro-derivative **40**.²⁴ Subsequent hydrogenation of compound **76** is accompanied by elimination of the 8-NMe₂ group and the formation of 1-dimethylamino-4-aminonaphthalene **133**. The amine **76** gives azomethine with *p*-nitro-

benzaldehyde and the *N*-acetyl derivative **77**; the latter was methylated to give quite stable 4-methylamino- **78** and 4-dimethylamino-derivatives **79** of the 'proton sponge'.⁴⁵ The latter can be regarded as a kind of a 'sesqui-sponge'.



5. Transformations of naphthylmethyl carbocations derived from the 'proton sponge'

It has recently been established in our laboratory that treatment of the alcohol **116a** with concentrated hydrochloric or phosphoric acid gave unexpectedly the spiro compound **93** containing two fragments of the 'proton sponge' in a nearly quantitative yield.^{134, 140}

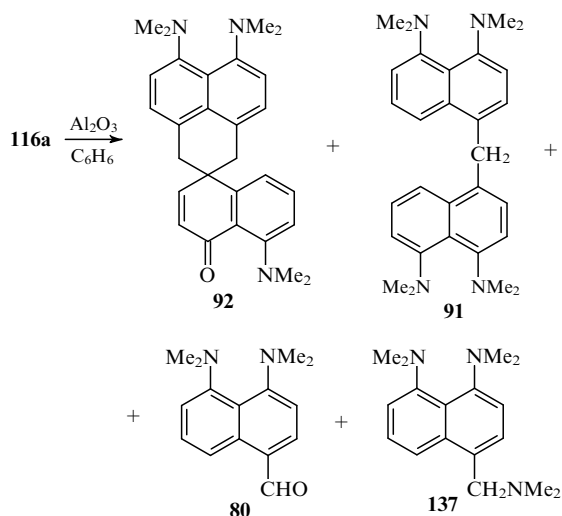


R = Me (**116a**, **93**), Et (**116b**, **136**).

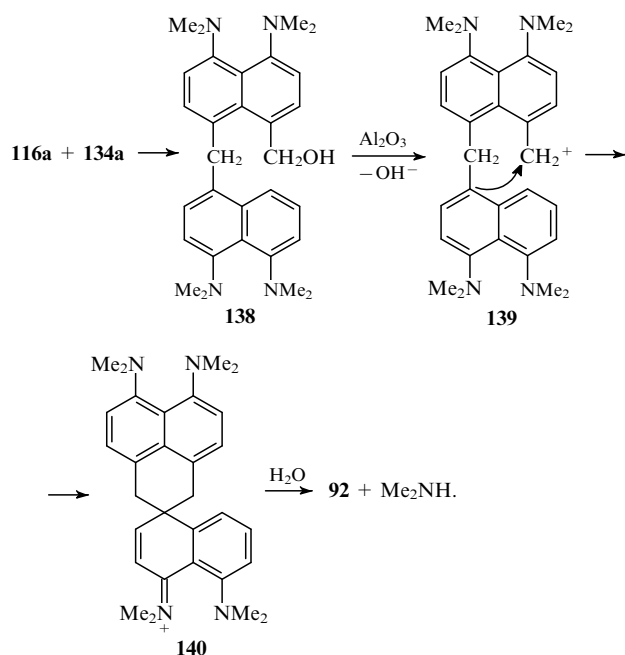
There are reasons to assume that the key intermediate in this synthesis is the naphthylmethyl carbocation **134a** (structure **A**) in which strong resonance stabilisation involving both dimethylamino groups provides the fixation of the diene system containing the *exo*- and *endo*-cyclic bonds CH₂=C and C(4a)=C(5) (structures **B** and **C**). In the subsequent [4π + 2π]-cycloaddition, one molecule of the carbocation behaves as a diene, whereas the second one plays the role of a dienophile; this reaction occurs in a 'head-to-head' mechanism as shown in the scheme. An analogous spiro compound (**136**) is obtained from the alcohol **116b**; however, this reaction is much slower and the yield is lower (~22%).¹³² This may evidently be due to insufficient stabilisation of the carbocation **134b** due to the more pronounced non-coplanarity of the ring and the diethylamino groups.

The cycloaddition reaction observed when the alcohol **116a** was heated in benzene in the presence of solid acidic adsorbents (Al₂O₃, SiO₂, or TiO₂) occurs in a different direction.^{132, 141} In this

case, the main reaction product is the isomeric spiro compound **92** of the 'head-to-tail' type (yield 23%). This reaction also gives dinaphthylmethane **91** (10%), the aldehyde **80** (19%), and the 4-dimethylaminomethyl derivative of the 'proton sponge' **137** (22%) (all the yields are given for Al_2O_3 ; for other supports they vary somewhat).



Most probably, all these compounds are the products of transformation of the carbocation **134a**. Thus the formation of the aldehyde **80** can be explained by the well-established ability of carbenium ions to oxidise alcohols to aldehydes through elimination of the hydride ion. The formation of the dinaphthylmethane derivative **91** seems to be due to the *ipso*-substitution of the CH_2OH group in the original alcohol **116a** by the carbocation **134a**. An attack by the carbocation at the second possible direction of the free *peri*-position 5 in the molecule of compound **116a** should lead to the formation of the alcohol **138**, which further generates the carbocation **139**. Subsequent intramolecular *ipso*-attack by the carbenium centre on the other residue of the 'proton sponge' at position 4 gives ultimately the spiro product **92** via the immonium salt **140**. The dimethylamine liberated in the hydrolysis of the immonium group reacts with the carbocation **134a** to give compound **137**.

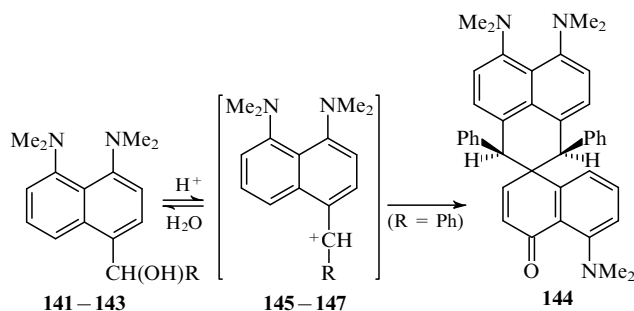


The different direction of cycloaddition reactions in protic media and in the presence of Lewis catalysts is explained in the following way. In a strongly acidic protic medium favouring the formation of the non-symmetrical spiro compounds **93** and **136**, the original alcohol appears to be fully protonated due to the high basicity of the 'proton sponge'. It is therefore hardly likely that it will easily interact with the carbocation **134a**. As a result, the $[4\pi + 2\pi]$ -cycloaddition remains the only possible reaction of the carbocation, especially when its concentration is high enough. At the same time, on the surface of an adsorbent the carbocation **134a** is formed in a low concentration. Being surrounded by an excess of the original alcohol, it will primarily react with the latter to give the symmetrical spiro compound **92**, or with another strong nucleophile. Thus for naphthyl carbocations derived from 'proton sponges' there exist two different cycloaddition reactions, which follow different mechanisms and give spiro compounds of two different types.

The most surprising feature in the formation of the spiro compounds **93** and **136** is that contrary to electrostatic laws, the positively charged carbon atoms from two methylene groups combine. Quantum mechanical calculations^{140, 142, 143} suggest that this process is favoured by the symmetry of their boundary orbitals. This process may not be synchronous and occurs *via* the formation of a biradical intermediate.

The secondary alcohols **141**–**143** behave differently in the presence of acids. Whereas the two former do not change even on prolonged heating in concentrated HCl or $\text{CF}_3\text{CO}_2\text{H}$, their phenyl analogue forms the spiro compound **144** in 87% yield.¹⁴⁰ At first, this compound was erroneously identified as **93**; however, subsequent X-ray analyses confirmed the validity of the symmetrical structure.¹⁴⁴ At present, it still remains obscure whether compound **144** is formed by a mechanism of two-step electrophilic substitution, as is the case with the spiro adduct **92**, or as a result of a $[4\pi + 2\pi]$ -cycloaddition of two molecules of the cation **147** and its abnormal direction is due to steric factors.

The behaviour of the alcohols **141**–**143** with respect to Al_2O_3 is also different. When boiled in benzene in the presence of Al_2O_3 , compound **141** underwent dehydration, presumably, by a mechanism of *E1*-elimination *via* the carbocation **145**. This reaction gives the 4-vinyl derivative **74** in good yield. The alcohols **142** and **143** do not change under these conditions.¹⁰⁹ The inertness of the alcohol **142** in both protic media and in the presence of Al_2O_3 might be due to stabilisation of the cation **146** by the electron-acceptor group CF_3 , so that it is not formed at a steady-state concentration that is sufficient for this reaction.

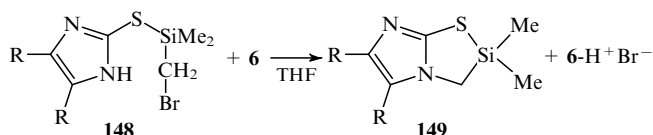


$\text{R} = \text{Me}$ (**141**, **145**); CF_3 (**142**, **146**), Ph (**143**, **147**).

Apparently, the specific reactivity of naphthalene 'proton sponges', which is ultimately due to the potent +*M*-effect of two dimethylamino groups, is manifested in cycloaddition reactions to a far greater degree than in any other conversion. Indeed, although these reactions have been later discovered in alcohols derived from 1,8-dimethoxy-, 1-dimethylamino-8-methoxy-,¹⁴⁵ and even 1-dimethylaminonaphthalene,⁹² they proceeded with considerable difficulty and gave spiro compounds in low yields and of only one specific type.

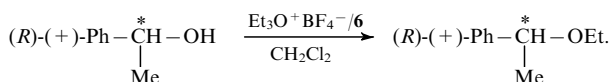
VI. Applications of the 'proton sponges' in organic syntheses

There are numerous indications of the use of 'proton sponge' in organic syntheses, mostly as a strong but low-nucleophilic base. Its application is useful in those cases where it is necessary to ionise the acidic X–H bond or to bind an acid liberated in the course of the reaction without any effect on other base-sensitive groups. A typical example is the cyclisation of the imidazoles **148** in 2-dimethylsila-3*H*-imidazo[2,1-*b*]thiazoles **149**, which occurs in the presence of the 'proton sponge' **6** and in more than 80% yield. Substitution of compound **6** by ordinary bases (OH[−], MeO[−], etc.) leads to the cleavage of the S–Si bond.¹⁴⁶

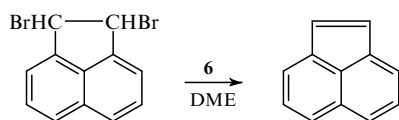


R = H, Ph.

In reactions of chiral compounds requiring the use of a base, the 'proton sponge' hardly causes any racemisation and favours the retention of high optical purity.^{147–149} An example is the conversion of optically active alcohols into ethers under the action of triethyloxonium tetrafluoroborate:¹⁴⁷



Quite unexpected was the use of the 'proton sponge' as a debrominating agent in the conversion of *vic*-dibromides into alkenes.¹⁵⁰ Thus, heating of compound **6** with dibromoacenaphthene in dimethoxyethane gives acenaphthylene in a nearly quantitative yield. Dibromides of coumarin, isocoumarin, chalcone, etc., enter into this reaction. However, the fate of the 'proton sponge' in this conversion could not be followed.



Other applications of the 'proton sponge' in organic syntheses are documented in several publications.^{151–154}

VII. Conclusion

The discovery of the high basicity of 1,8-bis(dialkylamino)-naphthalenes has given a strong impetus to the search for other, still stronger neutral organic bases. Developments in this field have led to the appearance of an interesting branch of organic chemistry, namely, the chemistry of 'proton sponges'. Although naphthalene 'proton sponges' are no longer record holders among neutral bases, their potential in the design of novel compounds possessing unusual physicochemical properties has by no means been exhausted. Of substantial interest are *inter alia* combined (e.g., proton-hydride) 'sponges', the synthesis and study of their hydroxy derivatives, and the development of organometallic chemistry based on them. Finally, it may be expected that the naphthalene 'proton sponges' will be effective building blocks in the construction of supramolecular structures manifesting specific receptor properties.

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

^b — *Chem. Heterocycl. Compd. (Engl. Transl.)*

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Simulation of reactions of fluoroalkenes by quantum chemistry methods

A V Fokin, M A Landau

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Abstract. The results of simulations of the reactions and reactivity of fluoroalkenes by semiempirical and non-empirical methods of quantum chemistry are summarised. In addition to the isolated molecule approximation, methods based on the calculations of potential energy surfaces of reactions and transition states are used. The shortcomings of such calculations are analysed. The nature of chemical bonds in fluoroalkenes and the applicability of quantum chemistry methods for the calculation of their physicochemical and energy characteristics (with ionisation potentials and dipole moments as examples) are discussed. The bibliography includes 106 references.

I. Introduction

Investigation into the reaction mechanisms of fluoroalkenes is not only of theoretical significance but it is of great practical importance as well. For instance, polymerisation and copolymerisation of these compounds lead to the formation of heat-resistant fluoroplastics, the properties of which depend, in particular, on the sequence of monomers in the copolymer. Fluoroorganic compounds (including those obtained in reactions of fluoroalkenes) are widely used as lubricants, dyes, medicines, *etc.* The kinetics and mechanisms of the reactions depend on the conditions (temperature, pressure, solvent), structures and physicochemical properties of reagents, and structures of transition states. The methods of quantum chemistry can be applied to the estimation of the influence of structural and electronic factors on the course of a reaction.

As a rule, quantum chemistry calculations of potential energy surfaces for reactions and transition states give useful information, which allows a qualitative description of the reaction mechanism. However, these calculations are time-consuming and can be performed only for relatively simple systems. Furthermore, due to the approximations implied in the computational methods, the results of the calculations do not always agree with the experimental data. General principles for the construction of

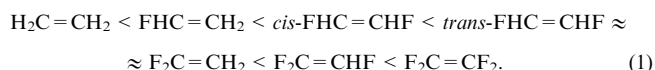
potential energy surfaces for reactions using quantum chemistry methods were described in detail elsewhere.^{1–3} For reactions of fluoroalkenes with the simplest radicals, these calculations were performed for the first time in the early 1980's (see below). Therefore, calculations within the isolated molecule approximation are still a current topic in the theory of reactivity of alkenes since they allow one to determine the most probable site of the bond to be cleaved, or to trace changes in reactivity along certain series of molecules, in terms of different reactivity indices.

Simulation of reaction mechanisms and reactivities is closely connected with the problem of the description of chemical bonding and with physicochemical parameters of molecules. However, in quantum-chemical calculations of such characteristics as ionisation potentials, electron affinity, dipole moments, *etc.*, problems as to their accuracy arise. These questions will be also discussed below.

Three chapters of our earlier monograph⁴ were devoted to the quantum chemistry of fluorine-containing molecules (including fluoroalkenes). However, a number of new studies using modern computational methods have appeared, and these studies should also be summarised. Many results of these studies are based on those of earlier investigations discussed in the monograph⁴, and thus we have to cite this reference often.

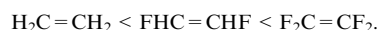
II. Isolated molecule approximation

The problem of the strength of the double bond in ethylene and fluoroethylenes is still far from being completely solved. According to the experimental data on bond lengths, frequencies of valence vibrations, and calculated force constants for the C=C bond, the energy of this bond should increase along the series⁴



The strength of the π -component of the C=C bond changes presumably in the same order (though, this conclusion was derived in earlier studies based on the primitive Hückel method).

According to the results of non-empirical calculations,⁵ some deviations for non-symmetrical fluoroethylenes were observed. In the case of symmetrical molecules, the energy of the double bond increases along the series:



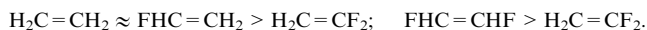
For non-symmetrical fluoroalkenes energy of the C=C bond changes as follows:

A V Fokin A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 85. Tel. (7-095) 135 64 89

M A Landau N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117877 Moscow, Russian Federation. Fax (7-095) 938-21 56. Tel. (7-095) 936 17 22

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However, these conclusions⁵ (as well as the results of other non-empirical and semiempirical calculations that use the optimised geometry) should be used with certain precautions (see below).

The maximum force required for the cleavage of the double bond in fluoroethylenes was taken as a criterion of its strength.⁵ Non-empirical calculations within the Hartree–Fock approximation with the 5-31G basis set (modified program HONDO) were used.

The thermochemical estimation of the energy of the π -bond is based on the heats of different reactions that occur with the cleavage of this bond (chlorination, bromination, hydrobromination, polymerisation, cyclisation, *etc.*). In all cases, the heat of the corresponding reaction of tetrafluoroethylene exceeds that of ethylene by 10–16 kcal mol⁻¹.^{4,6} However, further calculations of the energy of the C=C bond were performed assuming equality of the energies of the C–F bonds in CF₄ and C₂F₄, and of the C–H bonds in CH₄ and C₂H₄, which is in our opinion a very rough approximation. In one of our previous studies we attempted to explain the differences observed for the heats of reactions of ethylene and tetrafluoroethylene.⁴ Quite rough estimates using the Hückel method lead to agreement between the changes in the π -bond energies for a series of fluoroethylenes and the known data on bond lengths and frequencies of stretching vibrations [series (1)]. However, this result was also obtained within rather rough approximations.

An attempt to explain the thermochemical differences in energies of the double bonds in C₂H₄ and C₂F₄ was undertaken⁶ based on non-empirical calculations in the 6-31G* basis set with the use of the unrestricted Hartree–Fock (UHF) wavefunctions and Møller–Plesset second order perturbation theory (MP2). The energy required for the cleavage of the π -bond in ethylene and tetrafluoroethylene as a result of rotation of the molecule to a biradical transition state in the process of *cis*–*trans*-isomerisation was calculated. Thermochemical estimates of the bond energy were confirmed, and weakening of this bond in C₂F₄ compared to C₂H₄ was explained by a ‘planarisation’ of two CF₂ groups (since the carbon atoms in these groups in the biradical transition state are ‘pyramidised’ to a great extent).

An approach to estimating the energy of the π -bond as the difference between the energies of a triplet *twist*-biradical and a planar alkene⁶ does not take into account changes in the energy of C=C, C–F, and C–H σ -bonds in the rotation. Therefore, we suppose that the data on bond lengths and frequencies of stretching vibrations of the double bond in alkenes [series (1)] describe more adequately the order of changes in the energy of the C=C π -bond in fluoroalkenes (since, in general, substitution hardly affects the length of the σ -bond).

The rates of different reactions of fluoroalkenes that occur with cleavage of the C=C π -bond increase along the series (1). This refers to the reactions with nucleophilic reagents^{4,7} and to some radical reactions. Tetrafluoroethylene reacts with alcohols even at room temperature, whereas an analogous reaction for ethylene is impossible,^{8–10} which is explained only by kinetic rather than thermodynamic factors. For instance, at 25 °C the equilibrium for the reaction of ethylene is almost totally shifted towards etherification.¹¹

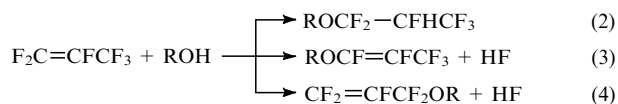
The reactions with nucleophilic reagents should proceed more easily the lower the energy of the lowest unoccupied molecular orbital (LUMO), *i.e.* the higher the affinity of the molecule for the electron. According to results of CNDO and INDO calculations,¹² the LUMO of fluoroethylenes is an antibonding π -orbital of ethylene perturbed by fluorine atoms. The values of E^n for ethylene and tetrafluoroethylene are 5.36 eV and 3.72 eV (CNDO) and 5.91 eV and 4.20 eV (INDO), respectively. These

values clearly explain why tetrafluoroethylene reacts much more easily with nucleophiles than ethylene.[†]

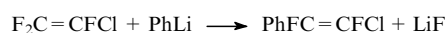
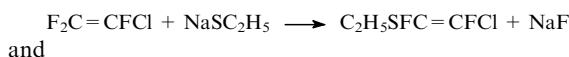
Of course, the values given are relative, but they agree qualitatively with the results of calculations by different modifications of non-empirical methods that use basis sets with only *s*- and *p*-orbitals. However, an introduction of *d*-orbitals into the basis leads to opposite results, which are in agreement with rather scarce and approximate experimental data (see below). A decrease in the calculated values of E^n along the series F₂C=CF₂ > F₂C=CFCF₃ > F₂C=C(CF₃)₂ is also in agreement with the experimentally observed increase in the reactivity of the above-mentioned molecules in reactions with nucleophiles.¹³

Populations on carbon atoms and overlapping populations of the C=C π -bond on lower occupied π -orbitals formed by conjugation of lone pairs on the fluorine atom with the π -bonding orbital of ethylene are negligibly small compared to the population of the highest occupied π -orbital formed primarily by the π -orbital of ethylene (see Ref. 4 in which the results of the *ab initio* calculations are given).

In reactions with alcohols, thiols, and amines, tetrafluoroethylene gives only addition products.^{7,13} Together with addition products (2), perfluoropropylene also gives products of vinylic (3) and allylic (4) substitution.



In the case of perfluoroisobutylene, only reactions (2) and (3) occurred.^{6,13,14} Vinylic substitutions



could be accomplished in the case of chlorotrifluoroethylene⁴ and perfluoro-*tert*-butylethylene.¹⁵ In the latter, only the fluorine atom *trans* to the (CF₃)₃ group undergoes substitution in reactions with carbonylmetallates. However, in the case of (CF₃)₃CCF=CFX (X=Cl or Br), in the reaction with carbonylmetallates, the substitution products are not formed.¹⁵ Other examples of analogous reactions with fluoroalkenes are given elsewhere.^{4,14–17}

Products of vinylic substitution, together with addition products, are also formed in reactions of 1,2-dibromo-1,2-difluoroethylene, tribromofluoroethylene, and bromotrifluoroethylene with alkoxides.^{18,19} In the case of F₂C=CFBr, the main site of attack by a nucleophile is the carbon atom of the CF₂ group (the yield of the addition products and the products of substitution of a fluorine atom in the CF₂ group by OR is 80%–94%). Oligomers or polymers and trifluoroethylene are also formed as by-products (less than 0.5%).

The above-mentioned features of reactions of perfluoropropylene and trifluorochloroethylene were interpreted in terms of the results of quantum-chemical calculations by the CNDO method.^{20–22} Allylic substitution in the case of perfluoropropylene occurs because, according to the results of the calculation, the carbon atom of the trifluoromethyl group carries the maximum positive charge. However, due to great steric hindrances, reaction (2) appears to be preferable (attack at the CF₂ group, which also carries a relatively large positive charge). In the case of perfluoroisobutylene, the reaction (4) is impossible due to steric hindrance. The same holds for the reaction of perfluoropropylene with bulky thiol molecules, which follow only pathways (2) and (3).¹³

[†] It should be noted that many features of reactions with fluoroethylenes and of changes in their reactivity have already been rationalised in the first quantum-chemical studies using the primitive Hückel method (for more details, see Ref. 4).

Vinylic substitution (3) can be explained by a substantial increase in the polarity of the C–F bond of the CF₂ group on going from tetrafluoroethylene to perfluoroisobutylene and chlorotrifluoroethylene.²⁰ Despite the fact that the negative charge on the fluorine atom is almost constant for all the four molecules considered, the positive charge on the carbon atom of the CF₂ group in perfluoropropylene, perfluoroisobutylene, and trifluoro-chloroethylene is substantially higher than in tetrafluoroethylene (Table 1).

In the case of phosphorus fluorides for which substitution of the fluorine atoms is typical, the P–F bond is even more polar according to calculations by the CNDO method.^{4,22,24} Vinylic substitution in fluoroethylenes for which experimental data are lacking, has been analysed based on the bond polarity criterion.²²

According to the polarity criterion for the C–F bond, the probability of vinylic substitution is low in monofluoroethylene and both (*cis* and *trans*) 1,2-difluoroethylenes: the difference between the charges on the carbon and fluorine atoms Δq (calculated by the CNDO method) is substantially smaller than in tetrafluoroethylene. However, these reactions are highly probable for 1,1-difluoroethylene and trifluoroethylene: the difference in charges on the carbon and fluorine atoms for these molecules is more than 0.55 (as for perfluoropropylene, perfluoroisobutylene, and chlorotrifluoroethylene), which is larger than the corresponding value for tetrafluoroethylene (0.48, Table 1).

Similar results were obtained in *ab initio* calculations, which are summarised in Table 1, *viz.* atomic charges and Δq values calculated from the data on populations of the corresponding atomic orbitals.²³ Values of Δq for 1,1-di- and tri-fluoroethylenes are also substantially larger than for other members of the series.

Similar results were obtained by the INDO method.²²

Charge distributions in non-symmetrical fluoroethylenes indicate^{4,12} that the addition of hydrogen halides to these molecules should obey the Markownikoff rule, which is in agreement with the experimental data.^{7,13} The results of the corresponding semi-empirical (CNDO, INDO) and non-empirical calculations⁴ also support this conclusion (see also charges of the carbon atoms given in Ref. 5). In reactions with alcohols and thiols, the RO[–](RS[–]) group also adds to the carbon atom, which according to calculations¹² has a relatively high positive charge. A similar conclusion was derived^{4,12,20} from calculations of 1,1-dichloro-2,2-difluoroethylene, chlorotrifluoroethylene, perfluoropropylene, and perfluoroisobutylene which is confirmed by the experimental data. The orientation of borane addition to monofluoroethylene according to calculations by the MNDO method,²⁵ is also in accordance with the experimental data (see also charges of fluoroalkenes calculated by the CNDO method²⁶).

Generally, in vinylic substitution in non-symmetrical haloethylenes, nucleophilic attack can occur at both carbon atoms of

the double bond (see, for example, Ref. 15). The probability of such attack should increase with a decrease in the charge difference between the two carbon atoms. If a molecule contains a CFX group (X = Cl, Br), substitution of both F and X is possible.¹⁵ This is observed, for example, in the reaction of β -chloro- α,β -difluorostyrene with phenyllithium and KFe(CO)₂Cp.¹⁵ The difference in charges on the carbon atoms of the double bond is small (0.171, calculated by the AM1 method).²⁷ Despite the fact that the charge of the carbon atom on the PhFC group is greater than that of the CFCl group, a nucleophile attacks only the =CFCl fragment (presumably, due to steric hindrances because of the presence of the benzene ring in PhFC=). A competitive substitution of both fluorine and chlorine atoms occurs.

Unfortunately, the charges on the F and Cl atoms were not given in Ref. 27, and thus it is impossible to estimate the probabilities of the two reactions in terms of polarity of the C–X bond. Presumably, the substitution of the F atom is more probable. This assumption is in agreement with the results of calculations for other molecules (chlorotrifluoroethylene, in particular²⁰) and with the above-mentioned data on reactions of tribromofluoroethylene.¹⁹ In addition, we believe that KFe(CO)₂Cp or Re(CO)₅, in general, cannot be considered as classical nucleophiles. In the course of the reaction, intermediate complexes can be formed through dative bonds between the Fe (Re) atom and the π -orbital of alkene as well as by donor–acceptor bonds between CO and the vinyl group.

A detailed study of electrochemically activated reactions of nucleophilic substitution of polyfluorinated vinyl halides was performed,^{27,28} and quantum-chemical calculations for the nine alkenes considered, four fluorinated butadienes, and fluorinated acetylenes were accomplished.²⁷ The semiempirical AM1 method with full geometry optimisation was used. Energies of frontier π -orbitals of the molecules studied and charges on the vinylic carbon atoms were determined. Other parameters (in particular, charges on halogen atoms, interatomic distances, bond angles) were not given in Ref. 27. However, certain problems in the interpretation of the results of quantum-chemical calculations that use optimised geometry may arise (see below). The electron acts as the simplest nucleophile. In the case of the formation of rather stable radical-anions upon interaction of a haloalkene with an electron [for instance, (RFC=CFX)^{•–}], the nucleophilic substitution is a ‘multi-step’ process.²⁷ If no radical-anions are formed, the nucleophilic substitution is a ‘one-step’ process.

Changes in frontier π -orbitals of ethylene upon substitution of halogens for hydrogen were thoroughly analysed.²⁷ Energetic, spatial, and kinetic factors were considered.

The energy of the π -orbitals of the double C=C bond perturbed by halogen atoms depends both on conjugation of a lone *p*-electron pair of the halogen with the electrons of the π -bond

Table 1. Charges on the carbon (q_C) and the fluorine (q_F) atoms in fluoroalkenes calculated by the CNDO²² (I) and *ab initio*²³ (II) methods and the difference between the charges of C and F (Δq).

Molecule	q_C		q_F		Δq	
	I	II	I	II	I	II
<u>F</u> HC=CH ₂	+0.209	+0.263	–0.186	–0.361	0.395	0.624
<i>cis</i> - <u>F</u> HC=CHF	+0.143	+0.101	–0.166	–0.335	0.309	0.436
<i>trans</i> - <u>F</u> HC=CHF	+0.141	–0.054	–0.169	–0.335	0.310	0.281
<u>F</u> ₂ C=CF ₂	+0.317	+0.534	–0.159	–0.274	0.476	0.808
<u>F</u> ₂ C=CClF	+0.398	–	–0.159 (–0.165)	–	0.557 (0.563)	–
<u>F</u> ₂ C=CFCF ₃	+0.418	–	–0.163 (–0.158)	–	0.581 (0.576)	–
<u>F</u> ₂ C=C(CF ₃) ₂	+0.520	–	–0.164	–	0.684	–
<u>F</u> ₂ C=CH ₂	+0.448	+0.654	–0.192	–0.313	0.640	0.967
<u>F</u> ₂ C=CFH	+0.379	+0.600	–0.173 (–0.174)	–0.294 (–0.291)	0.552 (0.553)	0.894 (0.891)

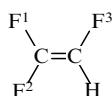
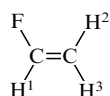
Note. The fluorine atoms for which values of q_F are given are underlined. Values of q_F are given for the fluorine atom in the *cis*- (no parentheses) and *trans*- (in parentheses) positions to the fluorine atom of the CFX group. In calculations on chlorotrifluoroethylene, vacant 3*d*-orbitals of the Cl atom were included into the basis set.

Other examples of similar studies are given elsewhere.⁴ A problem arises in the choice of the molecular geometry. In non-empirical and semiempirical calculations, the energy minimisation procedure is often applied, and further calculations of quantum-chemical characteristics are performed for the structure, which corresponds to the global energy minimum. However, noticeable deviations between the calculated and experimental geometrical parameters for the gas phase are often observed. For example, for fluoroethylenes, the difference between the experimental and calculated bond lengths does not exceed 0.03 Å, which can hardly affect substantially the calculated physicochemical parameters. Only for calculations by the MNDO method do the calculated bond lengths deviate strongly from the experimental ones. How-

ever, the difference between the calculated and experimental bond angles in some cases reaches 4° , which inevitably introduces errors in the values of some physicochemical parameters and quantum-chemical indices (dipole moments, ionisation potentials, *etc.*).⁴ For instance, changes in ionisation potentials for the series of fluoroethylenes obtained by the LCAO SCF *ab initio* calculations in the DZ basis not only disagree with the experimental data, but do not reflect any regularity in contrast to the results of semi-empirical calculations (EHT, CNDO, INDO), which use the experimental molecular geometry (see Refs 4 and 12).[‡]

The same problem was discussed in another study.³² It was shown that in the case of full geometry optimisation by the MNDO and *ab initio* methods, not only the calculated bond angles, but also the C=C and C–F bond lengths differ considerably from the experimental values.

Recently,³³ enthalpies of formation, moments of inertia, vibration frequencies, and geometrical parameters for more than 100 fluorinated hydrocarbons and radicals containing one or two carbon atoms were calculated using the non-empirical BAC-MP4 method (fourth order Møller–Plesset perturbation theory corrected for additivity of bonds). It was found that the bond angles coincide with the experimental data within 1° on average. However, as can be seen from the tables given in Ref. 33, this is not quite true for fluoroethylenes, especially for non-symmetrical ones. In some cases, as well as in the studies mentioned above, deviations from the experimental data reach 4° , for example,

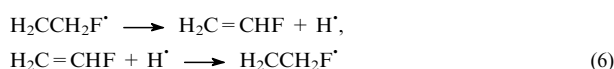


Angle	Value of angle /deg.		Angle	Value of angle /deg.	
	calcu- lation ³³	experi- ment ⁴		calcu- lation ³³	experi- ment ⁴
CCF	122.4	120.98	CCF ¹	125.4	125.43
CCH ¹	125.7	127.70	CCF ³	120.6	118.81
CCH ³	119.8	121.41	CCH	123.4	127.20
CCH ²	121.5	123.93			

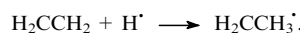
The problems discussed in Ref. 33 lie somewhat beyond the objectives of the present review (though the authors point to the need for kinetic studies). In the above-mentioned study, neither data on the energy of molecular orbitals, nor populations of atomic orbitals and atomic charges were given, and the mechanisms of the reaction with participation of the compounds studied were not considered.

III. Potential energy surfaces of reactions and structure of transition states

First studies devoted to calculations of potential energy surfaces of reactions with the participation of fluoroethylenes appeared in 1980.^{34,35} The unrestricted Hartree–Fock method with split valence basis set 4-31G was used. In particular, a mechanism of reaction of monofluoroethylene with atomic hydrogen was discussed.³⁴ Potential energy surfaces of the following reactions were studied by non-empirical MO LCAO methods:



as was of a similar reaction of ethylene.³⁵ The main contribution to the potential barrier (E) of reaction (6) equal to $5.6 \text{ kcal mol}^{-1}$ arises from deformation of the H_2CCHF segment in the transition state ($4.5 \text{ kcal mol}^{-1}$); the rest ($1.1 \text{ kcal mol}^{-1}$) is due to interactions of the $\text{FHC}=\text{CH}_2$ fragment with H. The potential barrier of reaction (6) exceeds by $3.3 \text{ kcal mol}^{-1}$ that of the reaction



The lifetime of $\text{H}_2\text{CCH}_2\text{F}^\bullet$ is relatively great (10^{-9} s). If the process has adiabatic character, the energy E converts to the translation energy of the reaction products³⁵ (see also Ref. 4).

The studies^{34,35} were based on general principles of analysis of potential energy surfaces for radical reactions developed by Nagase, Morokuma, and Kern.^{34,36,37}

Reactions of atomic hydrogen with 1,1-difluoroethylene and monofluoroacetylene were studied in detail.³⁸ An *ab initio* method within the unrestricted Hartree–Fock theory (modified version of Gaussian 70) was used. It was demonstrated that in both cases the preferential site for a nucleophilic attack is the carbon atom not bonded with the fluorine atom. The potential barrier to the reaction of 1,1-difluoroethylene ($4.1 \text{ kcal mol}^{-1}$)³⁸ is higher than that of ethylene ($2.2 \text{ kcal mol}^{-1}$).³⁴

Potential energy surfaces, structures of transition states for reactions of fluoroethylenes with alkyl radicals and heteroradicals as well as the regioselectivity of alkyl radicals in reactions with non-symmetrical fluoroethylenes were discussed in a number of papers^{39–44} (see also Ref. 4). The extended Hückel method (EHT) was used.^{39,40} The conclusions derived in Refs 39 and 40 are not always correct from our viewpoint. For instance, attempts to analyse the mechanisms of the reactions studied of ethylene and fluoroethylenes⁴⁰ with $\text{CH}_3^\bullet$ and $\text{CF}_3^\bullet$ using different correlations between the experimental activation energy and the calculated quantum-chemical indices do not meet any criteria of mathematical statistics.[§]

A more thorough analysis of the mechanisms of radical reactions was performed using the concept of ‘phility’ of free radicals in reactions of addition to alkenes.^{41–44} This concept is based on a hypothesis⁴⁵ of a parallelism between the direction of the charge transfer and localisation of the bonds formed and cleaved and on an assumption⁴⁶ that the potential barrier to a reaction depends on the charge transfer stage and that the strongest charge transfer in a transition state corresponds to the most preferable reaction pathway. A hypothesis⁴⁷ stating that the interaction of centres with the maximum electron density on frontier orbitals of the reagents (the HOMO of the alkene and the orbital with the unpaired electron of the radical for the stage of charge transfer from alkene to radical; and the LUMO of the alkene and the same orbital of the radical for the stage of charge transfer from the radical to the alkene) is the most preferable, is also implied.

Depending on the substrate, a radical can act as a nucleophile and an electrophile, and can exhibit ambiphilic properties (in the case that the charge transferred from the orbital of the radical occupied by one electron to the lowest unoccupied π -orbital of the alkene is close to the charge transferred in the opposite direction from the highest occupied π -orbital of the alkene to the radical orbital). In general, certain radicals and an alkene can act as nucleophiles and electrophiles (donors and acceptors) simultaneously donating and accepting electrons. The ‘phility’ is determined by the predominating process.

The ‘phility’ concept,⁴¹ first, allows one to determine the most reactive centre of a non-symmetrical alkene molecule; second, to predict changes in the reactivity of a given radical with different alkenes or a given alkene with different radicals; and third, to estimate the preferred direction of charge transfer in the system (from the alkene to the radical or, conversely, from the radical to the alkene).

To determine the reaction rate constants, the stabilisation energy method,¹ the concept of a ‘quasi- π -electron system’ of the

‡ Unfortunately, there are no published data on the orbital populations and all atomic charges of fluoroalkenes calculated *ab initio* with a more complete basis set.

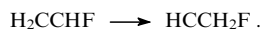
§ Plots of dependences of $(E - E_0)_{\text{exp}}$ on the theoretical value $(E - E_0)_{\text{theor}}$, the sum of contributions of charge transfer, and contributions of exchange repulsion were discussed⁴⁰ (E and E_0 are activation energies of fluoroethylene and ethylene, respectively). However, only four or five experimental points (equal to the number of molecules studied) were used in data processing, and strong deviations from the theoretical line were observed. No statistical criteria, except for the correlation coefficient, for the dependences obtained were given⁴⁰ (for details, see Ref. 4).

transition state (*i.e.* the electron system that comprises π -systems of the initial molecules),⁴⁸ and a one-electron method of perturbation theory within the frontier orbitals approximation have been used.^{42,43}

Reactions of ethylene and fluoroethylene with six alkyl and halogenoalkyl radicals ($\text{CH}_3^\bullet$, $\text{CH}_2\text{F}^\bullet$, $\text{CHF}_2^\bullet$, $\text{CF}_3^\bullet$, $\text{C}_2\text{F}_5^\bullet$, and $\text{CCl}_3^\bullet$) and four heteroradicals [$\text{PH}_2^\bullet$, $\text{P}(\text{CH}_3)_2^\bullet$, $\text{SH}^\bullet$, $\text{S}(\text{CH}_3)_2^\bullet$] were discussed.^{42,43} An analogous approach was also used for the qualitative prediction of the direction of radical substitution reactions in an aromatic ring⁴⁹ and for a investigation of the reactions of fluoroethylene copolymerisation.⁵⁰

The results obtained^{41–44,49,50} reflect adequately the experimental data on reaction mechanisms and reactivities of the molecules studied. Generalisation of these results has led to the development of a model of intermolecular ambivalence in organic reactions.⁵¹

After publication of the monograph,⁴ several studies devoted to quantum-chemical calculations of potential energy surfaces for reactions of fluoroalkenes appeared. Hydrogen migration in the monofluoroethylene molecule was studied⁵² *ab initio* on a Hartree–Fock atomic orbital basis using perturbation theory. It was shown that a local minimum on the energy surface does not correspond to the singlet state of the rearrangement product.



The problems of accounting for the correlation effects that arise when determining the geometry of transition states are the same as in calculations of the ground state structures of molecules. The authors of a study⁵³ of addition reactions of $\text{H}^\bullet$, $\text{OH}^\bullet$, $\text{NH}_2^\bullet$, and $\text{CH}_3^\bullet$ radicals to mono- and 1,1-di-fluoroethylenes using non-empirical calculations (up to MP4/6-31G**) came to a conclusion on the necessity of accounting for the electron correlation when determining the structures of transition states for reactions of fluoroalkenes with electrophilic radicals. The importance of accounting for the electron correlations in quantum-chemical calculations of reactions of fluoroethylenes with radicals was also discussed in other studies.^{52,54,55} In all these studies, different modifications of the *ab initio* method were used [Hartree–Fock atomic orbitals MP2–MP4/DZ + P; 6-31G**, 6-311G**, 6-311 + G(2d,p); 6-311 + G(3df,2p), *etc.*].

The relative reactivity of the above-mentioned radicals in reactions with monofluoroethylene and difluoroethylene obtained from calculations⁵³ is in agreement with the experimental data. However, the regioselectivity of $\text{OH}^\bullet$ and $\text{NH}_2^\bullet$ radicals is very 'sensitive' to the level of theoretical calculations, and an increase in this level up to MP4/6-31G** may lead to a contradiction with the experimental data (an attack at the carbon atom of the FHC and F_2C groups according to calculations rather than of the H_2C group according to experiment).⁵³

Non-empirical calculations of potential energy surfaces of addition reactions of $\text{H}^\bullet$, $\text{CH}_3^\bullet$, $\text{CH}_2\text{OH}^\bullet$, $\text{CH}_2\text{CN}^\bullet$, and *tert*- $\text{C}_4\text{H}_9^\bullet$ radicals to alkenes $\text{H}_2\text{C}=\text{CHX}$ ($\text{X} = \text{H}$, CH_3 , NH_2 , OH , F , SiH_3 , Cl , CN , CHO , NO_2) were performed.^{54,55} A correlation between the potential barrier and the reaction enthalpy was established ($R^2 = 0.973$). However, besides the correlation coefficient, no other statistical criteria were used for the dependence obtained, which does not allow one to judge its correctness. Problems of the statistical significance of correlation equations were analysed in detail elsewhere.^{56–59}

The methyl radical does not manifest nucleophilic properties in reactions with the alkenes studied ($\text{X} = \text{F}$, H , OH , CH_3 , SiH_3 , and NH_2) and acts as an electron acceptor (*i.e.* the charge is transferred from the alkene to $\text{CH}_3^\bullet$).⁵⁴ In the case where $\text{X} = \text{Cl}$, according to the results of calculations, charge transfer does not occur at all; for $\text{X} = \text{CHO}$, NO_2 , and CN , methyl acts as an electron donor (*i.e.* exhibits nucleophilic properties: the charge is transferred from $\text{CH}_3^\bullet$ to the alkene).

Electron-acceptor groups increase the reactivity of alkenes due to an increase in the exothermicity of the reaction rather than the polar character of the transition state.⁵⁴

The stability of fluorine-containing cations including $\text{H}_2\text{C}=\text{CHFCH}_3^+$ and $\text{H}_2\text{C}=\text{CHCHF}^+$ was studied by the *ab initio* SCF method in the 6-31G basis set (Gaussian 82 programme).⁶⁰ An analysis of singlet and triplet transition structures in the process of trifluoroethylene formation in the photolysis of 2,2,2-trifluorodiazoethane was performed⁶¹ using the *ab initio* method at the QCISD(T)-FC/6-311(2s,2p)/MP2-FC/6-31G** theory level.

The results of non-empirical calculations for $\text{C}_3\text{H}_2\text{F}^+$, C_3HF_2^+ , and C_3F_3^+ ions are given elsewhere⁶² (SCF, Hartree–Fock, 6-311G).

Potential energy surfaces for molecules of X_2F_4 type ($\text{X} = \text{C}$, Si , Ge , Sn , and Pb) were studied in detail using *ab initio* methods (RHF and UHF, DZ and DZd basis sets).⁶³ In particular, it was established that the planar structure of C_2F_4 corresponds to the energy minimum. Similar energy minima were found for ground states of Si_2F_4 , Ge_2F_4 , Sn_2F_4 , and for a singlet excited state of Pb_2F_4 . It was shown that a biradical triplet particle $\text{F}_2\text{X}^\bullet-\text{X}^\bullet\text{F}_2$ has higher energy than the singlet particle in the ground state.

IV. Quantum-chemical calculations of the physicochemical parameters of fluoroalkenes

Different aspects of the quantum chemistry of fluoroalkenes, such as the nature of the chemical bonds therein, relative stability of geometrical isomers, and calculations of physicochemical parameters, have been discussed in detail previously.⁴ Problems arising from the interpretation of the results of calculations and from calculations of certain parameters (ionisation potentials, dipole moments, different energy characteristics, magnetic shielding constants of ^{19}F and ^{13}C nuclei, and so on) have been also analysed. Most of these parameters affect the character and quantitative characteristics of reactions of fluoroalkenes and thus they are closely connected with the objectives of the current review. The results of quantum-chemical calculations of physicochemical parameters of fluoroalkenes obtained in the 1990's have been analysed in another review.⁶⁴ Here, we will discuss in brief only the problems that concern the reactivity and mechanisms of reactions of compounds of this class.

Difficulties arising from the calculations of geometrical parameters of molecules have already been mentioned. Non-empirical calculations of neutral molecules and dications of type $\text{C}_2\text{X}_2\text{Y}_2^{2+}$ were performed⁶⁵ in the 3-21G*(d) basis set using the Gaussian 88 programme. In particular, it was shown that dication $\text{C}_2\text{F}_4^{2+}$ has a planar configuration in the ground state in contrast to the *twist*-structure of $\text{C}_2\text{H}_2^{2+}$. Serious problems also arise in the calculation of the ionisation potentials and dipole moments of molecules.

1. First ionisation potentials; electron affinity

The first ionisation potential I , which corresponds to detachment of an electron from the HOMO, is the most interesting for chemists: the value of I to some extent correlates with the reactivity of a molecule in reactions with electrophilic reagents. Linear correlations between the logarithms of rate constants of certain reactions and I values are often found for narrow subsets of closely related compounds.

In order to estimate I , the difference between the energies of the ion formed and the initial molecule $\Delta E'$ has to be calculated.

According to Koopmans theorem,⁶⁶ if wavefunctions are not changed after detachment of an electron from certain MO, the corresponding ionisation potential is equal to the energy of this orbital E_i . This implies that the difference between the correlation energies of the ion and molecule ΔE_c is equal to the reorganisation energy ΔE_r taken with the opposite sign,⁶⁷ since

$$I + E_i = \Delta E_c + \Delta E_r,$$

where ΔE_r is the difference between the energy of the HOMO calculated in the optimum modification of the Hartree–Fock method and the ionisation potential.⁶⁸

Usually, ionisation potentials I calculated according to Koopmans theorem using different semiempirical and non-empirical methods of the self-consistent field (SCF) approach exceed the experimental values.

At the same time, the use of $\Delta E'$ may lead to errors due to the difference in the correlation energies of the ion formed and the initial molecule. This often results in lower values of the ionisation potentials I compared to the experimental ones. The results obtained according to Koopmans theorem may be corrected (for example, by changing the calculated values of I by 8%), however, such corrections give satisfactory results only for ionisation from the two lowest MOs.

As an alternative, averaged values of ionisation potentials obtained by the two above-mentioned methods can be used for a comparison of calculated and experimental results.²³ But this artificial approach does not lead to good results in all cases.⁴

According to the Frank–Condon principle, the internuclear distance should be kept constant as an electron is detached. But there is no reason to state that the ion formed in this case will be in its ground state. It is more probable that the interatomic distances of the ground state of the initial molecule correspond to an excited vibrational state of the ion. In this case, the so-called vertical ionisation potential I_v , which can be determined, for instance, by the electron impact method, includes energy from the excitation of the molecule in addition to the adiabatic ionisation potential (I_a). Discrepancies between the values of I_v determined in different studies are sometimes equal to 0.15–0.40 eV.^{4,64} At the same time, the accuracy of the experimental determination of the adiabatic ionisation potentials is very high (± 0.01 – 0.02 eV).⁴

Adiabatic ionisation potentials, which correspond to the difference in the energy of ground states of the ion and molecule,

can be measured with high precision using spectral and photo-ionisation methods.

Obviously, calculation of the adiabatic ionisation potentials requires that the difference in energies of the ion and molecule, calculated for optimised geometries corresponding to the energy minima of both particles, should be determined. Ionisation potentials calculated according to Koopmans theorem should correspond to the experimentally determined vertical ionisation potential. However, the change in, for example, energies of HOMOs calculated by the Hückel method as well as by EHT, CNDO, INDO methods^{12,69–74} for a series of haloethylenes corresponds to a change in the first adiabatic potentials and at the same time does not reflect changes in the vertical potentials. Therefore, in many studies the first ionisation potentials I_a of haloethylenes calculated using the corresponding parametrisation are taken to be equal to the energy of the HOMO.

Surprisingly, the best results were obtained using the Hückel method. Presumably, it is a relatively simple procedure to adjust the parameters required for the calculations using experimental data for a small subset of molecules that accounts for this fact.

Of course, it is possible to try to adjust the corresponding parameters for calculations of ionisation potentials of haloethylenes within semiempirical SCF quantum-chemical methods. However, such a procedure and subsequent calculations are much more time-consuming than the corresponding calculations by the Hückel method. Thus, merely from a pragmatic viewpoint, the results^{71–73} are still timely, and a similar approach can be successfully applied for other classes of compounds.

Attempts at calculations of ionisation potentials of fluoroethylenes using various semiempirical and non-empirical versions of the SCF method did not, in general, lead to positive results. The most complete study of ionisation potentials of molecules of the

Table 2. Calculated and experimental values of the first adiabatic ionisation potentials of haloethylenes (eV).

Molecule	Calculation ⁷⁹ (see ^a)	Calculation ^{72, 73}	Experiment ^{67, 68, 80}	Experiment ^{67, 81}	Experiment ^{26, 82–85}
FHC=CH ₂	—	10.40	10.37	10.36±0.015	10.37±0.02
F ₂ C=CH ₂	—	10.32	10.31	10.29±0.01	10.31±0.02
<i>cis</i> -FHC=CHF	—	10.30	—	10.23±0.02	10.25±0.02
<i>trans</i> -FHC=CHF	—	10.30	—	10.21±0.02	10.19±0.02
F ₂ C=CHF	—	10.21	—	10.14±0.02	10.14±0.02
F ₂ C=CF ₂	—	10.12	10.11	10.14	10.12±0.02
ClHC=CH ₂	10.06	10.00	10.00±0.02	9.995±0.01	10.00±0.02
<i>cis</i> -ClHC=CHCl	—	9.64	9.65±0.01	9.63±0.01	9.66±0.02
<i>trans</i> -ClHC=CHCl	9.65	9.64	9.64±0.02	9.65±0.01	9.64±0.02
Cl ₂ C=CH ₂	9.89	9.89	9.83	9.79±0.02	—
Cl ₂ C=CHCl	9.49	9.50	9.48±0.03	9.47±0.01	—
Cl ₂ C=CCl ₂	—	9.32	9.34±0.03	9.32±0.02	—
BrHC=CH ₂	9.93	9.89	—	9.80±0.02	9.82±0.02
<i>cis</i> -BrHC=CHBr	—	9.45	—	9.45±0.02	9.45±0.02
<i>trans</i> -BrHC=CHBr	9.46	9.45	—	9.47±0.02	9.46±0.01
Br ₂ C=CHBr	9.22	9.30	—	9.27±0.02	—
<i>cis</i> -FHC=CHCl	9.92	9.91	—	—	9.86±0.01; 9.87±0.01
<i>trans</i> -FHC=CHCl	9.89	9.91	—	—	9.87±0.02
<i>cis</i> -FHC=CClF	9.93	9.89	—	—	9.86±0.02
<i>trans</i> -FHC=CClF	9.90	9.89	—	—	9.83±0.02
F ₂ C=CHCl	—	9.84	9.84 ^b	—	—
F ₂ C=CCl ₂	—	9.70	9.65	—	9.69±0.01
F ₂ C=CClF	—	9.81	9.84	—	9.82 9.76
FCIC=CH ₂	—	9.98	9.97 ^b	—	—
F ₂ C=CBrF	—	9.71	9.67 ^b	—	—

^a In Ref. 79, the results of calculations on fluoroalkenes by the Hückel method with different complicating corrections were also given. ^b Experimental data were obtained after publication of the corresponding results of calculations.^{72, 73}

class considered was performed by the *ab initio* MO LCAO method in the DZ basis set,²³ these values were calculated both according to Koopmans theorem and as a difference in total energies of the ion formed and the initial neutral molecule. However, even the direction of change of the calculated ionisation potentials did not correspond to the change in experimental adiabatic and vertical ionisation potentials (see Refs 4, 23, 64 and results of Refs 32, 75–78). Possible reasons for this fact have already been mentioned.

Table 2 shows adiabatic ionisation potentials of haloethylenes calculated by the Hückel method. Differences between the calculated and experimental values do not exceed a few hundredths of an electron-volt. This suggests that the calculated ionisation potentials of 28 haloethylenes (Table 3) for which there are no experimental data are also reliable. After publication of the studies^{72–74}, adiabatic ionisation potentials of some mixed haloethylenes were measured; for them, good agreement between the calculated and experimental data was also observed (Table 2).

Table 2 shows that experimental ionisation potentials of *cis*- and *trans*-1,2-haloethylenes are virtually identical, and this fact justifies the application of the computational methods that do not take into consideration geometrical differences between the isomers.

It should be noted that according to mass spectrometric data,^{84,86} the first ionisation potential of fluoroethylenes can be interpreted as the energy of a π -electron of the C=C bond (taken with the opposite sign). This conclusion can also be derived from the calculations on these molecules by the CNDO, INDO, MNDO, and *ab initio* methods (see Refs 4 and 64): the orbital formed by a π -bonding orbital of ethylene perturbed by fluorine atoms has the highest energy of all the π -orbitals.

The great scatter of experimental data on electron affinity (*A*) does not allow one to derive unambiguous conclusions on changes in *A* for fluoroethylenes. For example, in a reference book,⁸³ the value $A > -2.15$ eV is indicated for ethylene, while for fluoroethylenes the data are absent. In more recent studies,^{54,87} the values of *A* for C₂H₄ and CH₂=CHF are -1.74 eV and -1.91 eV, respectively, *i.e.* ethylene manifests a higher electron affinity than monofluoroethylene. However, a non-empirical calculation⁵⁴ (MP2, 6-31G**/HF/6-31G* basis) gives other results: -1.86 eV and -1.62 eV. The same result was obtained in Ref. 88: calculations by the CNDO and *X_α* methods as well as non-empirical calculations using the Hartree–Fock functions in 6-31G and 6-31G* basis sets lead to a more stable lowest vacant orbital in fluoroethylenes compared to that in ethylene. Only the inclusion of *d*-functions into the 6-31G* basis set gives agreement with the above experimental results.

Table 3. Calculated⁷³ first adiabatic ionisation potentials (*I_a*/eV) for haloethylenes (experimental data for the given molecules are absent).

Molecule	<i>I_a</i>	Molecule	<i>I_a</i>
Br ₂ C=CH ₂	9.81	ClBrC=CHBr	9.34
Br ₂ C=CBr ₂	9.09	FBrC=CHBr	9.42
FBrC=CH ₂	9.88	Cl ₂ C=CClF	9.45
ClBrC=CH ₂	9.84	Cl ₂ C=CClBr	9.26
FHC=CHBr	9.80	Br ₂ C=CBrF	9.26
ClHC=CHBr	9.54	Br ₂ C=CClBr	9.15
ClBrC=CHF	9.74	F ₂ C=CBr ₂	9.61
FBrC=CHCl	9.52	Cl ₂ C=CBr ₂	9.21
FCIC=CHBr	9.50	FCIC=CClF	9.57
F ₂ C=CHBr	9.73	FBrC=CBrF	9.39
Cl ₂ C=CHF	9.79	ClBrC=CBrCl	9.20
Cl ₂ C=CHBr	9.39	F ₂ C=CClBr	9.64
Br ₂ C=CHF	9.70	Cl ₂ C=CBrF	9.36
Br ₂ C=CHCl	9.41	Br ₂ C=CClF	9.36
FBrC=CHF	9.79	FCIC=CBrF	9.48
FCIC=CHCl	9.61	FCIC=CClBr	9.40
ClBrC=CHCl	9.45	FBrC=CClBr	9.30

Probable experimental errors have also to be taken into account. However, due to the lack of experimental data, this question is open to discussion.

2. Dipole moments of molecules

The polarity of a molecule can substantially affect its reactivity and reaction mechanisms. Problems arising in quantum-chemical calculations of dipole moments have been considered in a number

Table 4. Calculated and experimental values of dipole moments of fluoroalkenes.

Molecule	Method of calculation ^a	Dipole moment /D	
		calculation	experiment
FHC=CH ₂	PPP ⁸⁹	0.77	1.427 ⁹⁸
	MNDO ⁹⁰	1.70	
	CNDO ⁹¹	1.51	
	CNDO ¹²	1.585	
	CNDO ⁹²	1.587	
	INDO ¹²	1.649	
	INDO ⁹²	1.686	
	INDO ⁹³	1.483	
	HAM/3 ⁹⁴	2.64	
	<i>ab initio</i> [STO-3G] ⁹⁵	0.71	
	<i>ab initio</i> [STO-4G] ⁹⁵	0.79	
	<i>ab initio</i> [STO-3G] ⁹⁶	0.90	
	<i>ab initio</i> [4-31G] ⁹⁶	2.10	
	MM ⁹⁷	1.43	
F ₂ C=CH ₂	CNDO ⁹⁹	0.88	1.37 ^{101–103}
	CNDO ¹²	1.389	
	INDO ⁹³	1.420	
	INDO ¹²	1.493	
	MNDO ⁹⁰	2.03	
	HAM/3 ⁹⁴	2.69	
	<i>ab initio</i> ^b (see ¹⁰⁰)		
	STO-3G.7.3	1.71 (1.83)	
	7.3.1	1.22	
	9.5	2.31	
	9.5	2.25	
	MM ⁹⁷	1.39	
	CNDO ⁹⁹	2.74	2.42 ^{102, 103}
<i>cis</i> -FHC=CHF	CNDO ¹²	2.806	
	INDO ¹²	2.900	
	INDO ⁹³	2.523	
	<i>ab initio</i> ^b (see ¹⁰⁰)		
	STO-3G.7.3	3.10 (3.36)	
	7.3.1	2.62	
	9.5	3.47	
	9.5	3.55	
	<i>ab initio</i> ^b (RHF) ¹⁰⁴		
	4.31G; 6.31G	3.50 (3.60)	
	6.311G	3.53	
	6.31G*	2.81	
	6.311G*	2.91	
	MM ⁹⁷	2.42	
F ₂ C=CHF	CNDO ¹²	1.459	1.30–1.32 ⁹⁸
	INDO ¹²	1.534	
	MNDO ⁹⁰	1.82	
	HAM/3 ⁹⁴	2.83	
	MM ⁹⁷	1.32	
F ₂ C=CClF	CNDO ²¹	0.33	0.38 ⁹⁸

^a MM is the molecular mechanics method. ^b Results of calculations with different basis sets for experimental (gas phase),¹⁰⁰ standard¹⁰⁴, and optimised (in parentheses) molecular geometry; fixed standard parameters are as follows:¹⁰⁴ bond lengths C–C, C–F, and C–H are equal to 1.34, 1.33, and 1.08 Å, respectively, all angles are equal to 120°.

of studies.^{4, 56} The calculated and experimental values of dipole moments of fluoroethylenes are summarised in Table 4. In the study,⁹⁴ which appeared at the same time as the monograph⁴, the HAM/3 method was used for the calculation of dipole moments of 97 molecules including fluoro-, 1,1-difluoro-, and trifluoro-ethylenes. However, as indicated by the authors of Ref. 94, this method overestimates the results compared to experiment.

In most cases, the CNDO method gives the dipole moments that are in better agreement with the experimental data than those obtained by the INDO, MNDO, HAM/3, and *ab initio* methods (see Table 4).

This holds for calculations of dipole moments of other fluorine-containing molecules, such as phosphorus fluorides^{4, 24, 105} and nitrogen fluorides.^{4, 106} However, it should be noted that calculations by molecular mechanics are more reliable than quantum-chemical calculations.

V. Conclusion

Quantum-chemical calculations on fluoroalkenes even within the isolated molecule approximation allow one to explain or predict many subtle features of their reactions. A more complete description can be achieved by determination of the structure and stability of possible intermediates⁵ (carbanions, radicals, *etc.*) and by calculation of potential energy surfaces of the reactions.

In calculations of physicochemical parameters of fluoroalkenes, semiempirical and non-empirical methods that make use of experimental molecular geometry lead to better results despite the rapid development of techniques of non-empirical calculations and determination of molecular geometry by a procedure of energy minimisation. Presumably, this is due to the fact that the geometrical parameters of fluoroalkenes (especially of non-symmetrical ones) first of all, bond angles calculated in such a way deviate strongly from the experimental values. Probably, an extension of the basis sets will finally allow one to overcome this problem.

Let us indicate some other problems that are still subjects of discussion, primarily the strength of the π -bonds in ethylene and fluoroethylenes. Our opinion on this point was outlined in the second section of this review.

Another unsolved problem was not considered here but it was extensively discussed in the monograph:⁴ the relative stability of geometrical non-halogenated isomers (in particular, 1,2-alkyl-substituted ones) and 1,2-dihaloethylenes. It was established experimentally that in the first case, the *trans*-isomer is more stable than the *cis*-isomer, whilst in the second case the situation is opposite. However, discussions on the probable reasons for the phenomenon still continue. We hope that all the problems mentioned will be successfully resolved in the near future.

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^e — *Pharm. Chem. J. (Engl. Transl.)*
^f — *Russ. J. Phys. Chem. (Engl. Transl.)*
^g — *Physics-Uspekhi (Engl. Transl.)*

Aliphatic nitro alcohols. Synthesis, chemical transformations and applications

M-G A Shvekhgeimer

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Abstract. The data on the synthesis, chemical transformations and practical use of aliphatic nitro alcohols published over the last 25 years are described systematically and analysed. The bibliography includes 316 references.

I. Introduction

Aliphatic nitro-derivatives attract considerable attention from researchers, because they are readily accessible and convenient starting compounds for the synthesis of organic derivatives of various classes. The diversity of chemical transformations of aliphatic nitro-compounds provided the basis for the paper 'Aliphatic nitro-compounds as perfect intermediates' published in 1979.¹ Nitro alcohols of the aliphatic series fully conform to this definition. Furthermore, since nitro alcohols contain the hydroxy group, their reactions can involve simultaneously several reaction sites; hence, the range of chemical transformations of these derivatives is even broader.

The results of numerous studies devoted to the chemistry of aliphatic nitro alcohols and published before 1972 have been surveyed quite comprehensively in reviews and monographs.^{2–4} However, no reviews describing systematically the data on the synthesis, transformations and practical use of aliphatic nitro alcohols obtained during the last 25 years have been published so far.

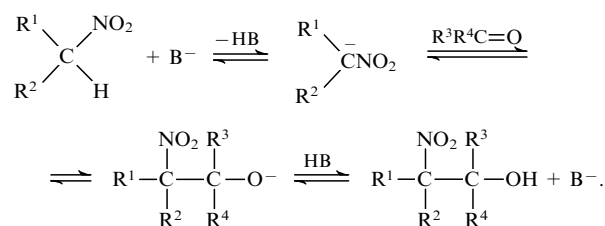
The purpose of this review is to fill this gap. We only briefly outline the preparation of nitro alcohols by nitroaldol condensation (Henry reaction), because its conditions have been described quite comprehensively in previous publications.^{3,4} The studies containing some novelty either in the procedure of condensation of nitro-compounds with carbonyl derivatives or in the use of the target compounds are discussed in greater detail. New data about other known methods for the synthesis of nitro alcohols and new information on their chemical transformations are presented. We also consider most of the studies that mention potential practical applications of these compounds, because this aspect has received little attention in earlier reviews.

M-G A Shvekhgeimer A N Kosygin Moscow State Textile Academy, ul. Malaya Kaluzhskaya 1, 117918 Moscow, Russian Federation.
Fax (7-095) 952 14 40. Tel. (7-095) 955 35 96

II. Methods for the synthesis of aliphatic nitro alcohols

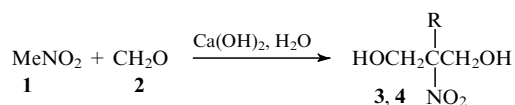
1. Nitroaldol condensation (the Henry reaction)

The Henry reaction consisting of condensation of aliphatic nitro-compounds with aldehydes or ketones is the most general method used widely for the synthesis of aliphatic nitro alcohols. The mechanism of this reaction has not yet been completely elucidated. It is generally accepted that nitroalkanes are condensed with carbonyl compounds according to the following scheme:



a. Reactions of nitromethane and its derivatives with aldehydes

The reaction of nitromethane **1** with formaldehyde **2** catalysed by $\text{Ca}(\text{OH})_2$ makes it possible to prepare both 2-nitropropane-1,3-diol **3**⁵ and 2-hydroxymethyl-2-nitropropane-1,3-diol **4**.⁶



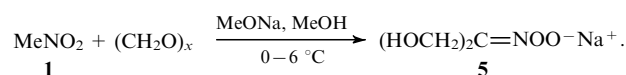
R = H (**3**); CH_2OH (**4**).

The diol **3** has also been prepared from the compounds **1** and **2** at 0–10 °C in the presence of sodium carbonate.⁷

The synthesis of **3** from **1** and an aqueous solution of formaldehyde or paraformaldehyde is carried out most often in the presence of alkali, NaOH ^{8–12} or KOH ,¹³ as catalysts.

Sodium and potassium hydroxides are also used as catalysts to synthesise the triol **4** from MeNO_2 and the aldehyde **2**.¹⁴

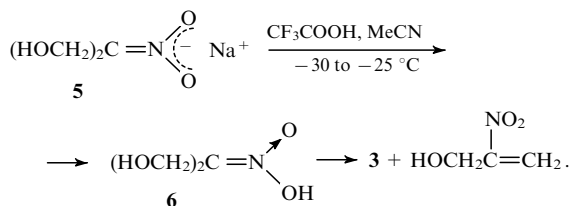
The condensation of nitromethane **1** with paraformaldehyde catalysed by sodium methoxide in methanol gives the sodium salt **5**.^{15, 16}



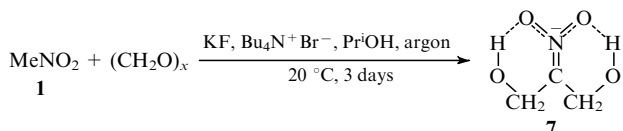
The condensation of MeNO_2 with paraform in the presence of $\text{Bu}_4\text{N}^+\text{Br}^-$ and KF under an inert atmosphere at 18–22 °C for

72 h affords a mixture of the diol **3** (yield 5% – 10%) and the triol **4** (yield 80% – 85%).¹⁶

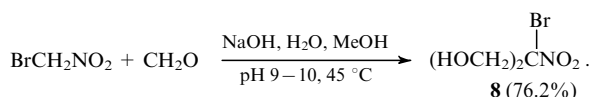
Treatment of the nitronate **5** with trifluoroacetic acid at low temperatures gives rise to the *aci*-form **6**, which is rapidly converted into the diol **3** and 2-nitroprop-2-en-1-ol.¹⁶



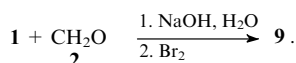
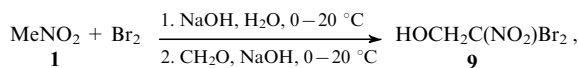
The diol **3** obtained from MeNO₂ and paraformaldehyde in the presence of KF and Bu₄N⁺Br[−] exists as a nitronate **7** stabilised by intramolecular interactions.¹⁷



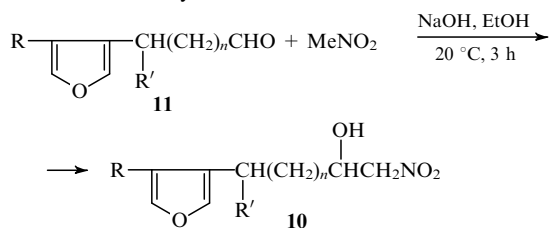
The condensation of bromonitromethane with formaldehyde **2** in the presence of NaOH in methanol gives the diol **8**.¹⁸



Treatment of nitromethane **1** with bromine in an alkaline medium followed by the reaction with formaldehyde in the presence of NaOH¹⁹ or the condensation of MeNO₂ with formaldehyde followed by treatment with bromine²⁰ afford the same compound **9**, the yield of which is up to 60%.



Nitro alcohols **10** containing a furyl substituent have been obtained by the condensation of MeNO₂ with aldehydes **11** in the presence of sodium hydroxide.^{21, 22}



R	R'	n	Yield (%)	Ref.
H	Me	2	49	21
Me	H	2	78	22
H	H	1	66–73	21, 22
H	Me	1	59–75	21, 22

The reaction of chiral complex **12** with nitromethane has been carried out in the presence of NaOH or KF and gave a mixture of diastereoisomeric nitro alcohols **13a** (1*S*,2*S*) and **13b** (1*S*,2*R*) in a high yield. It was found that the ratio of the resulting isomers varies over a wide range depending on the procedure used and the temperature (see Table 1).²³

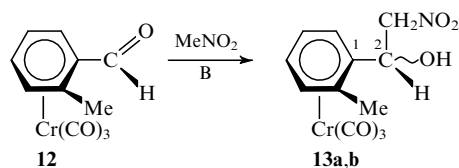
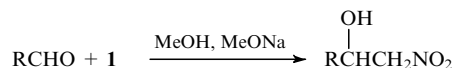


Table 1. Reaction conditions and the ratio of the products **13a** and **13b**.

Base	Temperature /°C	Yield (%)	Ratio 13a : 13b
NaOH	20	100	64 : 36
NaOH	−20	95	92 : 8
NaOH	−40	90	97 : 3
KF/Pr ⁱ OH	20	80	40 : 60
KF/Pr ⁱ OH	0	90	88 : 12

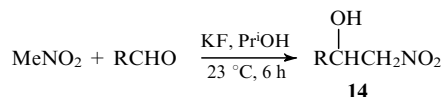
When nitromethane was treated with butyllithium (THF, HMPT, −90 to −60 °C), and the product was made to react with aldehyde **12** (THF, −70 to −60 °C, 1.5 h; −45 to −40 °C, 3 h), the isomer **13a** was obtained as the only product.²³

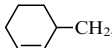
Sodium methoxide has been used as the catalyst in the reactions of nitromethane **1** with both aliphatic²⁴ and aromatic^{25, 26} aldehydes.



R = C₁₃H₂₇, 3-MeOC₆H₄, 4-PhCH₂OC₆H₄ (43%), Ph (59%), 4-MeC₆H₄ (50%), 4-ClC₆H₄ (63%).

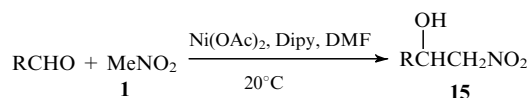
Potassium fluoride is an efficient catalyst of the reaction of MeNO₂ with aldehydes.²⁷

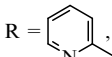


R = C₆H₁₃, C₇H₁₅, , .

Me₂C=CH(CH₂)₂C(Me)=CH(CH₂)₂.

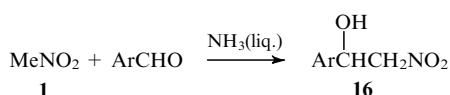
Study of the condensation of nitromethane with aldehydes carried out using IR and NMR spectroscopy has shown that the process occurs efficiently in DMF at 20 °C in the presence of a complex of nickel acetate with 2,2'-dipyridyl (Dipy) and gives nitro alcohols **15** in 81% – 87% yields.²⁸



R = , PhCH₂CH₂, 4-NO₂C₆H₄, 4-NCC₆H₄.

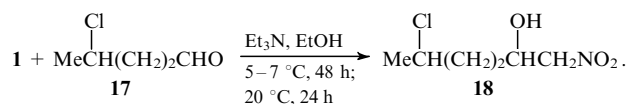
The reaction of MeNO₂ with acetaldehyde catalysed by Rh(PMe₃)₃Cl and carried out at 23 °C for 0.5 h affords 1-nitropropan-2-ol in 90% yield.²⁹

Nitromethane readily reacts with aromatic aldehydes in liquid ammonia giving rise to nitro alcohols **16** in good yields.³⁰



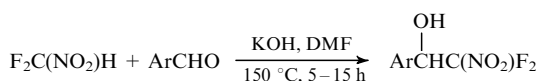
Ar = 2-H₂NC₆H₄ (53%), 3,4-(MeO)₂C₆H₃ (98%),
4-Br-3,4-(MeO)₂C₆H₂ (80%), 4-MeC₆H₄ (92%),
3,4-(CH₂O)₂C₆H₃ (83%), 4-BrC₆H₄ (93%), 3-BrC₆H₄ (91%),
3-ClC₆H₄ (75%), 4-MeOC₆H₄ (82%), 1-naphthyl (53%).

Triethylamine has been used as the catalyst in the reaction of MeNO₂ with 4-chloropentanal **17**; this resulted in the formation of nitro alcohol **18** in 42.5% yield.³¹



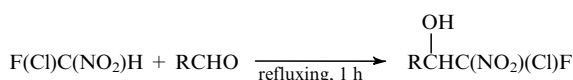
Difluoronitromethane condenses with trifluoroacetaldehyde on heating in the presence of sodium carbonate. The reaction gives 1,1,1,3,3-pentafluoro-3-nitropropan-2-ol in 38.5% yield.³²

The condensation of difluoronitromethane with aromatic aldehydes has been carried out using KOH as the catalyst.³³



Ar = 2-HOC₆H₄ (47%), 2-ClC₆H₄ (61%), 2-O₂NC₆H₄ (31.5%),
3-O₂NC₆H₄ (56%), 4-MeC₆H₄ (60%), 2,4-(MeO)₂C₆H₃ (53.5%).

It has been reported³⁴ that chlorofluoronitromethane reacts with aliphatic aldehydes without a catalyst.



R = H (83%), Me (55%), Et (73%), Pr (86%).

b. Reactions of nitromethane homologues and their derivatives with aldehydes

It should be noted that even when primary nitro-compounds are used, the synthesis usually affords products resulting from condensation with one formaldehyde molecule.

2-Nitrobutan-1-ol has been obtained in an almost quantitative yield by the reaction of 1-nitropropane with formaldehyde **2** in the presence of Ca(OH)₂ at 30 °C.³⁵

In a number of publications,^{36–39} synthesis of nitro alcohols **19** from nitroalkane **20** and formaldehyde catalysed by an alkali (NaOH or KOH) or by Amberlites IRA-410 has been described (Table 2).

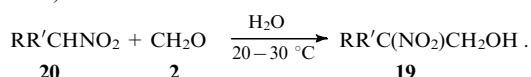


Table 2. Reaction conditions and yields of products in the condensation of the nitro-derivatives **20** with formaldehyde.

R	R'	Catalyst	Time /h	Yield (%)	Ref.
Bu ¹	Me	KOH	—	56.5	36
MeC(NO ₂) ₂ CH ₂	H	NaOH	48	—	37
Et	H	NaOH	5	see ^a	38
C ₁₂ H ₂₅ –C ₁₈ H ₃₇	H	Amberlites IRA-410	—	30	39

^a The reaction also yields EtC(NO₂)(CH₂OH)₂.

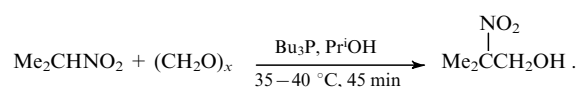
Condensation of nitrated butadiene or isoprene oligomers with formaldehyde in the presence of alkaline catalysts gave the corresponding nitro alcohols.⁴⁰

The process of condensation of nitroalkanes with formaldehyde has been optimised by experiment design.^{41,42} It was found that the reaction of paraformaldehyde with nitroethane in the presence of KOH occurs over a period of 2–3 min.⁴¹ The highest yields of nitro alcohols in the reaction between an aqueous solution of the aldehyde **2** and a mixture of C₁–C₄ nitroalkanes are attained when the process is carried out at an RNO₂:CH₂O ratio of 2.5:1 and at a temperature of 50–60 °C for 35–40 min.⁴²

The condensation of 2-nitropropane with paraformaldehyde in the presence of KF affords 2-methyl-2-nitropropan-1-ol in 86% yield.⁴³

2-Nitropropan-1-ol has been obtained in a yield of 62%–74% by the reaction of nitroethane with the aldehyde **2** in the presence of triethylamine.⁴⁴

Tributylphosphine has been used as the catalyst in the synthesis of 2-methyl-2-nitropropan-1-ol from 2-nitropropane and paraformaldehyde.⁴⁵



As a rule, high yields of nitro alcohols are achieved when formaldehyde is condensed with functionally substituted nitroalkanes **21** in the presence of NaOH (Table 3).^{46–48}

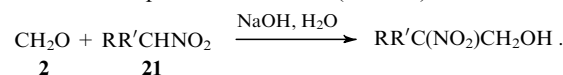


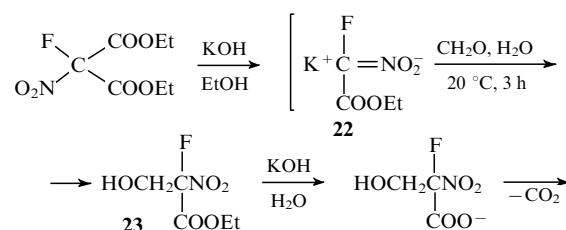
Table 3. Reaction conditions and yields of products for the condensation of the nitro-derivative **21** with formaldehyde.

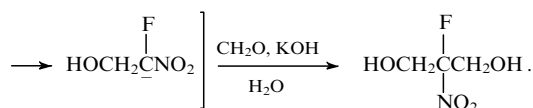
R	R'	Temperature /°C	Time /h	Yield (%)	Ref.
Et	F	76–80	2–3	80	46
Pr	F	76–80	2–3	87	46
Bu	F	76–80	2–3	86	46
C ₅ H ₁₁	F	76–80	2–3	79	46
C ₆ H ₁₃	F	76–80	2–3	83	46
C ₇ H ₁₅	F	76–80	2–3	85	46
C ₈ H ₁₇	F	76–80	2–3	81	46
F ₂ CCl	H	–10	—	—	47
COOEt	Me	20	2	60 ^a	48
COOEt	Et	20	2	67 ^a	48
COOEt	Pr	20	2	67 ^a	48
COOEt	Pr ⁱ	20	2	79 ^a	48
COOEt	Bu	20	2	82 ^a	48

^a Found for the acetylated product.

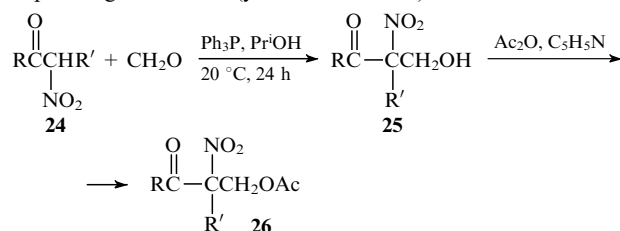
It can be seen from Table 3 that in the case of fluorine-containing nitroalkanes, approximately the same yields of nitro alcohols are obtained when the reaction is carried out with heating. On the other hand, homologues of ethyl nitroacetate readily react with formaldehyde at room temperature.

Treatment of diethyl fluoronitromalonate with potassium hydroxide gives rise to salt **22**, which reacts with the aldehyde **2** to yield compound **23**; the latter reacts with one more molecule of formaldehyde being thus converted into 2-fluoro-2-nitropropane-1,3-diol in a yield of more than 70%.⁴⁹



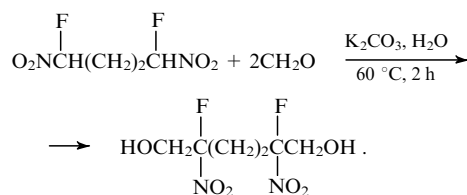


Reactions of aldehydes with nitro ketones carried out in the presence of strong bases are substantially complicated by side reactions of the initial compounds and reaction products. To avoid these problems and to obtain the products of nitroaldol condensation in higher yields, a convenient procedure was developed⁴⁸ according to which the condensation of nitro ketones with formaldehyde was carried out in the presence of triphenylphosphine. The intermediate alcohols were isolated as the corresponding acetates after treatment with acetic anhydride. Thus the reaction of nitro ketones **24** with formaldehyde in the presence of triphenylphosphine gave nitro alcohols **25**, which were treated *in situ* with acetic anhydride in the presence of pyridine to give the corresponding acetates **26** (yields 73%–91%).⁴⁸

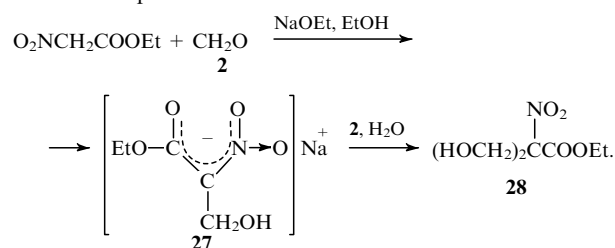


R, R' = Alk.

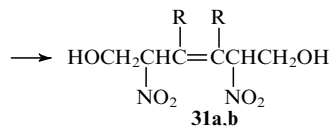
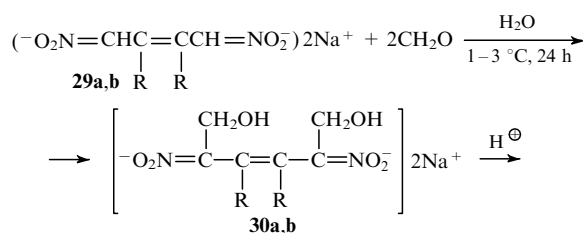
1,4-Difluoro-1,4-dinitrobutane reacts with two molecules of the aldehyde **2** in the presence of potassium carbonate giving 2,5-difluoro-2,5-dinitrohexane-1,6-diol in 75% yield.⁵⁰



Some researchers have synthesised nitro alcohols by reactions of formaldehyde with the salts of nitro-compounds prepared previously. The sodium salt **27** prepared from ethyl nitroacetate and the aldehyde **2** under the action of sodium ethoxide has been made to react with a second molecule of **2**; this resulted in the synthesis of compound **28**.⁵¹



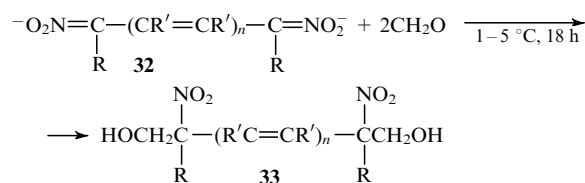
The reaction of bis-salts **29** with the aldehyde **2** at 1–3 °C gave bis-salts **30**, which were converted into the corresponding diols **31**. Thus treatment of the salt **30b** with $\text{HONH}_2 \cdot \text{HCl}$ in water at pH 4 gives the diol **31b** in 54.5% yield; treatment of the salt **30a** with 18% hydrochloric acid or with 75% acetic acid affords **31a** in a yield of 9.2% or 6.6%, respectively.⁵²



R = H (a), Me (b).

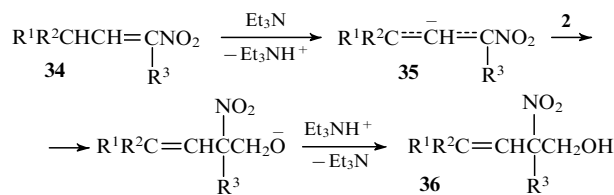
Under the same conditions, the bis-salt $(-\text{O}_2\text{N}=\text{CHCH}_2\text{CH}_2\text{CH}=\text{NO}_2)_2 2\text{Na}^+$ reacts with two molecules of CH_2O and is thus converted into the salt of bis-hydroxymethyl derivative $[-\text{O}_2\text{N}=\text{C}(\text{CH}_2\text{OH})\text{CH}_2\text{CH}_2\text{C}(\text{CH}_2\text{OH})=\text{NO}_2] 2\text{Na}^+$ in 93.6% yield.⁵²

Whereas the anions of non-conjugated mononitro-derivatives react with formaldehyde only at pH > 7, the dianions of conjugated dinitroalkanes **32** are able to react with the aldehyde **2** giving rise to diols **33** both at pH > 7 (yields 70%–90%) and at pH = 4 (yields 40%–70%).⁵³



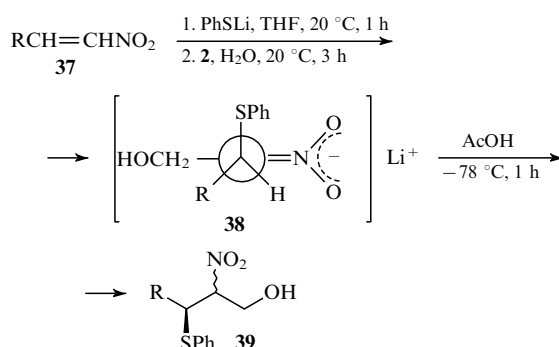
n = 0, R = H; n = 1: R = H, R' = H, Me.

The reaction of conjugated nitroalkenes **34** with the aldehyde **2** in the presence of Et_3N in acetonitrile starts with the formation of allylic anions **35**, which are attacked by the aldehyde at the carbon atom carrying the nitro group to give nitro alcohols **36** (yields 60%–94%).⁵⁴



R¹ = H, Bu, PhCH₂; R² = H; R³ = Me, Et, C₇H₁₅, (CH₂)₂COOMe.

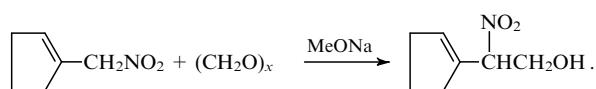
Nitroalkenes **37** react successively with lithium phenylthiolate and the aldehyde **2** to afford salts of *aci*-forms **38**, which are converted, on treatment with acetic acid, into mixtures of *erythro*- and *threo*-isomers (in a ratio ranging from 86:14 to 93:7) of nitro alcohols **39** (yields 57%–91%).⁵⁵



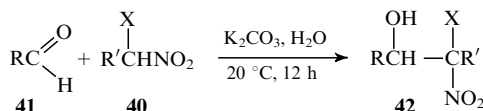
R = Me, Et, Pr, Prⁱ, Bu, C₅H₁₁, Ph, PhCH₂CH₂.

The reaction of the nitroalkenes **37** with PhSH and CH_2O in the presence of bases yields mixtures of the *erythro*- and *threo*-isomers of **39** (1:1) together with nitro diols $\text{RCH}(\text{SPh})-\text{C}(\text{CH}_2\text{OH})\text{NO}_2$.⁵⁵

Sodium methoxide has been used as the catalyst in the reaction of 1-(nitromethyl)cyclopentene with paraformaldehyde.⁵⁶



1-Halo-1-nitroalkanes **40** smoothly react with aldehydes **41** in the presence of potassium carbonate at 20 °C, and this leads to halo-substituted nitro alcohols **42** (yields 37%–75%).⁵⁷



R = Alk, CCl₃; R' = H, Cl, Br, Me, Et; X = Cl, Br.

Several nitro-compounds **43** have been condensed with aliphatic or arylalkyl aldehydes **44** in the presence of sodium hydroxide in methanol or ethanol; this resulted in the formation of *threo*-isomers of nitro alcohols **45**, as a rule, in good yields.^{59, 60} However, the reactions of butyraldehyde with nitrobutane (**43**, R¹ = Pr) and nitrooctane (R¹ = C₇H₁₅) gave the corresponding nitro alcohols in yields of 26% and 30% (Table 4).⁶⁰ When the same nitro-compounds **43** were made to react with aldehydes in the presence of KF, the *erythro*-isomers of **45** were obtained.^{59, 60} In some cases, water was added to the reaction mixture.⁶⁰

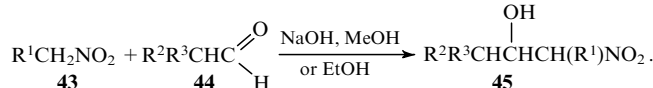
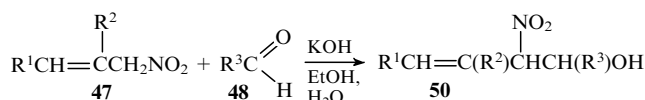
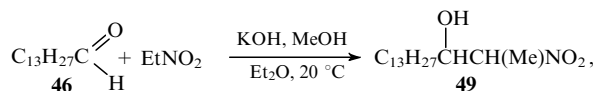


Table 4. Reaction conditions and yields of the compounds **45**.

R ²	R ³	R ¹	Temperature /°C	Time /h	Yield (%)	Ref.
Me	H	Cl(CH ₂) ₃	5–10	—	65 ^a	58
Ph	H	H	30–35	45	67 ^a	59
Ph	H	Me	30–35	45	69 ^a	59
Ph	H	Et	30–35	45	65 ^a	59
H	H	Ph	30–35	45	63 ^a	59
Me	H	Ph	30–35	45	58 ^a	59
Ph	H	Ph	30–35	45	60 ^a	59
Me	Me	Ph	30–35	45	58 ^a	59
H	Ph	Ph	20	144	85 ^a	59
Me	H	Et	38	65	80 ^b	60
Et	H	Et	38	65	63 ^b	60
Bu	H	Me	38	65	52 ^b	60
Bu	H	Et	38	65	58 ^b	60
Et	H	C ₇ H ₁₅	38	65	30 ^b	60
C ₉ H ₁₉	H	Me	38	65	61 ^b	60
Bu	H	C ₇ H ₁₅	38	65	70 ^b	60
Me	Me	Et	38	65	54 ^b	60
Et	H	Pr ⁱ	38	65	26 ^b	60

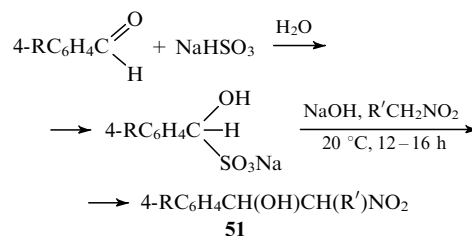
^a (R*, R*) *threo*-Isomers are formed; if the reaction is carried out in the presence of KF, the nitro alcohols **45** are mostly formed as (R*, S*) *erythro*-isomers; ^b water was added to the reaction mixture.

Potassium hydroxide has been used as the catalyst in the reactions of myristaldehyde **46** with nitroethane⁶¹ and of unsaturated nitro-compounds **47** with aldehydes **48**;⁶² these reactions gave nitro alcohols **49** and **50** in 64% and 30%–65% yields, respectively.



R¹, R² = H, Me; R³ = Me, Et, Pr, Prⁱ.

A method for the synthesis of nitro alcohols **51** by condensation of aromatic aldehydes with nitroalkanes has been patented.⁶³ According to this method, aldehydes are treated first with sodium hydrogensulfite and then with nitroalkanes in the presence of aqueous sodium hydroxide at 20 °C.⁶³



R = Bu^t, Bu^s; R' = Me, Et.

In the synthesis of 1,1,1-trichloro-3-nitrobutan-2-ol (yield 30%), the initial chloral was also converted first into the hydrogensulfite derivative, and the latter was made to react with nitroethane in the presence of aqueous sodium hydroxide at 20 °C for 12 h.⁶⁴

In the same study,⁶⁴ condensation of primary or secondary nitroalkanes with aliphatic or aromatic aldehydes at 20 °C in the presence of NaHCO₃, K₂CO₃ or NaOH was studied. The yields of the target nitro alcohols **52** were found to depend crucially on the nature of the initial aldehyde (Table 5).

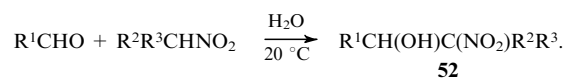
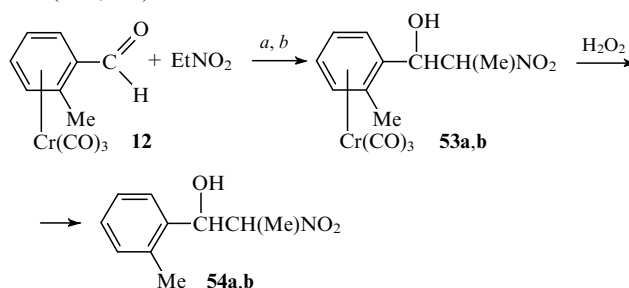


Table 5. Reaction conditions and yields of the nitro alcohols **52**.

R ¹	R ²	R ³	Catalyst	Time /h	Yield (%)
Me	Me	H	K ₂ CO ₃	5	54
Pr ⁱ	Me	H	K ₂ CO ₃	5	40
CF ₃	Me	H	NaOH	5	8.2
4-O ₂ NC ₆ H ₄	Et	H	NaHCO ₃	5	16.3
4-O ₂ NC ₆ H ₄	Me	Me	K ₂ CO ₃	5	—
Br ₃ C	Me	H	K ₂ CO ₃	0.5	10

Synthesis of 2-nitro-1-phenylpropan-1-ol from benzaldehyde and nitroethane under mild conditions in the presence of bases in DMSO or DMF has been reported.⁶⁵

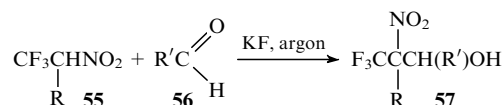
Condensation of the complex **12** with nitroethane in the presence of NaOH yields a mixture of diastereoisomers **53a,b**; on treatment with hydrogen peroxide, this mixture is converted into a mixture of diastereoisomeric nitro alcohols **54a** (1R*, 2R*) and **54b** (1R*, 2S*) in a ratio of 36 : 64.²³



(a) NaOH, EtOH, H₂O, –40 °C, 0.5 h; (b) NH₄Cl, H₂O.

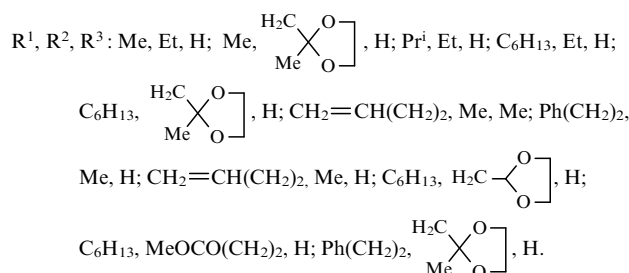
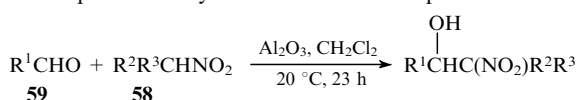
The reaction of **12** with the nitronate prepared previously from nitroethane resulted in the formation of a mixture of diastereoisomers **54a,b** in a ratio of 77 : 23.²³

Nitro-compounds **55** containing a CF₃ group condense with aldehydes **56** in the presence of potassium fluoride in isopropyl alcohol or without a solvent to give nitro alcohols **57**.⁶⁶

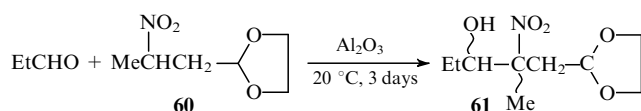


R	R'	Solvent	Yield (%)
H	Pr	Pr ⁱ OH	71
H	Pr	—	73
H	C ₆ H ₁₃	Pr ⁱ OH	65
H	C ₆ H ₁₃	—	71
H	Ph(CH ₂) ₂	—	83
H	Me(Ph)CH	—	46
H	Ph	Pr ⁱ OH	26
H	Ph	—	9.5
Me	Pr	Pr ⁱ OH	54
Me	Pr	—	35
Me	C ₆ H ₁₃	Pr ⁱ OH	54
Me	PhCH ₂ CH ₂	—	40

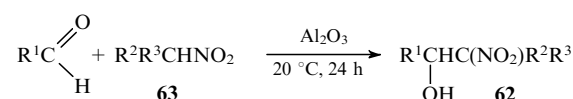
During the last 10–15 years, neutral alumina (Brockmann activity I) has been used as a catalyst in the Henry reaction. In the presence of this catalyst, nitro-compounds **58** condense with various aliphatic aldehydes **59** at ambient temperature.⁶⁷



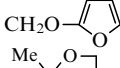
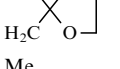
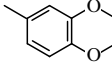
The reaction of nitro-compound **60** with propanal carried out in the presence of Al₂O₃ at 20 °C affords condensation product **61** as a mixture of *erythro*- and *threo*-isomers in a 54 : 46 ratio and in 22% overall yield.⁶⁸



Nitro alcohols **62** have been prepared by the reactions of primary or secondary nitro-compounds **63** with aldehydes in the presence of neutral Al₂O₃ without solvents.^{66, 69}

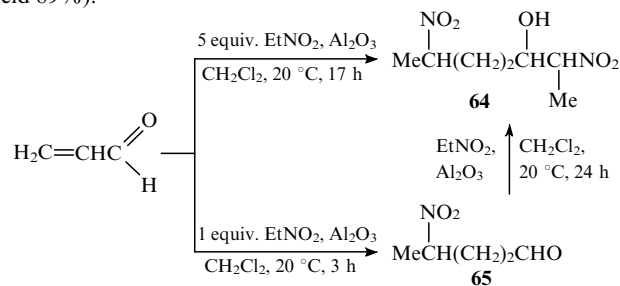


R ¹	R ²	R ³	Yield (%)	Ref.
Me	Et	H	80	69
Et	Me	H	71	69
Et	(CH ₂) ₂ COOMe	H	84	69
Pr ⁱ	MeCH(OH)	H	69	69
	Me	H	75	69

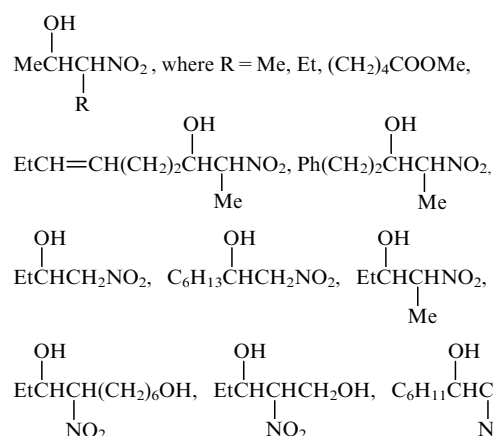
R ¹	R ²	R ³	Yield (%)	Ref.
C ₆ H ₁₃		H	86	69
C ₆ H ₁₃		H	86	69
Ph(CH ₂) ₂	Me	H	71	69
Ph(CH ₂) ₂	Me	Me	69	69
Ph(CH ₂) ₂	see ^a	H	82	69
See ^b	Me	H	78	69
Pr	CF ₃	H	73	66
Ph	CF ₃	H	9.5	66
	CF ₃	H	3	66
Pr	CF ₃	Me	33	66

^a R² = Me(CH₂)₃OCH(Me)OCH₂; ^b R¹ = Me₂C=CH(CH₂)₂CH(-Me)CH₂.

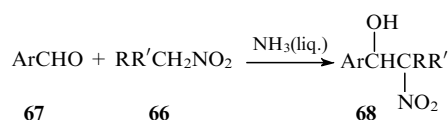
The product **64** resulting from interaction of acrolein with two molecules of nitroethane has been synthesised by two procedures: by the reaction of the aldehyde with a fivefold excess of EtNO₂ (yield 39%) or by the addition of one molecule of EtNO₂ to the double bond of the aldehyde followed by condensation of the resulting adduct **65** with a second molecule of the nitro-derivative (yield 89%).⁷⁰



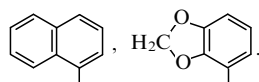
It has been reported⁷¹ that the following nitro alcohols are formed as mixtures of *erythro*- and *threo*-isomers upon reaction of the corresponding aldehydes with nitro-compounds in the presence of Al₂O₃ (Brockmann activity I) at 20 °C for 23 h:



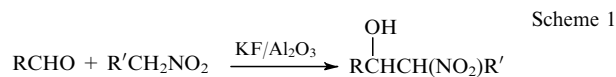
It can be seen from published results^{66, 69} that the condensation of nitro-compounds with aromatic aldehydes in the presence of KF or Al₂O₃ gives the corresponding nitro alcohols in low yields. When the reactions of nitroalkanes **66** with aromatic aldehydes **67** are conducted³⁰ in liquid ammonia, the corresponding nitro alcohols **68** are formed in 53%–98% yields.



R = H, Me; R' = H, Me; Ar = 3-ClC₆H₄, 4-ClC₆H₄, 3-BrC₆H₄, 4-BrC₆H₄, 4-MeOC₆H₄, 4-MeC₆H₄, 2-O₂NC₆H₄, 2-H₂NC₆H₄, 3,4-(MeO)₂C₆H₃, 6-Br-3,4-(MeO)₂C₆H₂,



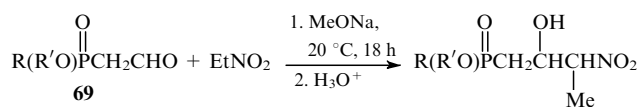
Nitro alcohols have been obtained in good yields by the condensation of nitromethane, nitroethane or 1-nitropropane with the corresponding aliphatic, aromatic or heterocyclic aldehydes in the presence of KF supported on Al₂O₃ (Scheme 1).⁷²



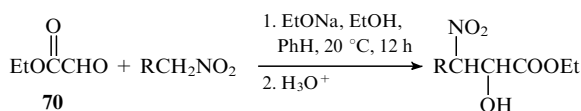
R	R'	Time /h	Yield (%)
Et	H	5	71
Pr ⁱ	Me	5	75
Et	Me	5	75
Pr ⁱ	Et	5	78
Me	Et	5	77
Bu	Me	5	62
See ^a	Me	5	79
See ^a	H	5	50
Ph	Et	6	55
	Me	15(N ₂)	77

^a R = Me₂C=CH(CH₂)₂CH(Me)CH₂.

Sodium methoxide⁷³ and sodium ethoxide⁷⁴ have been used as catalysts in the nitroaldol condensation of primary nitroalkanes with functionally substituted aldehydes **69** and **70**.

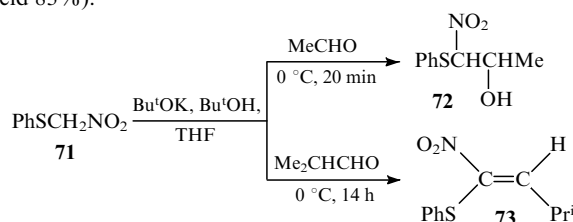


R, R' (yield, %): MeO, Me (66); EtO, Et (60); PrⁱO, Prⁱ (50); Bu, Prⁱ (46); MeCH=CHCH₂, Prⁱ (20); MeCH=CHCH₂, Pr (20).

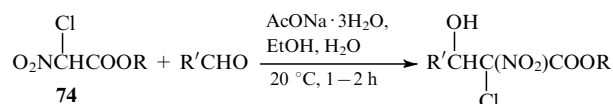


R = Me (52%), Et (51.5%), Pr (54%), Prⁱ (28%), Ph (65%).

The reaction of sulfide **71** with acetaldehyde carried out in the presence of potassium *tert*-butoxide (0 °C, 20 min) gives nitro alcohol **72** (yield 95%), whereas the reaction with isobutyraldehyde carried out under the same conditions affords nitroalkene **73** (yield 83%).⁷⁵

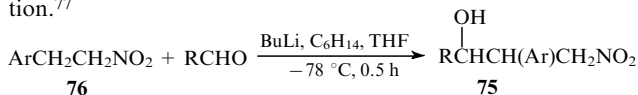


Esters of chloronitroacetic acid **74** react with aliphatic aldehydes in the presence of sodium acetate.⁷⁶



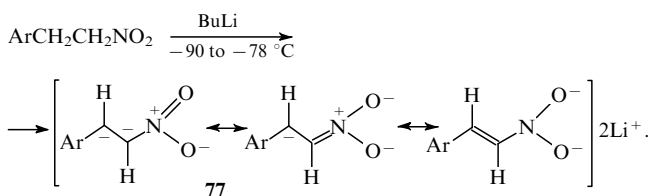
R, R' (yield, %): Me, Me (65); Me, Et (92); Et, Me (98); Et, Et (45); PhCH₂, H (71).

The reaction of nitro-compounds **76** with aldehydes in the presence of butyllithium led to γ -nitro alcohols **75** in 75%–80% yields instead of the normal products of nitroaldol condensation.⁷⁷



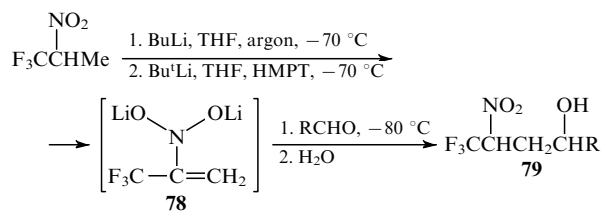
Ar, R: 4-ClC₆H₄, Et; Ph, Ph; Ph, 4-ClC₆H₄.

This unusual reaction pathway was explained⁷⁷ by the fact that at low temperatures nitro-compounds **76** are doubly deprotonated at the α - and β -positions with respect to the nitro group to give dilithio-derivatives **77**.



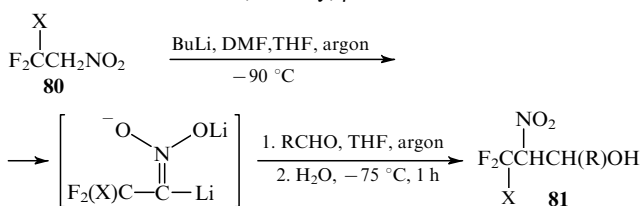
The formation of γ -nitro alcohols in the condensation of nitro-compounds with aldehydes in the presence of BuLi is not a specific feature peculiar only to 2-arylnitroethanes. It was found that γ -nitro alcohols are also formed in the reactions of some secondary nitro-compounds with aldehydes in the presence of BuLi or Bu^tLi. For example, 3-nitro-1-phenylbutan-1-ol was synthesised in 50% yield by the reaction of 2-nitropropane with benzaldehyde in the presence of BuLi and Bu^tLi.⁷⁷

The condensation of 1,1,1-trifluoro-2-nitropropane with aliphatic and aromatic aldehydes in the presence of BuLi and Bu^tLi occurs *via* unusual doubly deprotonated products **78** and yields γ -nitro alcohols **79**.⁶⁷



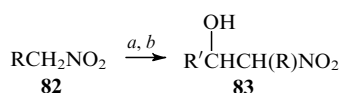
R = C₆H₁₃ (12%), PhCH₂CH₂ (9%), Ph (21%).

Primary nitro-compounds **80**, doubly deprotonated upon treatment with BuLi, react with aldehydes to give products of nitroaldol condensation, namely, β -nitro alcohols **81**.⁶⁶

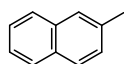


X, R (yield, %): F, Bu^t (90); H, Bu^t (40); F, Ph (67); H, Ph (32); H, 4-O₂NC₆H₄ (52); F, 3,4-(CH₂O)₂C₆H₃ (40).

The reactions of primary nitro-compounds **82** with aldehydes in the presence of butyllithium and TiCl₃(OPrⁱ) at nitroalkane: aldehyde ratios of 1:1 or 2:1 have been studied in detail. This process was found to afford β -nitro alcohols **83** as mixtures of *erythro*- and *threo*-isomers.⁷⁸



R = Et; R' = 4-O₂NC₆H₄, Ph, 4-MeOC₆H₄, 2-CF₃C₆H₄, 4-MeOCOC₆H₄,



, PhCH=CH, Bu, C₅H₁₁, Bu^t, COOMe;

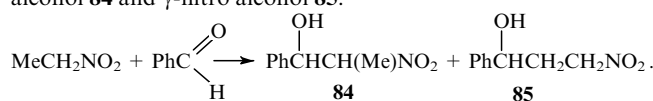
R = Bu; R' = 4-O₂NC₆H₄.

(a) BuLi, THF, -78 °C, 15 min;

(b) R'CHO, TiCl₃(OPrⁱ), CH₂Cl₂, -78 °C, 1 h; 20 °C, 3.5 h.

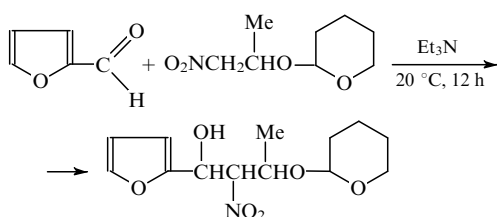
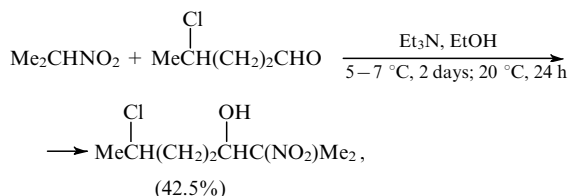
The ratio of the *erythro*- and *threo*-isomers formed varies over a wide range. For a nitroalkane:aldehyde ratio of 1:1, it varies from 3.9:1 (in the case of R' = 4-O₂NC₆H₄, R = Bu) to 11.2:1 (in the case of R' = MeOOC₆H₄, R = Et); for a nitroalkane:aldehyde ratio of 2:1, it ranges from 2:1 (R' = COOMe, R = Et) to 8:1 (R' = PhCH=CH, R = Et).⁷⁸

The reaction of nitroethane with benzaldehyde in the presence of butyllithium has been studied systematically using two approaches.⁷⁹ According to one of them, EtNO₂ was treated with BuLi in THF and HMPT at various temperatures and various HMPT/BuLi ratios, and after that, the aldehyde was added at a temperature between -78 and -35 °C, and the reaction mixture was quenched with acetic acid (procedure A). The second approach included treatment of the aldehyde with butyllithium in THF and HMPT at -90 °C and subsequent addition of the nitro-compound at various temperatures and various HMPT/BuLi ratios followed by acidification of the reaction mixture (procedure B). It was found that in both cases, the reaction resulted in the formation of a mixture of β-nitro alcohol **84** and γ-nitro alcohol **85**.



When the reaction was carried out by procedure A at an HMPT/BuLi ratio of 2.6 and at a temperature of -90 to -25 °C, the yields of the compound **84** varied in the range 68.8%–11.3%. In the absence of HMPT, the yield of **84** was 47.3%, and that of the compound **85** was 3% (at -90 °C). At higher temperatures, the yield of **85** increased, whereas the overall yield decreased. The reaction carried out by procedure B without HMPA afforded only the nitro alcohol **84** (yield 56.8%). At HMPT/BuLi ratios greater than 2, the nitro alcohol **85** was formed as the major product (yields 50.8%–72.6%, the yields of **84** formed simultaneously being 3.8%–10.6%).

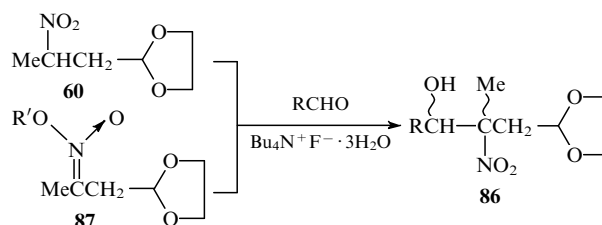
Triethylamine has been used as the catalyst in the condensation of nitro-compounds with both aliphatic³⁰ and heteroaromatic⁸⁰ aldehydes.



Mixtures of *erythro*- and *threo*-isomers of nitro alcohols **86** are formed when the nitro compound **60** or its derivative **87** is made to react with acetaldehyde or propionaldehyde in the presence of tetrabutylammonium fluoride trihydrate (Table 6).⁶⁹

Table 6. Reaction conditions, yields and isomeric ratios of the nitro alcohols **86**.

R	Nitro-compound	Temperature /°C	Time /h	Yield (%)	Ratio <i>erythro</i> : <i>threo</i>
Me	87	-78–20	15.5	20	56:44
Me	87	0	2.3	89	55:45
Et	87	0	0.75	74	54:46
Me	60	0–6	23	52	62:38

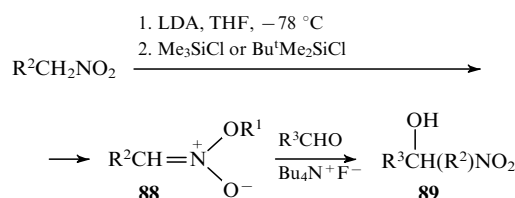


R' = Bu^tMe₂Si.

In a study on the development of the synthesis of β-amino alcohols according to the scheme

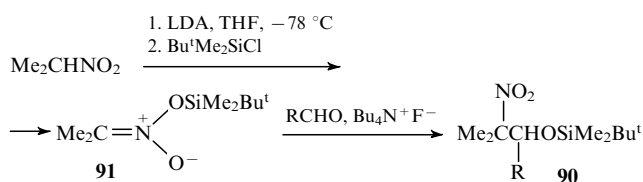


it was found^{81–83} that the nitroaldol condensation of nitroalkanes with molecular weights much greater than that of nitromethane in the presence of conventional catalysts gives β-nitro alcohols in low yields. In order to increase the yields of the target compounds, the researchers studied the nitroaldol condensation of aldehydes with silyl ethers **88**, which were obtained from nitroalkanes and chlorotrimethylsilane or *tert*-butyl(chloro)dimethylsilane under the action of Pr₂NLi (LDA), in the presence of tetrabutylammonium fluoride. This resulted in the formation of nitro alcohol derivatives **89** in good or high yields.



R¹ = SiMe₃, SiMe₂Bu^t; R² = C₅H₁₁, R³ = C₆H₁₃ (71–80%);
 R² = C₅H₁₁, R³ = Bu^t (57%); R² = C₅H₁₁, R³ = Ph (75–83%);
 R² = C₅H₁₁, R³ = 4-MeOC₆H₄ (70%); R² = C₅H₁₁,
 R³ = 4-O₂NC₆H₁₁ (91%); R² = Et, R³ = Pr (82%,
erythro:*threo* = 20:1); R² = Et, R³ = Pr;
 R² = Me, R³ = C₅H₁₁ (*erythro*:*threo* = 20:1); R² = Et,
 R³ = C₅H₁₁ (*erythro*:*threo* = 20:1); R² = C₇H₁₅, R³ = Pr
 (*erythro*:*threo* = 20:1); R² = Me, R³ = C₁₀H₂₁; R² = Me,
 R³ = C₉H₁₉; R² = Et, R³ = Ph (*erythro*:*threo* = 3.5:1).

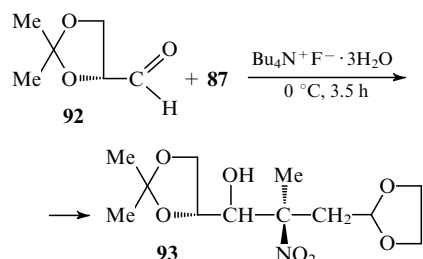
Silyl ethers of nitro alcohols **90** have been prepared in 30%–40% yields by treatment of 2-nitropropane derivative **91** with aldehydes.⁸¹



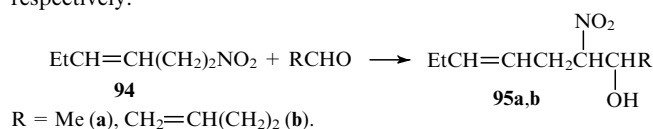
R = C₆H₁₃, Bu^t, Ph, 4-MeOC₆H₄, 4-O₂NC₆H₄.

The reaction of the silyl ether **87** with aldehyde **92** gives rise to four isomeric nitro alcohols (overall yield 59%, isomer ratio

58:28:12:2). The isomer **93** was isolated from this mixture in a pure state in a yield of 34%.⁶⁹

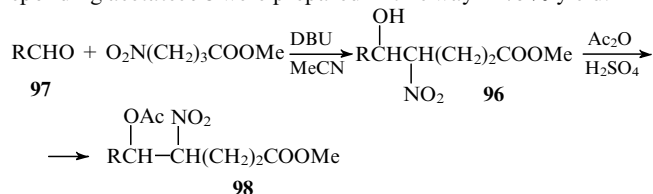


The condensation of 1-nitrohex-3-ene **94** with aldehydes catalysed by Amberlyst A-21 occurs successfully at 20 °C; this gives nitro alcohols **95a,b**, their yields being 74% and 71%, respectively.⁸⁴



The reactions of nitroalkanes RCH₂CH(R')NO₂ with 4-ethoxybenzaldehyde carried out in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) give rise to the corresponding nitro alcohols 4-EtOC₆H₄CH(OH)C(R')(NO₂)CH₂R (R, R': H, H; H, Me; Me, H).⁸⁵

Nitro alcohols **96** resulting from the condensation of aldehydes **97** with methyl 4-nitrobutyrate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) have been treated *in situ* with acetic anhydride in the presence of sulfuric acid; the corresponding acetates **98** were prepared in this way in 75% yield.⁸⁶



The reaction of nitroalkenes MeCH(R)CH=CHNO₂ (R = H, Me) with propionaldehyde in the presence of DBN is accompanied by isomerisation of the double bond in the nitroalkene and gives unsaturated β-nitro alcohols EtCH(OH)CH(NO₂)–CH=C(Me)R (R = H, Me).⁵⁴

To synthesise nitro alcohols **99**, a mixture of nitroethane and aldehydes was treated with a mixed acetal of dimethylketene in the presence of [Rh(C₅Me₅)Cl]₂(μ-Cl)₂ and then with tetrabutylammonium fluoride. The reaction conditions and the product yields are listed in Table 7.⁸⁷

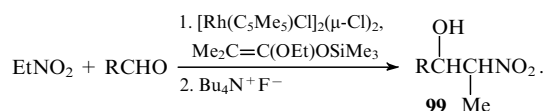


Table 7. Reaction conditions and yields of the nitro alcohols **99**.

R	Solvent	Number of equivalents of EtNO ₂	Yield (%)
Ph	CH ₂ Cl ₂	5	—
Ph	THF	10	16
Ph	THF	43	82 ^a
PhCH=CH	THF	43	48
PhCH ₂ CH ₂	THF	43	54

^a The ratio *syn:anti* = 39:61.

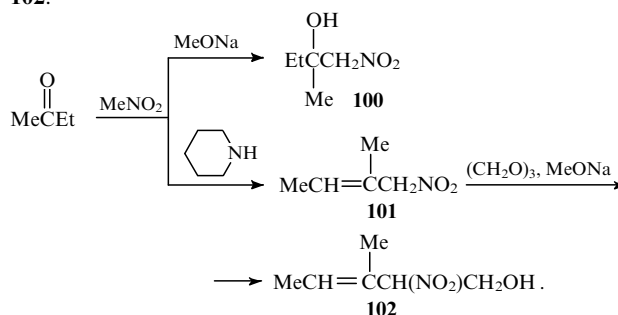
c. Reactions of nitroalkanes with ketones

Reactions of nitro-compounds with ketones have been much less studied than the nitroaldol condensation involving aldehydes. This is due to some features peculiar to the reactions with ketones. These reactions are often accompanied by spontaneous dehydration of the adducts yielding nitroalkenes, which enter into the Michael reaction with the initial nitro-derivatives.

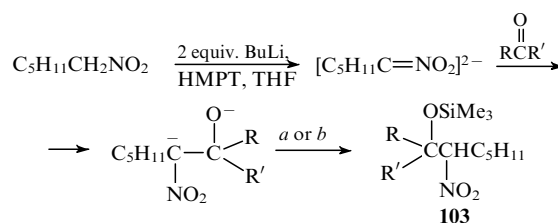
Only few studies dealing with the reactions of nitro-compounds with ketones have been published over the last 25 years.

The reaction of phenylnitromethane with acetone in the presence of sodium methoxide at 20 °C for 50 h gave the corresponding nitro alcohol, 2-methyl-1-nitro-1-phenylpropan-2-ol, in a yield of only 10%.⁵⁹

When nitromethane **1** was made to react with ethyl methyl ketone in the presence of sodium methoxide, the product of nitroaldol condensation, 2-methyl-1-nitrobutan-2-ol **100**, was obtained. When this reaction was carried out in the presence of piperidine, 2-methyl-1-nitrobut-2-ene **101** was isolated from the reaction mixture. In the presence of sodium methoxide, **101** reacted with 1,3,5-trioxane being thus converted into nitro alcohol **102**.⁵⁶



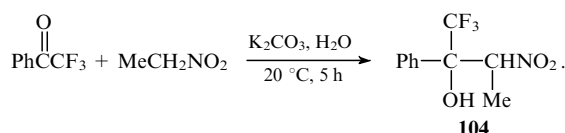
The method for the synthesis of β-nitro alcohols from aldehydes and nitroalkanes developed by Colvin *et al.*^{81,82} and described above proved to be inapplicable to nitroaldol condensation between nitroalkanes and ketones. Therefore, a modified procedure for the synthesis of silyl ethers of β-nitro alcohols **103** from 1-nitrohexane and ketones RCOR' was proposed.⁸¹



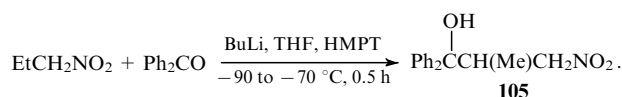
R = R' = Ph, R, R' = (CH₂)₅;

(a) Me₃SiCl; (b) 1. AcOH; 2. Me₃SiCl–(Me₃Si)₂NH.

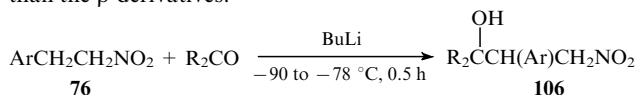
When trifluoroacetophenone was treated with nitroethane in the presence of an aqueous solution of potassium carbonate for 5 h, nitro alcohol **104** was formed.⁶



γ-Nitro alcohol **105** was synthesised in 77% yield by condensation of 1-nitropropane with benzophenone in the presence of butyllithium in THF and HMPT at low temperatures.⁷⁹



The reactions of 2-arylnitroethanes **76** with ketones in the presence of butyllithium also afford γ -nitro alcohols **106** rather than the β -derivatives.⁷⁷

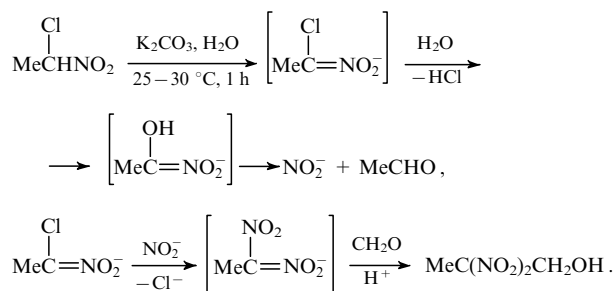


R, Ar (yield, %): Me, Ph (70); Ph, 4-ClC₆H₄ (67); (CH₂)₅, Ph (69).

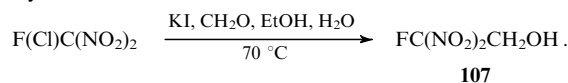
d. Reactions of 1,1-dinitro- and 1,1,1-trinitro-derivatives with aldehydes

In a study dealing with the kinetics and mechanism of the condensation of acetaldehyde with 1,1-dinitroethane or with methyl 2-nitropropionate in DMSO,⁸⁸ it has been found that the addition of the anions derived from nitro-compounds to the carbonyl group of the aldehyde is the rate-determining step of this reaction. The researchers determined the equilibrium and rate constants of the process, which characterise the basicity and nucleophilicity of the nitronate anions. It was found that there exists a normal correlation between the basicity and nucleophilicity of the two anions in DMSO: the more basic anion reacts faster than the less basic one. In the presence of alkali, 1,1-dinitroethane reacts with an aqueous solution of formaldehyde to give 2,2-dinitropropan-1-ol in 80% yield.⁸⁹

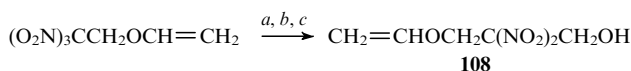
Condensation of the potassium salt of 1,1-dinitroethane, formed upon treatment of 1-chloro-1-nitroethane with an aqueous solution of potassium carbonate for 1 h at 25–30 °C, with excess formaldehyde resulted in the formation of 2,2-dinitropropan-1-ol in 20%–25% yield.⁹⁰



2-Fluoro-2,2-dinitroethanol **107** was prepared by the reaction of chlorofluorodinitromethane with potassium iodide and formaldehyde at 70 °C.⁹¹

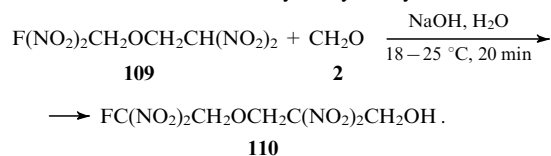


2,2-Dinitro-3-vinylxypropan-1-ol is formed in 19.2% yield when 2,2,2-trinitroethyl vinyl ether is treated successively with alkaline hydrogen peroxide and with formaldehyde in the presence of sodium hydroxide, and the reaction mixture is then acidified by HCl to pH 2.⁹²

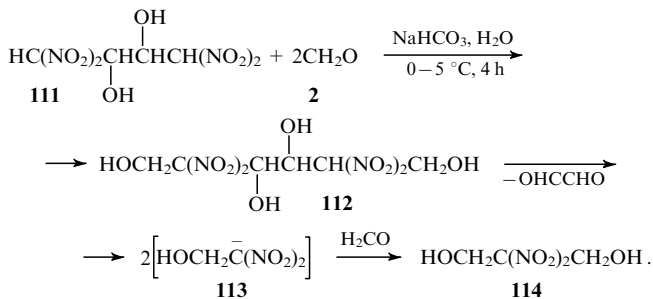


(a) H₂O₂, NaOH, H₂O, MeOH, –4 °C; (b) CH₂O, H₂O; (c) HCl, MeOH, 40 °C.

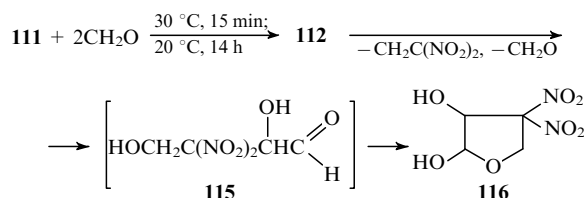
The ether **109** containing an HC(NO₂)₂ group reacts readily and rapidly with formaldehyde in the presence of sodium hydroxide and is thus converted into hydroxymethyl derivative **110**.⁹³



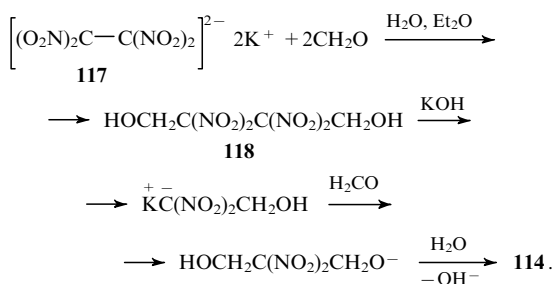
Compound **111** containing two HC(NO₂)₂ groups reacts with two molecules of formaldehyde in the presence of sodium hydrogencarbonate to give tetrol **112**; under the action of a base, it eliminates a glyoxal molecule giving rise to salt **113**. The latter reacts with the aldehyde **2** to give 2,2-dinitropropane-1,3-diol **114** in an overall yield of 74%.⁹⁴



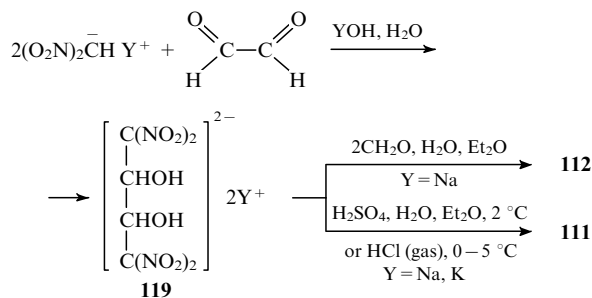
The compound **111** can also react with formaldehyde without a catalyst yielding the tetrol **112**, which eliminates a dinitromethane molecule and CH₂O even at 20–30 °C being thus converted into aldehyde **115**, which cyclises *in situ* into tetrahydrofuran derivative **116**.⁹⁴



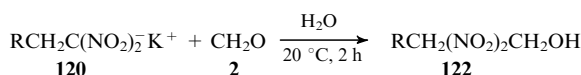
When the dipotassium salt of 1,1,2,2-tetranitroethane **117** is made to react with formaldehyde, this gives tetranitrodiol **118**, which is cleaved on treatment with KOH to give 2,2-dinitroethane salt. This salt reacts with the aldehyde **2** yielding diol **114**.⁹⁵



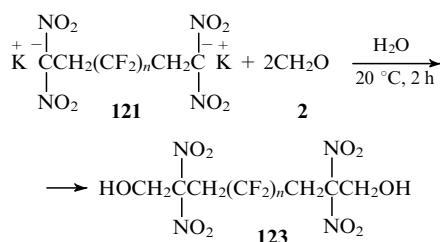
The sodium⁹⁵ or potassium⁹⁶ salts of dinitromethane react with glyoxal to give salts of 1,1,4,4-tetranitrobutane-2,3-diol **119**. The salt **119** (Y = Na) is converted into the tetrol **112** by the reaction with formaldehyde.⁹⁵ Treatment of the salts **119** (Y = Na or K) with 10% sulfuric acid⁹⁵ or hydrogen chloride⁹⁶ results in the formation of the diol **111** in a yield of 71.8% or 57.2%, respectively.



Potassium salts of fluoro-containing dinitroalkanes **120** or tetranitroalkanes **121** react readily with formaldehyde to give the corresponding nitro alcohols **122** or tetranitro-diols **123**.⁹⁷



R = C₆F₁₃ (36%); C₁₀F₂₁ (62%);



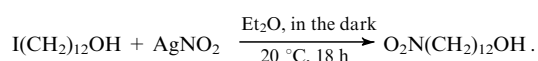
n = 4 (55%), 6 (75%).

Synthesis of 2,2,2-trinitroethanol by the condensation of trinitromethane with formaldehyde in the presence⁹⁸ or in the absence⁹⁹ of CuSO₄ has been reported.

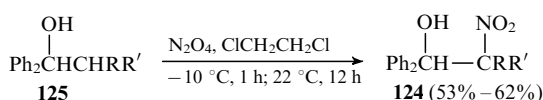
2. Synthesis of nitro alcohols by introduction of a nitro group into hydroxyl-containing compounds

This route for the preparation of nitro alcohols has not found wide application, because the two existing methods for the introduction of a nitro group into compounds containing a hydroxy group suffer from serious drawbacks restricting their use. One of these methods, namely, treatment of halo-substituted alcohols with some metal nitrites, normally permits preparation only of nitro alcohols containing a primary nitro group. In addition, there are some limitations as regards the use of the initial haloalcohols and solvents. The second method, namely, nitration of alcohols, has also found limited use, because only in some cases does it permit the target compounds to be obtained in reasonable yields. The main reaction pathway in this case is the oxidation of alcohols yielding carboxylic acids and the corresponding nitroalkanes.

During the last 25 years, the former method has hardly been used to synthesise aliphatic nitro alcohols. It was not until 1987 that the synthesis of 12-nitrododecan-1-ol (yield 79.5%) by the Meyer reaction of 12-iodododecan-1-ol was reported.¹⁰⁰



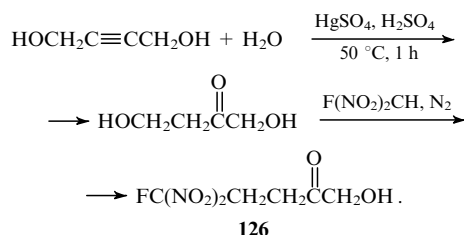
Over the period of time considered, only in rare cases has nitration of alcohols been used to prepare nitro alcohols; for example, nitro alcohols **124** have been obtained in this way by treating alcohols **125** with dinitrogen tetroxide.¹⁰¹



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

The reaction of Ph₂C(OH)Et with N₂O₃ or N₂O₄ at 20–25 °C in chloroform affords nitro alcohol Ph₂C(OH)CH(Me)NO₂ in a yield of 47% or 62%. When the same alcohol is treated with N₂O₅ in chloroform or with HNO₃ (20 °C, 1 h; 80 °C, 4 h), nitration involves not only the side chain but also the aromatic ring and the hydroxy group and results in the formation of O₂NC₆H₄C(Ph)(O-NO₂)CH(Me)NO₂ (yields 35% and 70%, respectively).¹⁰²

An original method for the synthesis of nitro alcohol **126** reported in a patent¹⁰³ consists of the transformation of butyne-1,4-diol into 1,4-dihydroxybutan-2-one by the Kucherov reaction followed by replacement of the β-hydroxyl with respect to the carbonyl group by a fluorodinitromethyl group by treatment with fluorodinitromethane.

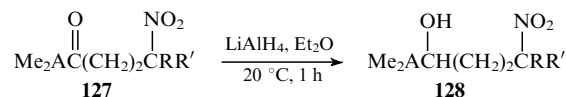


3. Synthesis of nitro alcohols by introduction of a hydroxy group into compounds containing a nitro group

Syntheses of nitro alcohols by this route can be clearly divided into two groups: (a) formation of a hydroxy group in nitro-compounds from other oxygen-containing groups incorporated in the initial molecule and (b) the formation of nitro alcohols from nitro-compounds containing no oxygen-containing groups.

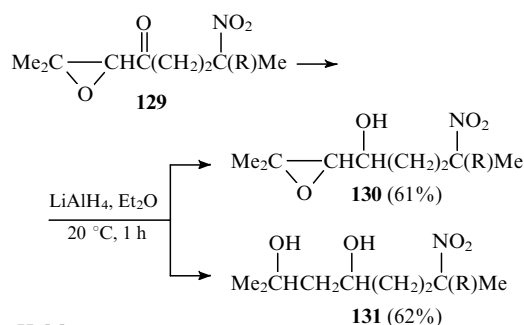
a. The formation of a hydroxy group from other oxygen-containing groups present in nitro-compounds

The reaction of unsaturated nitro ketones **127** (A = C=CH) or saturated nitro ketones (A = CHCH₂) with lithium aluminium hydride at 20 °C and at a LiAlH₄ : **127** ratio of 1 : 4 involves only transformation of the carbonyl group into a hydroxy group and affords nitro alcohols **128** (yields 64%–95%).¹⁰⁴



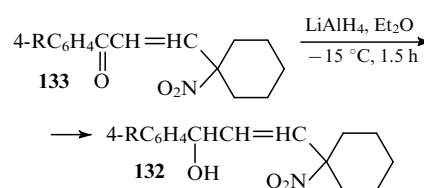
R = H, Me; R' = H, Me, Et, Pr; A = C=CH, CHCH₂.

When nitro ketones **129** containing an epoxy group are reduced with lithium aluminium hydride, the structure of the reaction product depends on the LiAlH₄ : **129** ratio. When this ratio is 1 : 4, only the carbonyl group is reduced, and nitro alcohols **130** are formed (yields 67% and 74%); at a ratio of 1 : 2, cleavage of the epoxide ring occurs, in addition to the reduction of the carbonyl group, and the process gives nitro-diols **131**.¹⁰⁴



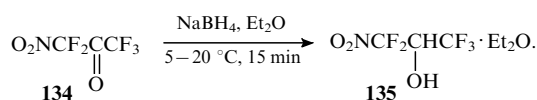
R = H, Me.

Unsaturated nitro alcohols **132** have been synthesised in 62%–68% yields by the reduction of nitro ketones **133** with lithium aluminium hydride at –15 °C and at an LiAlH₄ : **132** ratio of 1 : 4.¹⁰⁵

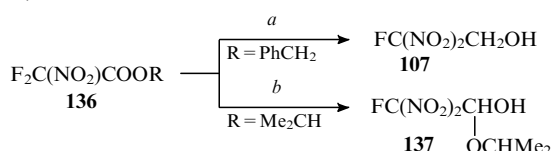


R = H, Me, Cl, Br.

Ketone **134** is converted into nitro alcohol **135** in 71% yield on treatment with sodium tetrahydridoborate.³²



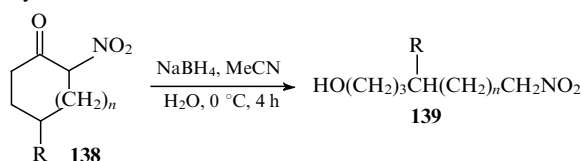
The outcome of the reduction of esters **136** with sodium tetrahydridoborate depends on the nature of the radical R; if R = PhCH₂, the reaction gives rise to the nitro alcohol **107** (yield 70%), whereas with R = Me₂CH, hemiacetal **137** is formed.¹⁰⁶



(a) NaBH₄, THF, H₂O, 10–12 °C, 0.5 h;

(b) NaBH₄, (MeOCH₂)₂, 20–25 °C, 0.5 h.

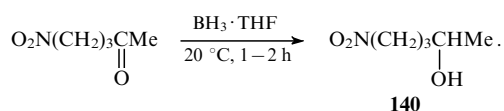
When cyclic α-nitro ketones **138** are treated with sodium tetrahydridoborate, the reduction is accompanied by ring opening and yields nitro alcohols **139**.¹⁰⁷



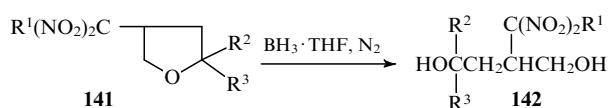
R = H, n = 0–10 (50%–85%); R = Bu^t, n = 1 (75%).

3-Nitropropanal was converted into 3-nitropropan-1-ol in 89% yield by treatment with the complex BH₃·SMe₂ in Et₂O at 20 °C for 4 h under a nitrogen atmosphere.¹⁰⁸

Nitro alcohol **140** was synthesised in 77.5% yield by the reduction of 5-nitropentan-2-one with diborane in THF.³¹



The reaction of tetrahydrofuran derivatives **141** with borane in THF results in ring opening and formation of diols **142**.^{109, 110}

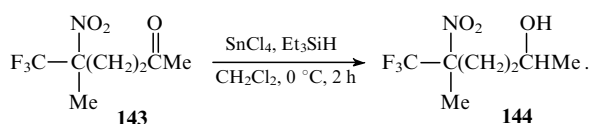


R¹ = NO₂, R² = H, R³ = OH (35 °C, 72 h, 98%);¹⁰⁹

R¹ = F, R² = H, R³ = OH (25 °C, 24 h, 100%);¹⁰⁹

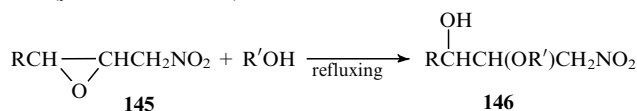
R¹ = NO₂, R², R³ = O (35 °C, 72 h, 98%).¹¹⁰

Nitro ketone **143** was converted into nitro alcohol **144** in 72% yield on treatment with SnCl₄ and Et₃SiH at 0 °C.⁶⁶



The reduction of the compounds RCOCH(R')(CH₂)₂NO₂ (R, R' = Me, H;¹¹¹ Ph, H; MeO, 2-MeOC₆H₄¹¹²) in the presence of baker's yeast occurs stereoselectively to give (S)-nitro alcohols as the major products; the highest stereoselectivity (99%) is observed in the case of R = MeO, R' = 2-MeOC₆H₄.^{111, 112}

When epoxide **145** (R = Me) is heated in water at 50 °C, the corresponding diol MeCH(OH)CH(OH)CH₂NO₂ is formed in 56% yield.¹¹³ Heating of **145** in aliphatic alcohols leads to ethers **146** (yields 55%–68%).¹¹³



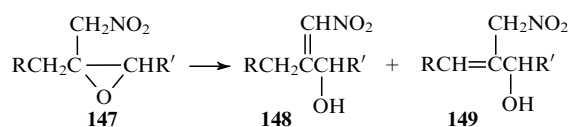
R = H; R' = Me, Et, Prⁱ; R = Me, R' = Me, Prⁱ.

In the presence of triethylamine at 18–20 °C, the epoxide **145** (R = Me) isomerises into the unsaturated nitro alcohol MeCH(OH)CH=CHNO₂ (yield 62%).¹¹³

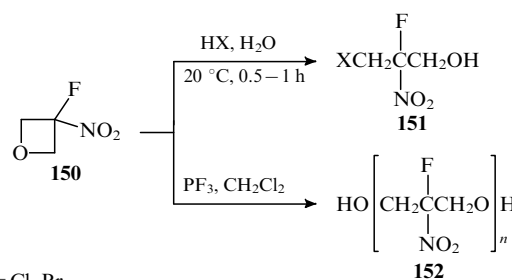
2,3-Epoxy-1-nitropropane reacts with hydrazines RC₆H₄NHNH₂ (R = 2-NO₂, 4-NO₂) at 20 °C in aqueous ethanol affording 2- or 4-O₂NC₆H₄NHNHCH(CH₂OH)–CH₂NO₂ in 86% yield.¹¹⁴

Epoxides **147** with a more complicated structure have been converted into mixtures of unsaturated nitro alcohols **148** and **149** in four ways: by treatment with triethylamine in aqueous acetonitrile (procedure A); in the presence of alumina in diethyl ether and in dichloromethane (procedure B); at 25 °C over silica gel (procedure C); over aluminium isopropoxide (procedure D) (Scheme 2).¹¹⁵ The reaction conditions and the yields of the alcohols **148** and **149** are listed in Table 8.

Scheme 2



On treatment with hydrohalic acids, 3-fluoro-3-nitrooxetane **150** is converted into nitro alcohols **151** in high yields (96.5% and 93.1%), whereas on treatment with phosphorus trifluoride, it is converted into polymer **152** (yield 82.6%).⁴⁹



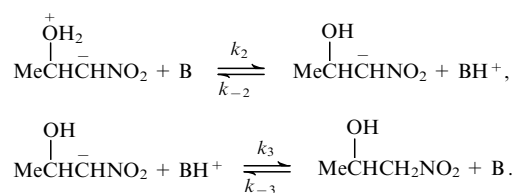
X = Cl, Br.

Table 8. Reaction conditions and yields of the nitro alcohols **148** and **149**.

R	R'	Time/ h				Yield of (148 + 149) (%)				Yield of 148 (%)				E/Z Ratio in 148			
		A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
H	Me	2	2	2	—	97	92	92	—	16	15	0	—	—	—	78/22	—
H	Et	2	4	4	—	82	96	96	—	15	11	0	—	—	—	78/22	—
H	C ₅ H ₁₁	2	4	5	—	89	82	84	—	33	18	0	—	—	—	80/20	—
H	Pr ⁱ	2	3	3	—	90	87	83	—	17	15	0	—	—	—	84/26	—
Me	Me	—	3	2	—	—	85	85	—	—	9	0	—	—	—	65/35	—
Et	Et	—	4	48	1	—	86	0	80	—	—	—	traces	—	—	—	70/30
Bu	Bu	—	5	48	1	—	80	0	83	—	2	—	traces	—	83/17	—	71/29

$$\begin{array}{c}
 \text{O} \\
 \parallel \\
 \text{O}_2\text{NCF}_2\text{CCF}_3 \longrightarrow \\
 \mathbf{153}
 \end{array}$$

$$\begin{array}{l}
 \xrightarrow[\text{CH}_2=\text{C}(\text{OEt})_2]{-30^\circ\text{C}, 2\text{ h}} \text{O}_2\text{NCF}_2\text{C}(\text{CF}_3)\text{CH}=\text{C}(\text{OEt})_2 \quad \mathbf{154} \\
 \xrightarrow[\text{CH}_2(\text{COOH})_2, \text{C}_5\text{H}_5\text{N}]{20^\circ\text{C}, 0.5\text{ h}} \text{O}_2\text{NCF}_2\text{C}(\text{CF}_3)\text{CH}_2\text{COOH} \quad \mathbf{155}
 \end{array}$$

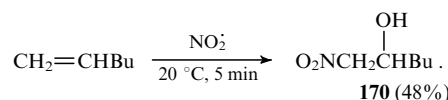
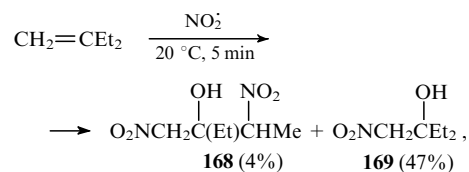
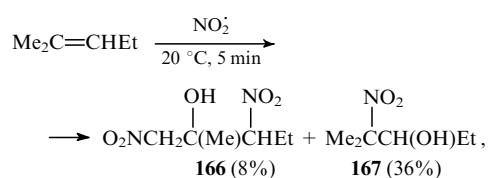
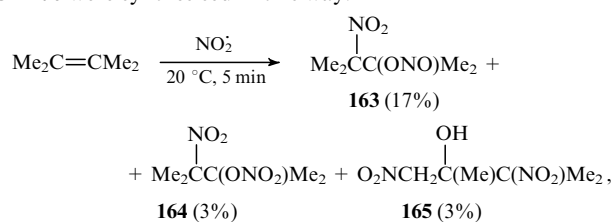
$$\begin{array}{c}
 \text{EtOH, H}_2\text{SO}_4 \\
 \xrightarrow{\text{refluxing for 25 h}} \text{O}_2\text{NCF}_2\text{C}(\text{CF}_3)\text{CH}_2\text{COOEt} \quad \mathbf{156}
 \end{array}$$
$$\text{MeCH=CHNO}_2 + \text{H}_2\text{O} \xrightleftharpoons[k_{-1}]{k_1} \begin{array}{c} \text{OH}_2^+ \\ | \\ \text{MeCHCHNO}_2^- \end{array},$$


Reactions of alkenes with nitrogen oxides are used most often for the synthesis of nitro alcohols with simultaneous introduction of NO_2 and OH groups to vicinal positions.

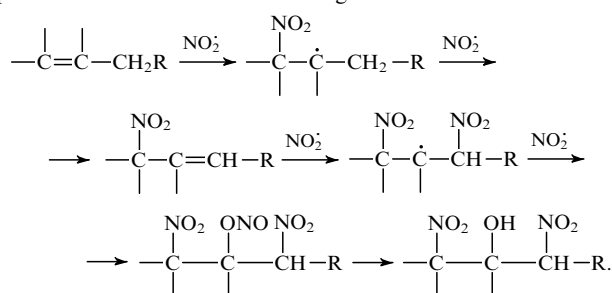
The nitro alcohol $C_{12}H_{25}CH(OH)CH_2NO_2$ (yield 10%) and its nitrate $C_{12}H_{25}CH(ONO_2)CH_2NO_2$ (yield 86%) have been prepared by the reaction of $C_{12}H_{25}CH=CH_2$ with N_2O_4 in CCl_4 in the presence of sulfuric acid at $0-5^\circ C$ for 0.5 h.¹²⁵

The nitro alcohol $Ph_2C(OH)CH(Me)NO_2$ has been synthesised by the reactions of the alkene $Ph_2C=CHMe$ with N_2O_4 ($CHCl_3$, $20-25^\circ C$, 6 h), N_2O_3 ($CHCl_3$, $20^\circ C$, 17 h) or HNO_3 (d 1.51, $CHCl_3$, $100^\circ C$, 4 h), the yields of the product being 56%, 46% or 50.8%, respectively.¹⁰³ When the same alkene was treated with N_2O_5 ($CHCl_3$, $18^\circ C$, 12 h), the product $O_2NC_6H_4-(Ph)C(ONO_2)CH(Me)NO_2$ containing a nitro group instead of a hydrogen atom in one of the benzene rings was obtained in 32.2% yield.¹⁰²

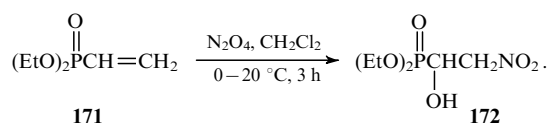
The reactions of various alkenes with NO_2 in hexane at $20^\circ C$ have been studied in detail. Nitro alcohols and their derivatives **163–170** were synthesised in this way.¹²⁶



The formation of the compounds **165**, **166** and **168** was explained¹²⁶ in terms of the following scheme:

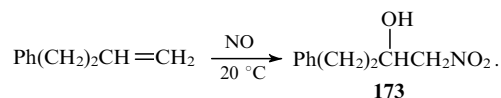


Diethyl vinylphosphonate **171** readily reacts with N_2O_4 in dichloromethane to give nitro alcohol **172** (yield 34%).¹²⁷

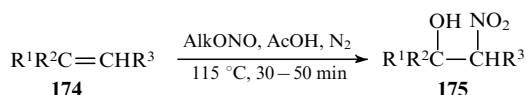


2-Hydroxy-3-nitropropionic acid was synthesised in 60% yield by the reaction of acrylic acid with N_2O_4 in dichloroethane at $18-20^\circ C$ over a period of 10 h.¹²⁸

Nitro alcohol **173** is formed in 23%–25% yield in the reaction of nitrogen oxide with 4-phenylbut-1-ene in various solvents (dichloroethane, tetrachloromethane or benzene) at $20^\circ C$.¹²⁹

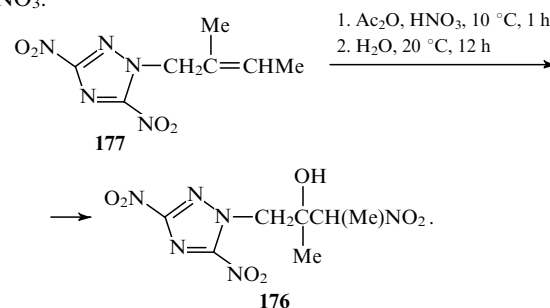


Simultaneous introduction of NO_2 and OH groups into alkenes **174** was accomplished by treating them with alkyl nitrites with heating in acetic acid under an inert atmosphere; the yields of nitro alcohols **175** were 20%–33%.¹³⁰

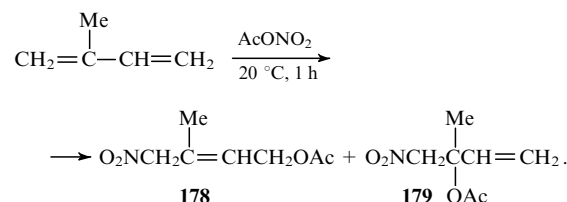


R^1, R^2, R^3 : Ph, Ph, H; Me, Ph, H; Me, COOMe, H; Et, Et, Me.

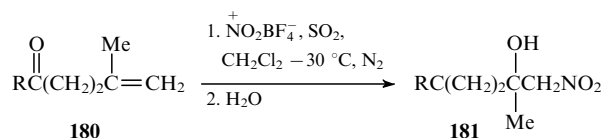
The synthesis of compound **176** (yield 55%) from alkene **177** was carried out using acetyl nitrate formed *in situ* from Ac_2O and HNO_3 .¹³¹



The reaction of isoprene with acetyl nitrate at $20^\circ C$ affords a mixture of nitroalkenyl acetates **178** and **179** in a ratio of 7 : 3.¹³²

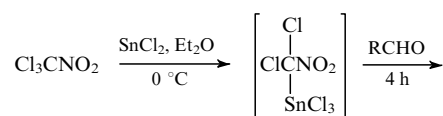


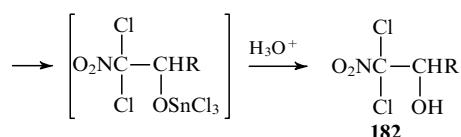
Treatment of unsaturated ketones **180** with nitronium tetrafluoroborate at $-30^\circ C$ in a solution in SO_2 followed by treatment with water gives compounds **181** in low yields.¹³³



$R = Me$ (4%), Pr (17%), Pr^i (34%).

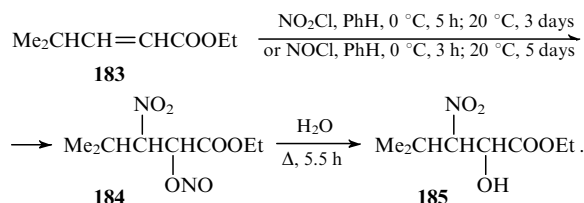
An original method has been proposed¹³⁴ for the synthesis of dichloro-substituted nitro alcohols **182**. It is based on the reaction of trichloronitromethane with aldehydes in the presence of $SnCl_2$.





R = H (67%), Me (76%), Et (82%), Pr (83%), Bu (92%), C₅H₁₁ (85%), Ph (52%), CCl₃ (77%), 4-MeC₆H₄ (57%), 4-ClC₆H₄ (59%), 2-furyl (53%), 2-thienyl (61%).

The reaction of ethyl 4-methylpent-2-enoate **183** with nitril chloride or nitrosyl chloride yields nitrite **184**, which is converted into compound **185** on refluxing with water, the overall yield of the latter being 34%.⁷⁴



III. Chemical transformations of nitro alcohols

1. Reactions involving the nitro group

The reduction of 2-nitrobutan-1-ol in the presence of Raney nickel at 35–40 °C under a hydrogen pressure of 10 atm results in the formation of 2-aminobutan-1-ol in 62%–74% yield.^{44, 135}

The same catalyst is effective in the reduction of nitro alcohols **186** to amino alcohols **187** (Table 9).⁶⁶

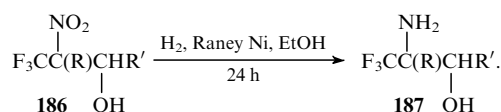
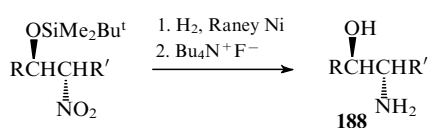


Table 9. Reaction conditions and yields of the amino alcohols **187**.

R	R'	Pressure /atm	Temperature /°C	Yield (%)
H	Pr	1	20	52
H	C ₆ H ₁₃	25	50	76
H	Ph(CH ₂) ₂	1	20	79
H	PhCHMe	25	50	82
H	Pr	30	50	59
Me	Pr	30	50	5
Me	C ₆ H ₁₃	25	50	22
Me	Ph(CH ₂) ₂	25	50	53

Raney nickel has also been used to reduce the compounds PhCH(OH)(CH₂)₂NO₂ and Ph₂CHCH(OH)CH₂NO₂ to amino alcohols PhCH(OH)(CH₂)₂NH₂ (yield 49%) and Ph₂CHCH(OH)CH₂NH₂ (yield 18%).⁷⁹

The reduction of the *erythro*-isomers of silyl ethers of nitro alcohols in the presence of Raney nickel occurs stereoselectively; treatment of the reaction mixture with Bu₄N⁺F[−] gives the *erythro*-isomers of amino alcohols **188**.⁸²



R, R': Pr, Et, Prⁱ, Et; C₅H₁₁, Me; C₅H₁₁, Et; Pr, C₇H₁₅; C₁₀H₂₁, Me; C₉H₁₉, Me; Ph, Et.

2-Hydroxymethyl-2-nitropropane-1,3-diol **4** is converted into the amine H₂NC(CH₂OH)₃ (yield 89%) by hydrogenation in the presence of the Pd/C catalyst at 59–63 °C for 4.5 h.¹³⁶

When 4-MeOC₆H₄CH₂C(OH)(Et)NO₂ is reduced with ammonium formate in the presence of Pd/C in THF and MeOH, the amino alcohol 4-MeOC₆H₄CH₂C(OH)(Et)NH₂ is formed in 73% yield.¹³⁷

The amino-diols HOCH₂C(R)(NH₂)CH(OH)C₁₃H₂₇ (R = H, Me) have been synthesised in high yields (83% and 86%) by the reduction of the corresponding nitro-diols with ammonium formate in the presence of Pd/C in MeOH at 20 °C for 16 h under an atmosphere of nitrogen.⁶¹

An active catalyst of reduction, Ni₂B, which is formed *in situ* from NiCl₂·6H₂O and NaBH₄, has been used to convert the nitro alcohol O₂NCMe₂(CH₂)₂CH(OH)Me into the corresponding amino alcohol (yield 76%). The reaction occurs in MeOH at 20 °C over a period of 5 min.¹³⁸

Reduction of nitro alcohols to amino alcohols with hydrogen has also been carried out in the presence of a number of rhodium-containing catalysts. For example, 2-nitrobutan-1-ol has been converted into 2-aminobutan-1-ol by hydrogenation in the presence of di(rhodiumnorbornadienechloride) and Ph₂PCH₂CH(PPh₂)Me at 60 °C under a hydrogen pressure of 67 atm for 20 h.¹³⁹

The reduction of 2-nitrobutan-1-ol to 2-aminobutan-1-ol catalysed by rhodium-, iridium- and palladium-containing systems has been studied in detail (Table 10).¹⁴⁰

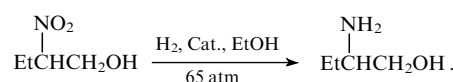


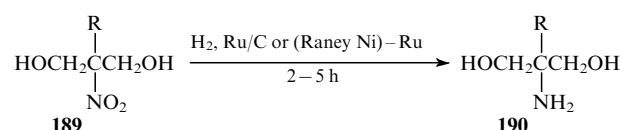
Table 10. Hydrogenation of 2-nitrobutan-1-ol.¹⁴⁰

Catalyst	Phosphine	Catalyst: phosphine	Time/h	Temperature/°	Yield (%)
Rh ₂ Cl ₂ (NBD) ₂ ^a	see ^b	1 : 1	20	60	78
Rh ₂ Cl ₂ (NBD) ₂	PPh ₃	1 : 1	16	50	36
Rh ₂ Cl ₂ (NBD) ₂	DIOP ^c	1 : 1	65	80	57
Ir ₂ Cl ₂ (COD) ₂ ^d	PPFA ^e	1 : 2	16	50	67
Ir ₂ Cl ₂ (COD) ₂	BPPFA ^f	1 : 2	16	50	56
Ir ₂ Cl ₂ (COD) ₂	DIOP	1 : 2	16	50	54
Ir ₂ Cl ₂ (COD) ₂	DIPHOS ^g	1 : 2	16	50	47
PdCl ₂ (COD) ₂	DIPHOS	1 : 2	18	75	24
PdCl ₂ (PhCN) ₂	BPPFOH ^h	1 : 1	18	75	41

^a NBD — norbornadiene; ^b Ph₂PCH₂CH(Me)PPh₂; ^c DIOP — (*S,S*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane;

^d COD — cyclooctadiene; ^e PPFA — (*R*)-α-[(*S*)-2-(diphenylphosphino)-ferrocenyl]ethyl dimethylamine; ^f BPPFA — (*R*)-α-[(*S*)-2,1'-bis(diphenylphosphino)ferrocenyl]ethyl dimethylamine; ^g DIPHOS — bis(1,2-diphenylphosphino)ethane; ^h BPPFOH — (*R*)-α-[(*S*)-2,1'-bis(diphenylphosphino)ferrocenyl]ethane.

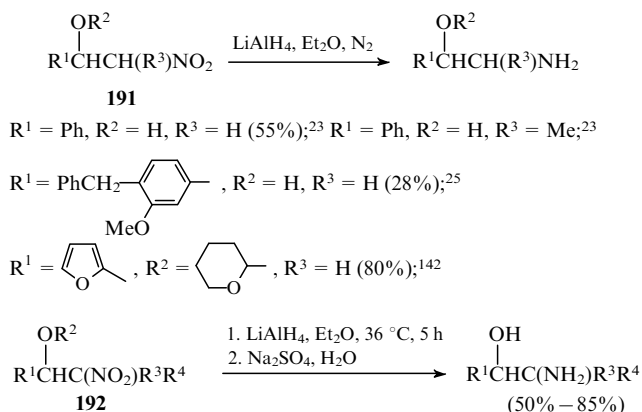
Nitro glycols **189** have been hydrogenated at 80–100 atm in the presence of Ru/C catalyst or Raney Ni–Ru for 2–5 h; this gave amino glycols **190** in 78%–96% yields.¹⁴¹



R = H, Me, Et, CH₂OH.

Hydrogenation of the nitro alcohols 4-RC₆H₄CH(OH).CH₂NO₂ (R = H, Me, Cl) in the presence of PdO₂ in 80% AcOH at 1 atm gives rise to the corresponding amino alcohols RC₆H₄CH(OH)CH₂NH₂ in 59%, 50% and 63% yields, respectively.²⁶

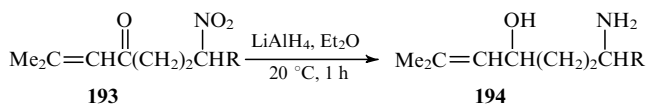
The nitro groups in nitro alcohols and their derivatives **191** and **192** have been reduced to amino groups using LiAlH₄.^{23, 25, 81, 83, 142}



$\text{R}^1 = \text{C}_6\text{H}_{13}, \text{Bu}^t, \text{Ph}, 4\text{-MeOC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4;$

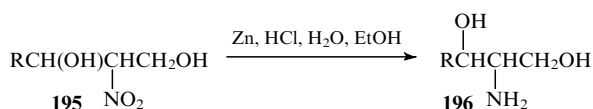
$\text{R}^2 = \text{SiMe}_3 \text{ or } \text{SiMe}_2\text{Bu}^t; \text{R}^3 = \text{H, Me}; \text{R}^4 = \text{C}_5\text{H}_{11}, \text{Me}.^{81, 83}$

When unsaturated nitro ketones **193** are reduced with a twofold excess of lithium aluminium hydride, the nitro groups are converted into amino groups, whereas the carbonyl groups are reduced to hydroxy groups; thus, the reaction yields amino alcohols **194**.¹⁰⁴



$\text{R} = \text{H} (35\%), \text{Me} (37\%), \text{Et} (38\%).$

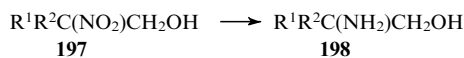
Nitro-diols **195** have been converted into amino-diols **196** by treatment with zinc and hydrochloric acid in ethanol.¹⁴³



$\text{R} = \text{C}_7\text{H}_{15} (25\%), \text{C}_9\text{H}_{19} (33\%), \text{C}_{11}\text{H}_{23} (38\%), \text{C}_{13}\text{H}_{27} (40\%).$

Electroreduction of 2-methyl-2-nitropropane-1,3-diol giving 2-amino-2-methylpropane-1,3-diol in 99% yield has been patented.¹⁴⁴

Nitro alcohols or nitro-diols **197** have been converted into the corresponding amino-derivatives **198** by electroreduction at bimetallic electrodes consisting of copper deposited on zinc or cadmium.¹⁴⁵

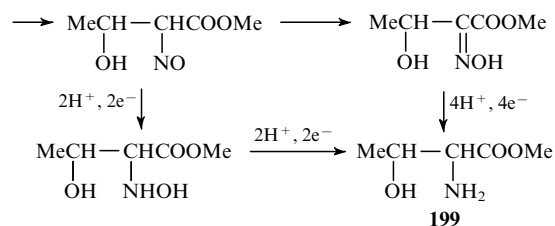
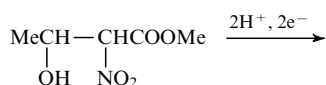


$\text{R}^1, \text{R}^2: \text{H, Me; Me, CH}_2\text{OH; H, Et; Et, CH}_2\text{OH}.$

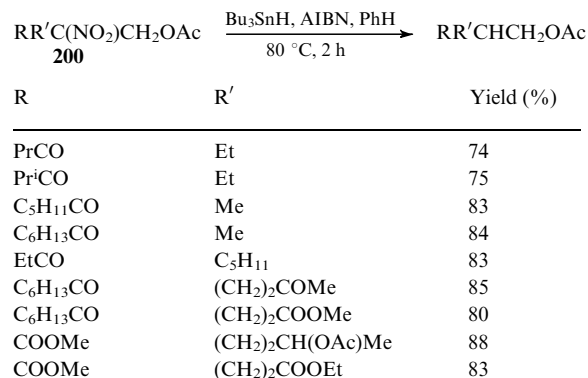
Electroreduction of the triol **4** in the presence of sulfuric acid at 75–80 °C and at a current density of 0.1 A cm⁻² for 12–13 h affords amino-derivative H₂NC(CH₂OH)₃ in 40%–50% yield.⁶

The hydrochloride (HOCH₂)₃CNH₂·HCl has been synthesised by electroreduction of the triol **4** at a perforated palladium cathode at 75–80 °C in the presence of 6.5% HCl.¹⁴⁶

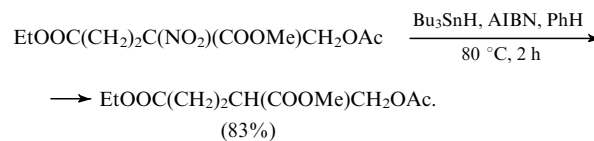
Electroreduction of methyl 3-hydroxy-2-nitrobutyrate giving rise to the DL-threonine ester **199** (substance yield 72%–77%; current yield 7%–10%) can be described by the following scheme:^{147, 148}



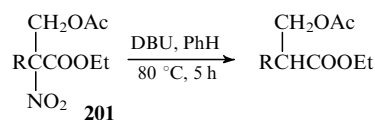
Treatment of nitro alcohol acetates **200** with tributylstannane in the presence of azobis(isobutyronitrile) in boiling benzene results in the replacement of the nitro group by a hydrogen atom.⁴⁸



The reduction of the nitro group in an acetate of a more complicated structure occurs under the same conditions.⁴⁸



The researchers cited⁴⁸ proposed yet another method for the introduction of a hydrogen atom instead of the nitro group in nitro alcohol acetates **201**. The method involves treatment of **201** with 1,8-diazabicyclo[5.4.0]undec-7-ene in boiling benzene.

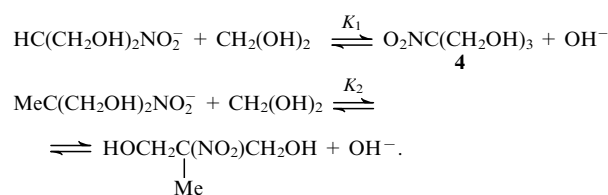


$\text{R} = \text{Me} (66\%), \text{Et} (71\%), \text{Pr} (88\%), \text{Pr}^i (83\%), \text{Bu} (78\%).$

2. Reactions involving hydrogen atoms attached to a carbon atom carrying nitro groups

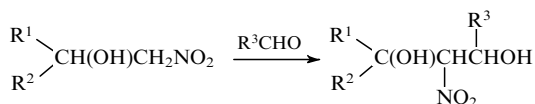
Nitro alcohols containing one or two hydrogen atoms at the carbon atom carrying the nitro group are able to enter into nitroaldol condensation. The reaction of the salt $[-\text{O}_2\text{N}=\text{CHCH}(\text{OH})\text{CH}(\text{OH})\text{CH}=\text{NO}_2^-]2\text{Na}^+$ with formaldehyde at 0–5 °C and pH = 10 in Et₂O gives the tetrol HOCH₂C(NO₂)₂CH(OH)CH(OH)C(NO₂)₂CH₂OH.⁹⁵

The reactions of salts derived from 2-nitropropane-1,3-diol **3** or from 2-nitropropan-1-ol with an aqueous solution of formaldehyde have been studied.¹⁴⁹ Reversible reactions give 2-hydroxymethyl-2-nitropropane-1,3-diol **4** or 2-methyl-2-nitropropane-1,3-diol, respectively.



The equilibrium constants K_1 and K_2 are $(4.3 \pm 0.4) \times 10^{-3}$ and $(3.6 \pm 0.2) \times 10^{-2}$, respectively. The characteristics of these reactions are retained over a broad range of concentrations: $[\text{CH}_2(\text{OH})_2] = 0.058\text{--}3.06\text{ M}$ and $[\text{OH}^-] = 1.8 \times 10^{-2}\text{--}0.36\text{ M}$.

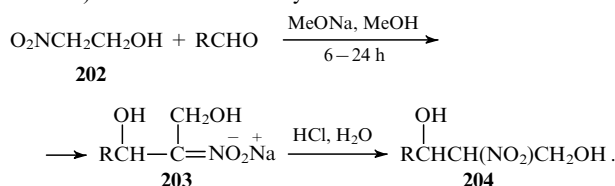
In the presence of Dowex-1 anion-exchange resin, the condensation of nitro alcohols with formaldehyde or acetaldehyde at 20 °C is completed over a period of 1–2 h.¹⁵⁰



$\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{H}$ (63%); $\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$ (79%);

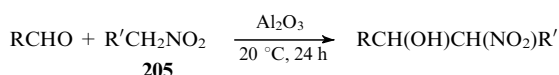
$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{R}^3 = \text{H}$ (91%).

2-Nitroethanol **202** reacts with aliphatic aldehydes in the presence of sodium methoxide to give salts **203** (yields 67%–99%), which are converted into nitro-diols **204** (yields 91%–98%) on treatment with hydrochloric acid.¹⁴³



$\text{R} = \text{C}_7\text{H}_{15}$, C_9H_{19} , $\text{C}_{11}\text{H}_{23}$, $\text{C}_{13}\text{H}_{27}$.

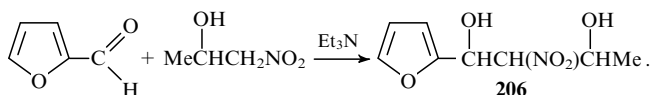
Alumina (Brockmann activity I) has been used as the catalyst in the condensation of nitro alcohols **205** with aldehydes.⁶⁹



R, R' : Me, MeCH(OH)CH₂; Et, (CH₂)₆OH; Et, CH₂OH.

The reaction of the nitro alcohol **202** with benzaldehyde in the presence of triethylamine at 0 °C is completed over a period of 23 h resulting in the formation of DL-*threo*-2-nitro-3-phenylpropane-1,3-diol (yield 98.7%).¹⁵¹

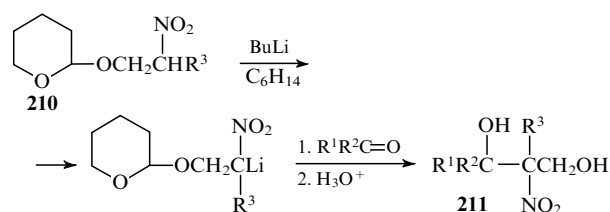
The reaction of furfural with 1-nitropropan-2-ol in the presence of triethylamine gave the corresponding nitro-diol **206** in a yield of only 35%.¹⁵²



The condensation of the nitro alcohol **202** with hexadec-2-enal in the presence of K₂CO₃ or Et₃N at 20 °C affords nitro-diol **207** and a minor quantity of the product of its cyclisation **208**.¹⁵³

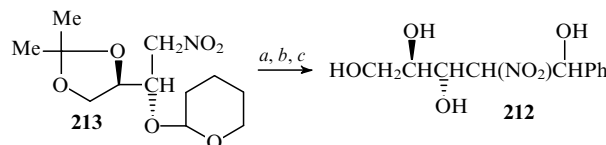
When this reaction is carried out in methanol in the presence of K₂CO₃ at 20 °C, the tetrahydropyran derivative **208** (yield 50%) is formed together with compound **209** (yield 12%) (see Scheme 3).¹⁵³

On treatment with butyllithium, compounds **210** were converted into the corresponding lithio-derivatives. Condensation of the latter with carbonyl compounds R¹R²C=O followed by hydrolysis of the condensation products gave nitro-diols **211** in 52%–88% yields.¹⁵⁴



$\text{R}^1, \text{R}^2, \text{R}^3$: H, Prⁱ, H; H, Br, H; H, , H;
trans-PhCH=CH, H, H; H, C₁₃H₂₇, C, H; H, Ph, H;
 H, 4-MeOC₆H₄, H; Me, Ph, H; H, (*S*)-MeCH₂CH(Me), H;
 H, Prⁱ, Me; H, 4-CNC₆H₄, H; H, , Me; H, Ph, Me;
 $\text{R}^1, \text{R}^2 = (\text{CH}_2)_5$, $\text{R}^3 = \text{H}$, Me.

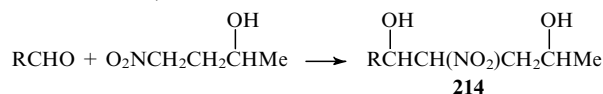
A single diastereoisomer of nitro-tetrol **212** was obtained in a similar way from compound **213** and benzaldehyde (yield 73%).¹⁵⁴



(a) BuLi, THF, HMPTA –90 to –40 °C, 3 h;

(b) PhCHO, –90 to –60 °C, 1.5 h; (c) AcONa, H₂O.

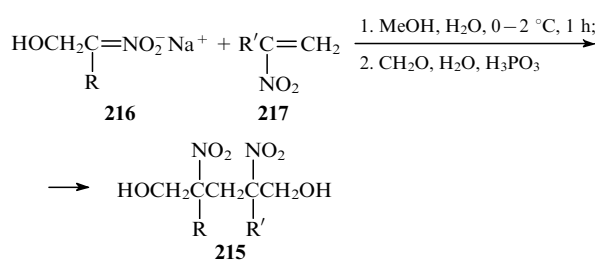
Aldehydes have been made to condense with 4-nitrobutan-2-ol in the presence of the Amberlyst A-21 ion-exchange resin at 0 °C for 15 h. This resulted in the formation of nitro-diols **214** (yields 45%–70%).¹⁵⁵



$\text{R} = \text{Me}$, Prⁱ, C₅H₁₁, C₁₀H₂₁, , Ph(CH₂)₂,

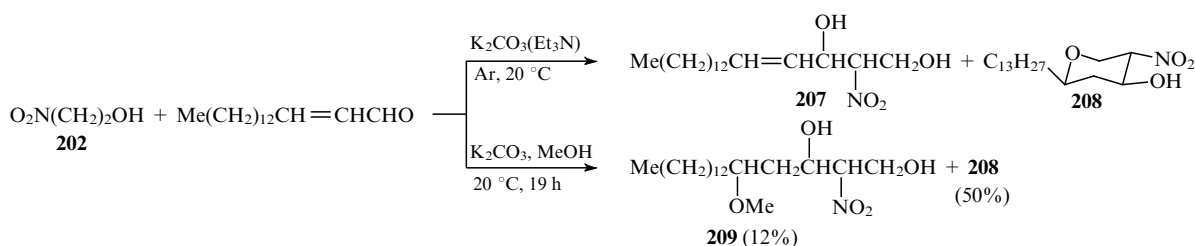
(*Z*)-Me(CH₂)₇CH=CH(CH₂)₇, Me(CH₂)₄CH(NO₂)(CH₂)₂.

Dinitro-diols **215** have been prepared in two stages, namely, by the reaction of salts **216** with nitroalkenes **217** and subsequent treatment of the resulting reaction mixtures with formaldehyde in the presence of phosphorous acid at pH 6–5.5.¹⁵⁶



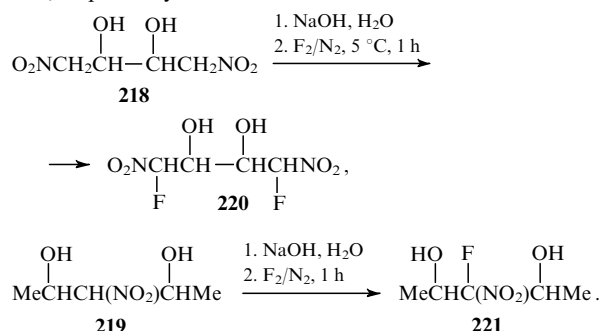
$\text{R} = \text{Me}$; $\text{R}' = \text{Me}$ (45%), Et (42%); $\text{R} = \text{R}' = \text{Et}$ (31%).

The reaction of 1-nitropropane with formaldehyde in the presence of Ca(OH)₂ in water at 30 °C for 1 h followed by treatment of the reaction mixture with bromine in CCl₄ at 20 °C gives rise to 2-bromo-2-nitrobutan-1-ol in 90% yield.³⁵



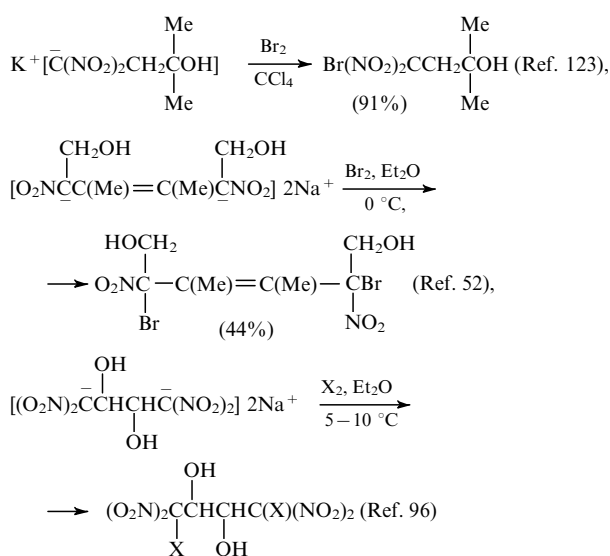
Scheme 3

When nitro-diol **218** or **219** is treated with an aqueous solution of sodium hydroxide and then with a mixture of fluorine and nitrogen, fluoro-derivative **220** or **221** is formed in a yield of 71% or 68%, respectively.⁵⁰



The potassium salt of 2,2-dinitroethanol is converted into 2-chloro-2,2-dinitroethanol on treatment with chlorine in water at 0–5 °C.¹⁵⁷

When salts of nitro alcohols react with chlorine or bromine, halogenation products are formed:



X = Cl (73.8%), Br (75%).

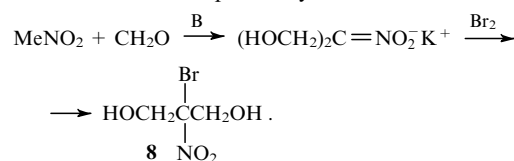
When the products resulting from reactions of MeNO₂ with aldehydes (CH₂O or Cl₃CCHO) were treated with bromine, 2,2-dibromo-2-nitroethanol¹⁵⁸ or 3-bromo-1,1,1-trichloro-3-nitropropan-1-ol³⁵ were synthesised.

Table 11. Reaction conditions and yields of the compound **8**.

Conditions of nitroaldol condensation				Conditions of bromination		Yield (%)	Ref.
Base	Solvent	T / °C	t / min	T / °C	t / h		
Ca(OH) ₂	H ₂ O	0	30	0	1	74	5
Na ₂ CO ₃		0–10		10	1	80	7
NaOH	H ₂ O	5–10		5–10		86	9
NaOH	MeOH			20	0.5	83	10
NaOH	H ₂ O, DEG ^a	20	60	5–20		98	11
MeONa	MeOH	5		5		86 ^b	20
NaOH	H ₂ O			see ^c			12

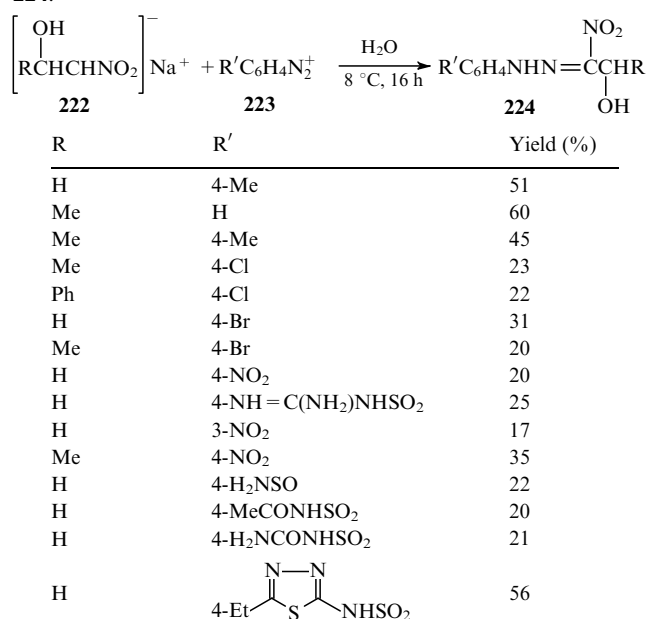
^a DEG — diethyleneglycol; ^b CHCl₃, ^c paraform, CCl₄, BrCl.

In a number of patents,^{5, 7, 9–12, 20} it has been proposed to synthesise 2-bromo-2-nitropropane-1,3-diol **8**, which is a known bactericide agent ‘Biocide’, according to the following scheme (the reaction conditions and product yields are listed in Table 11):

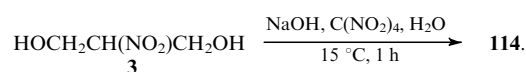


Similarly, Cl₃CCH(OH)C(NO₂)Br was prepared from MeNO₂ and Cl₃CCHO;^{5, 7} MeCH(OH)C(NO₂)BrCH(OH)Me was synthesised from MeNO₂ and MeCHO;¹⁰ and MeCH(OH)C-Me(NO₂)BrCH(OH)Me was obtained from EtNO₂ and MeCHO.¹¹

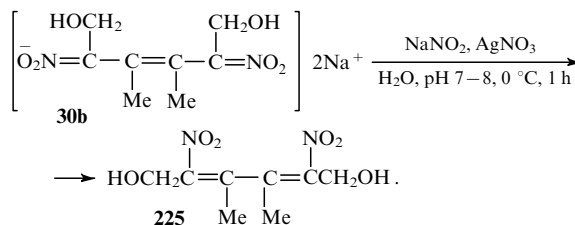
The reactions of salts of nitro alcohols **222** with aryldiazonium cations **223** in water at low temperatures yield arylhydrazones **224**.¹⁵⁹



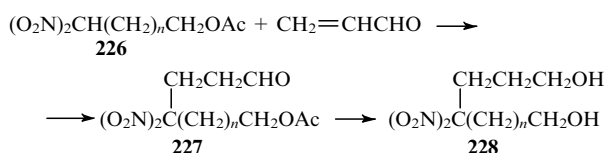
2-Nitropropane-1,3-diol **3** is nitrated with tetranitromethane in an alkaline medium giving 2,2-dinitropropane-1,3-diol **114**.⁸



However, an attempt to carry out alkaline nitration of the salt **30b** was unsuccessful; the reaction resulted in the formation of diene **225** (yield 21.4%).⁵²

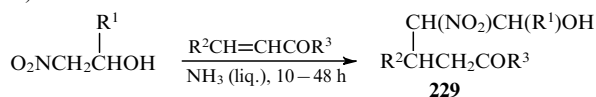


Dinitro alcohol acetates **226** [the compound **226** with $n = 3$ has been obtained by catalytic oxidative nitration of the nitro alcohol O₂NCH(CH₂)₃OH] have been introduced into the Michael reaction with acrolein. This afforded compounds **227**, which were then converted into dinitro-diols **228**.¹⁶⁰



$n = 1, 3$.

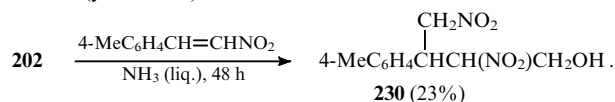
The nitro alcohols $\text{O}_2\text{NCH}_2\text{CH}(\text{R}')\text{OH}$ add to α,β -unsaturated ketones in liquid ammonia to give adducts **229** (yields 45%–96%).¹⁶¹



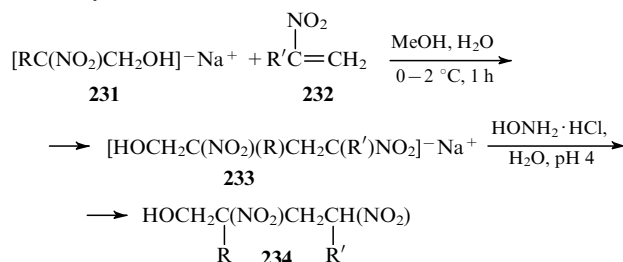
$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, 4- BrC_6H_4 , 4- $\text{O}_2\text{NC}_6\text{H}_4$, ;

$\text{R}^3 = \text{Me}$, Ph , 4- MeC_6H_4 , 4- MeOC_6H_4 ; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{R}^3 = \text{Ph}$.

Adduct **230** was synthesised by the reaction of the nitro alcohol **202** with 2-(4-methylphenyl)-1-nitroethene under similar conditions (yield 23%).¹⁶¹

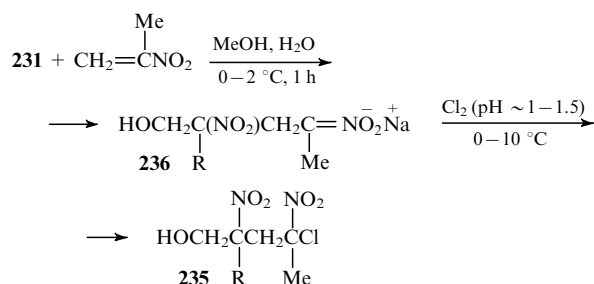


The reaction of salts of nitro alcohols **231** with nitroalkenes **232** in aqueous methanol gives adducts **233** in quantitative yields. On treatment with an aqueous solution of hydroxylamine hydrochloride, the adducts **233** are converted into dinitro alcohols **234** in 37%–55% yields.¹⁶²



$\text{R}, \text{R}' = \text{Me}, \text{Et}$.

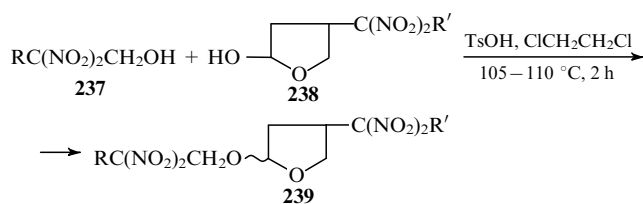
Chloro-substituted dinitro alcohols **235** have been synthesised by the reaction of the salts **231** with 2-nitroprop-1-ene in aqueous methanol followed by treatment of the resulting adducts **236** with chlorine.¹⁶³



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

3. Reactions involving the hydroxy group

When dinitro alcohols **237** react with compound **238** in the presence of toluene-*p*-sulfonic acid, intermolecular elimination of water occurs to give acetals **239** (yields 73%–100%) as mixtures of *cis*- and *trans*-isomers (in a ratio of 15–35 : 85–65).¹⁰⁹

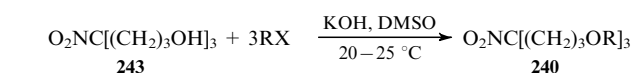


$\text{R} = \text{F}, \text{Me}, \text{NO}_2$; $\text{R}' = \text{F}, \text{NO}_2$.

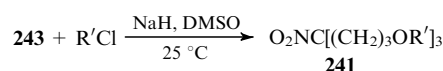
Ethers derived from nitro alcohols are often synthesised by reactions of nitro alcohols with halo-derivatives in the presence of bases.

The reaction of 3-nitropropan-1-ol with $\text{Bu}^t\text{Me}_2\text{SiCl}$ carried out in DMF in the presence of imidazoline at 20°C for 15 h gave the ether $\text{O}_2\text{N}(\text{CH}_2)_3\text{OSiMe}_2\text{Bu}^t$ in 91% yield.¹⁰⁸

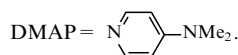
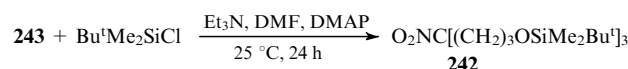
Ethers **240**, **241** and **242** have been prepared in high yields by the reactions of triol **243** with various halo-derivatives at $20-25^\circ\text{C}$ in the presence of KOH , NaH or Et_3N .¹⁶⁴



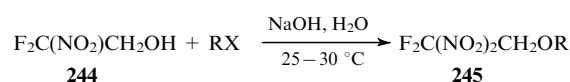
R	X	Time /h	Yield (%)
Me	I	2	89
Bu	Br	0.5	78



$\text{R}' = \text{Bu}$ (78%); 4- ClC_6H_4 (63%);

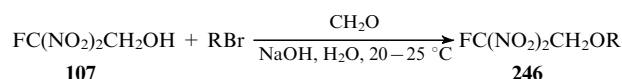


The reaction of 2,2-difluoro-2-nitroethanol **244** with compounds RX in the presence of 5% aqueous sodium hydroxide at $25-30^\circ\text{C}$ affords ethers **245**.¹⁶⁵



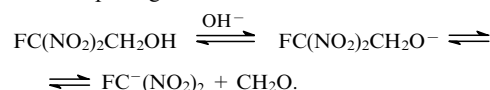
R, X (yield, %): $\text{Me}, \text{MeOSO}_2$ (78); $\text{CH}_2\text{CHCH}_2, \text{Cl}$ (75.5); $\text{HC}\equiv\text{CCH}_2, \text{Br}$ (27).

Condensation of the nitro alcohol **107** with allyl bromide or propargyl bromide catalysed by sodium hydroxide has been carried out in the presence of formaldehyde; this led to ethers **246** in 66% or 55% yield, respectively.⁹³

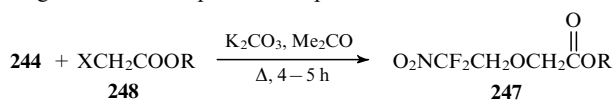


R (time /h): $\text{CH}_2\text{CH}=\text{CH}_2$ (45); $\text{HC}\equiv\text{CCH}_2$ (30).

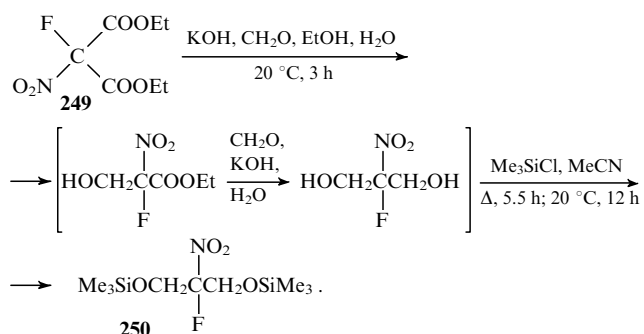
The role of formaldehyde was to prevent the nitro alcohol **107** from decomposing in the alkaline medium.⁹³



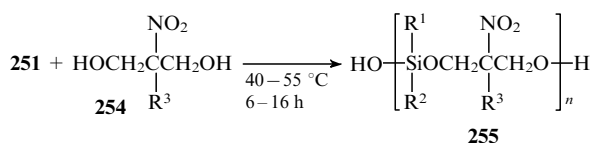
1,3-Dichloropropan-2-ol reacts with two molecules of the nitro alcohol **244** in the presence of 20% aqueous sodium hydroxide to give the diether $(\text{NO}_2\text{CF}_2\text{CH}_2\text{OCH}_2)_2\text{CHOH}$ in a yield of 78.6%.¹⁶⁶

$$\text{244} + \text{XCH}_2\text{COOR} \xrightarrow[\Delta, 4-5 \text{ h}]{\text{K}_2\text{CO}_3, \text{Me}_2\text{CO}} \text{O}_2\text{NCF}_2\text{CH}_2\text{OCH}_2\overset{\text{O}}{\parallel}\text{COR} \quad \text{247}$$


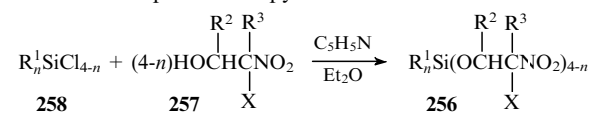
2-Fluoro-2-nitropropane-1,3-diol resulting from the reaction of diethyl 2-fluoro-2-nitromalonate **249** and the aldehyde **2** in the presence of potassium hydroxide has been introduced *in situ* in the reaction with chlorotrimethylsilane in boiling acetonitrile; this gave bis-silyl ether **250**.⁴⁹


$$\begin{array}{ccccc} \text{R}^1\text{R}^2\text{SiCl}_2 & + & \text{HOCHCH}_2\text{NO}_2 & \longrightarrow & \text{R}^1\text{R}^2\text{Si}(\text{OCHCH}_2\text{NO}_2)_2 \\ \text{251} & & \begin{array}{c} | \\ \text{R}^3 \end{array} \text{252} & & \begin{array}{c} | \\ \text{R}^3 \end{array} \text{253} \end{array}$$

Polysiloxanes **255** have been synthesised by the condensation of dichlorosilanes **251** with nitro-diols.¹⁶⁹



Compounds **256** containing one, two or three residues of nitro alcohols **257** are formed in the condensation of **257** with chlorosilanes **258** in the presence of pyridine.¹⁷⁰



<i>n</i>	R ¹	R ²	R ³	X	Yield (%)
3	Me	H	Me	Cl	44
2	Me	H	Me	Cl	66
2	Me	Me	H	Cl	40
3	Me	CCl ₃	H	H	14
2	Me	CCl ₃	H	H	15
1	H	H	Me	Cl	—
1	H	CCl ₃	H	H	30
3	Me	Et	Et	Br	12

The nitro alcohol **244** reacts with ethylene oxide or propylene oxide in the presence of aqueous sodium hydroxide at 0 °C for 16 h to give ethers $\text{RCH(OH)CH}_2\text{OCH}_2\text{C(NO}_2\text{)F}_2$ (R = H, Me) (yields 32% and 67%); in the case of ethylene oxide, the compound $\text{F}_2\text{C(NO}_2\text{)CH}_2\text{O(CH}_2\text{)}_2\text{OCH}_2\text{CH}_2\text{OH}$ is also formed (yield 4%).¹⁷³

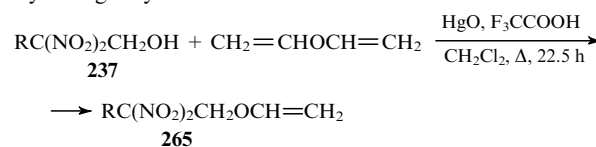
$$\begin{array}{ccc} \text{R} \begin{array}{c} \diagup \text{O} \diagdown \\ \triangle \end{array} + \text{O}_2\text{NCH}_2\text{CH}_2\text{OH} & \xrightarrow[50^\circ\text{C, 3 h}]{\text{BF}_3 \cdot \text{Et}_2\text{O or H}_2\text{SO}_4} & \\ \text{259} & & \text{202} \\ \longrightarrow & & \text{RCH(OH)CH}_2\text{OCH}_2\text{CH}_2\text{NO}_2 \\ & & \text{260} \end{array}$$

The compounds $\text{CH}\equiv\text{C}(\text{R})\text{C}(\text{OH})\text{CH}(\text{R}')-\text{OCH}_2\text{CH}_2\text{NO}_2$ have been obtained by the reaction of the nitro alcohol **202** with epoxides $\text{HC}\equiv\text{C}(\text{R})-\text{COCH}(\text{R}')$ (R and R' are H or lower alkyls) in the presence of 4-MeC₆H₄SO₃H or the KU-2 ion-exchange resin.¹⁷⁵

$$\begin{array}{c}
 \text{RC(NO}_2)_2(\text{CH}_2)_2\text{OH} \xrightarrow[\text{ClCH}_2\text{CH}_2\text{Cl}]{\text{CF}_3\text{SO}_3\text{H, N}_2} [\text{RC(NO}_2)_2(\text{CH}_2)_2\text{OH}_2^+] \xrightleftharpoons{-\text{H}_2\text{O}} \\
 \text{261} \\
 \rightleftharpoons \text{RC(NO}_2)_2(\text{CH}_2)_2^+ \xrightarrow{\text{R}'\text{C(NO}_2)_2(\text{CH}_2)_n\text{OH (263)}} \\
 \text{262} \\
 \longrightarrow \text{RC(NO}_2)_2(\text{CH}_2)_2\text{O(CH}_2)_n\text{C(NO}_2)_2\text{R}'. \\
 \text{264}
 \end{array}$$

R	R'	<i>n</i>	Temperature /°C	Time /h	Yield (%)
Me	F	2	60	20	9
Me	Me	2	60	20	80
F	F	2	60	96	15
NO ₂	NO ₂	2	65–70	72	16
F	F	1	30–35	168	20
NO ₂	Me	1	70–75	72	46
NO ₂	F	1	60–70	72	48

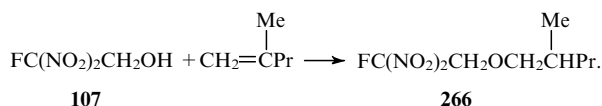
Refluxing of the nitro alcohols **237** with divinyl ether in the presence of HgO and trifluoroacetic acid leads to transesterification yielding vinyl ethers **265**.⁹²



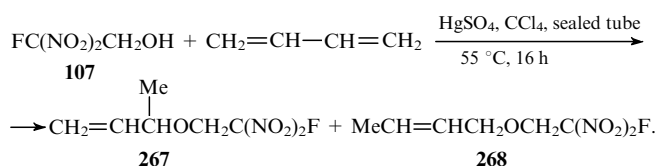
R = Me (64.2%), F (64%), NO₂ (25.9%).

The addition of nitro alcohols to alkenes or to buta-1,3-diene and the addition of alcohols to nitroalkenes have been used to synthesise ethers of nitro alcohols. For example, the reaction of 3-nitropropan-1-ol with 2-methylpropene in CH_2Cl_2 in the presence of sulfuric acid (20 °C, 12 h) gave the ether $\text{Bu}^t\text{O}(\text{CH}_2)_3\text{NO}_2$ (yield 95%).¹⁰⁸

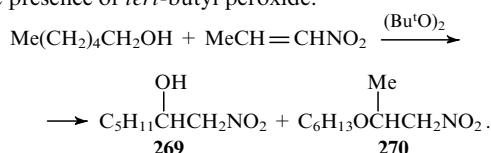
Adduct **266** was obtained by reaction of **107** with 2-methylpent-1-ene at 20 °C in the presence of HgSO_4 or Hg_2SO_4 (yields 74% and 58%, respectively).¹⁷⁸



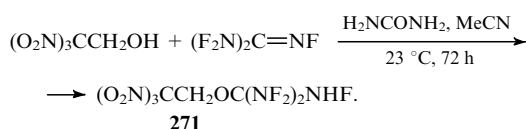
The reaction of the nitro alcohol **107** with buta-1,3-diene affords a mixture of 1,2-addition product **267** and 1,4-addition product **268** in a ratio of 77 : 23, their total yield being 53%.¹⁷⁸



Two products **269** and **270** resulting from radical C- and O-addition (yields 28% and 70%, respectively) have been synthesised by the reaction of hexan-1-ol with 1-nitroprop-1-ene in the presence of *tert*-butyl peroxide.¹⁷⁹

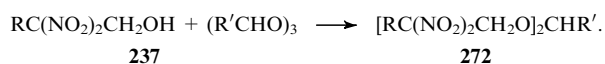


1,1,1-Trinitroethanol adds to the C=N bond in perfluoroguanidine at ambient temperature to give compound **271**.¹⁸⁰



Acyclic and cyclic acetals containing one or two nitro-alcohol residues are promising compounds for practical purposes.

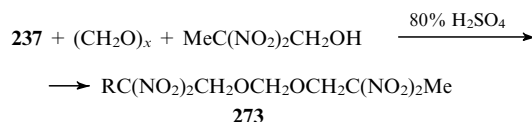
Acetals **272** have been synthesised by the reactions of the nitro alcohols **237** with 1,3,5-trioxane or with paraldehyde in the presence of sulfuric acid^{181, 182} or sodium hydroxide. The reaction conditions and the yields of products are presented in Table 13.⁸⁹



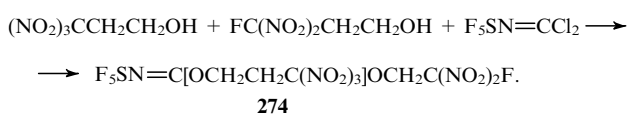
Mixed acetals **273**^{182, 183} and **274**¹⁸⁴ have been prepared by condensation of three components.

Table 13. Reaction condition and yields of the compounds **272**.

R	R'	Catalyst	Yield (%)	Ref.
F	H	H_2SO_4	—	181
Me	H	NaOH	78	89
Me	H	H_2SO_4	78	182
Me	Me	NaOH	35	89
NO_2	H	H_2SO_4	—	182



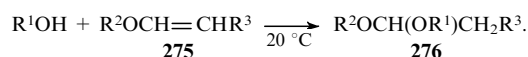
R = NO_2 ,¹⁸² F,¹⁸³



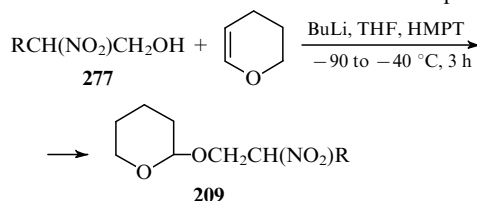
The acetal **273** (R = F) was synthesised by the reaction of the nitro alcohol $\text{FC}(\text{NO}_2)_2\text{CH}_2\text{OH}$ with the ether $\text{MeC}(\text{NO}_2)_2\text{CH}_2\text{OCH}_2\text{Cl}$ in the presence of TiCl_4 .¹⁸³

Polycondensation of formaldehyde with the diol $\text{HOCH}_2\text{C}(\text{NO}_2)_2\text{CH}_2\text{CH}_2\text{C}(\text{NO}_2)_2\text{CH}_2\text{OH}$ in the presence of sulfuric acid affords poly(nitroformal).¹⁸⁵

Nitro alcohols add to acyclic^{178, 186} or cyclic^{108, 142, 178} vinyl ethers **275** in the presence of catalysts to give acetals **276** (see Table 14).



The addition of nitro alcohols **277** to 2,3-dihydropyran in THF and HMPT in the presence of butyllithium at a temperature between −90 °C and −40 °C leads to the compounds **209**.¹⁵⁴



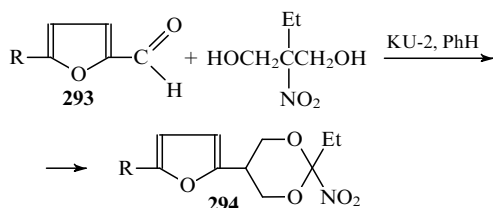
R = H, Me.

The nitro alcohol **107** adds to ethoxyacetylene in CH_2Cl_2 at 20 °C in the presence of HgSO_4 ¹⁸⁷ or $\text{Hg}(\text{OAc})_2$ ¹⁷⁸ or in the presence of HgO in CF_3COOH ⁹² giving rise to 2 : 1 adduct **278** (yields 100%, 95%, or 70%, respectively). When this reaction is carried out in the presence of $\text{Hg}(\text{OAc})_2$ in CH_2Cl_2 and hexane at 20 °C, the 1 : 1 adduct **279** is produced in 73% yield in addition to the adduct **278** (yield 27%).¹⁷⁸

Table 14. Conditions for the formation of the acetals **276**.

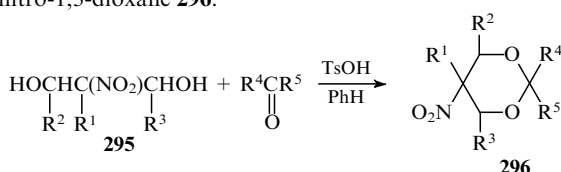
R ¹	R ²	R ³	Catalyst	Solvent	T / °C	Time / h	Yield (%)	Ref.
$\text{O}_2\text{N}(\text{CH}_2)_3$	$-(\text{CH}_2)_3-$		TsOH	Et_2O	20	5	95	108
 CHCH_2NO_2	$-(\text{CH}_2)_3-$		TsOH	Et_2O	20	12	90.5	142
$\text{FC}(\text{NO}_2)_2\text{CH}_2$	Et	H	$\text{Hg}(\text{OAc})_2$	CH_2Cl_2	20	16	73	178
$\text{FC}(\text{NO}_2)_2\text{CH}_2$	$-(\text{CH}_2)_3-$		$\text{Hg}(\text{OAc})_2$	CH_2Cl_2	42	17	100	178
$\text{FC}(\text{NO}_2)_2\text{CH}_2$	$\text{FC}(\text{NO}_2)_2\text{CH}_2$	H	$\text{Hg}(\text{OAc})_2$	CH_2Cl_2	20	24	61	178
$(\text{O}_2\text{N})_3\text{CH}_2\text{CH}_2$	$\text{FC}(\text{NO}_2)_2\text{CH}_2$	H	$\text{BF}_3 \cdot \text{Et}_2\text{O}$	—	0	12	—	186
$\text{MeC}(\text{NO}_2)_2\text{CH}_2$	$\text{FC}(\text{NO}_2)_2\text{CH}_2$	H	Mol. sieve 5 Å	—	0	12	—	186
$\text{FC}(\text{NO}_2)_2\text{CH}_2$	$\text{FC}(\text{NO}_2)_2\text{CH}_2$	H	Mol. sieve 5 Å	—	0	12	—	186

The rate of the reaction of 5-substituted furfural derivatives **293** with 2-ethyl-2-nitropropane-1,3-diol in the presence of the KU-2 ion-exchange resin (H-form) has been shown to decrease in the series $\text{NO}_2 > \text{I} > \text{Br} > \text{H} > \text{Me}$. It was assumed that attack by the diol on the protonated formyl group is the rate-determining step of the reaction.¹⁹⁶



$\text{R} = \text{H}$ (66%), Me (70%), Br (84%), I (79%), NO_2 (82%).

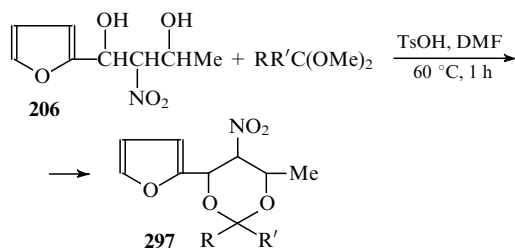
Cyclocondensation of mono- and disubstituted 2-nitropropane-1,3-diol derivatives **295** with aldehydes or ketones in the presence of TsOH gave di-, tri- or tetra-substituted derivatives of 5-nitro-1,3-dioxane **296**.¹⁹⁷



$\text{R}^1 = \text{H}, \text{Me}, \text{CH}_2\text{OH}$; $\text{R}^2 = \text{H}, \text{Me}, \text{Pr}, \text{Pr}^i$; $\text{R}^3 = \text{H}, \text{Me}, \text{Pr}, \text{Pr}^i$;
 $\text{R}^4 = \text{H}, \text{Me}$; $\text{R}^5 = \text{H}, \text{Me}, \text{Et}, \text{Pr}^i, \text{Bu}, \text{Ph}, 2\text{-HOC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4$,
 $\text{PhCH}=\text{CH}$; $\text{R}^4, \text{R}^5 = (\text{CH}_2)_5$.

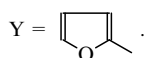
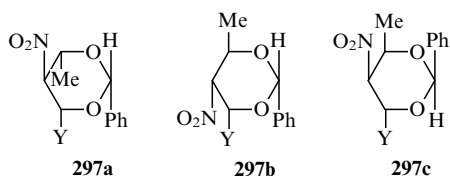
The compounds **296** were obtained in low yields for $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{Me}$ (27%); $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Me}$, $\text{R}^4 = \text{R}^5 = \text{H}$ (30%) and $\text{R}^1 = \text{R}^4 = \text{R}^5 = \text{H}$, $\text{R}^2 = \text{R}^3 = \text{Pr}^i$ (32%).¹⁹⁷

1,3-Dioxane derivatives **297** were synthesised from the nitro-diol **206** using acetone dimethyl ketal or benzaldehyde dimethyl acetal as the second reactant.^{152, 198}



$\text{R} = \text{H}, \text{R}' = \text{Ph}$; $\text{R} = \text{R}' = \text{Me}$.

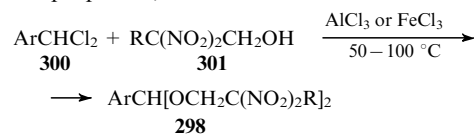
The reaction of **206** with benzaldehyde dimethyl acetal affords three diastereoisomers **297a,b,c** in 55.5% overall yield and in a ratio of 4:1:1.¹⁵²



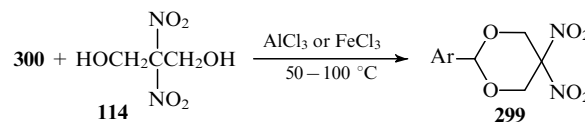
Refluxing of the nitro-diol $\text{HOCH}_2\text{CH}(\text{NO}_2)\text{CH}(\text{OH})\text{C}_{13}\text{H}_{27}$ with acetone dimethyl ketal in acetone in the presence of toluene-*p*-sulfonic acid results in the formation of 2,2-dimethyl-5-nitro-4-tridecyl-1,3-dioxane in 61.5% yield.⁶¹

Yet another method for the synthesis of acyclic and cyclic acetals of aromatic aldehydes and nitro alcohols consists of the reaction of dichloromethyl arenes with alcohols or 1,3-diols. This

procedure was used, for example, to prepare acetals **298** or **299** from dichloromethylarenes **300** and polynitro alcohols **301** or 2,2-dinitropropane-1,3-diol **114**.¹⁹⁹



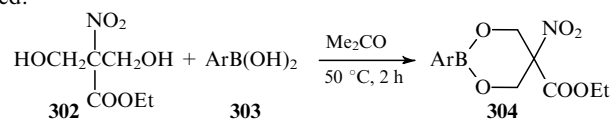
$\text{R} = \text{Cl}, \text{Me}, \text{NO}_2$; $\text{Ar} = \text{Ph}, 3\text{-O}_2\text{NC}_6\text{H}_4, 4\text{-O}_2\text{NC}_6\text{H}_4$;



$\text{Ar} = \text{Ph}, 3\text{-O}_2\text{NC}_6\text{H}_4$ (AlCl_3), $4\text{-O}_2\text{NC}_6\text{H}_4$ (FeCl_3).

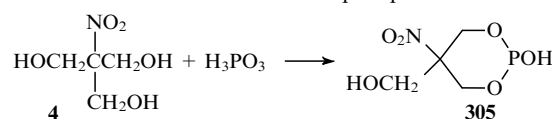
The reactivity of nitro alcohols decreases in the order $\text{NO}_2 > \text{Cl} > \text{HCCH}_2 > \text{Me}$, i.e. in parallel with their acidity.¹⁹⁹

By refluxing nitro-diol **302** with arylboronic acids **303** in acetone, 2-bora-1,3-dioxane derivatives **304** have been synthesised.²⁰⁰

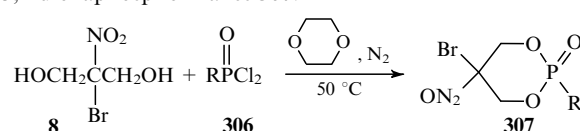


$\text{Ar} = \text{Ph}$ (90.5%), $4\text{-ClC}_6\text{H}_4$ (67%).

Cyclic compound **305** containing two oxygen atoms and a phosphorus atom in the six-membered ring has been obtained by cyclocondensation of the triol **4** with phosphorous acid.²⁰¹

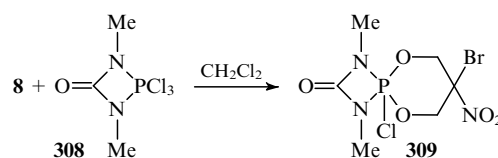


2-Bromo-2-nitropropane-1,3-diol **8** reacts with dichloro-derivatives **306** at 50 °C to give 5-bromo-5-nitro-2-R-2-oxo-1,3,2-dioxaphosphorinanes **307**.²⁰²

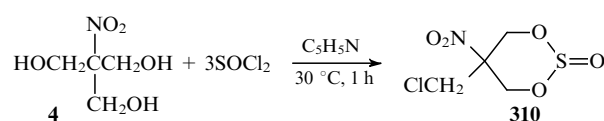


$\text{R} = \text{Me}$ (60%), Cl (28%), PhO (56%), $4\text{-MeC}_6\text{H}_4\text{O}$ (49%),
 $3\text{-MeC}_6\text{H}_4\text{O}$ (42%), $4\text{-O}_2\text{NC}_6\text{H}_4\text{O}$ (60%), OH (39%).

Cyclocondensation of the diol **8** with 2,2,2-trichloro-1,3-dimethyl-1,3,2λ⁵-diazaphosphetidin-4-one **308** gives rise to compound **309**.²⁰³



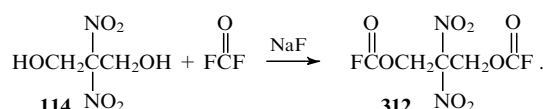
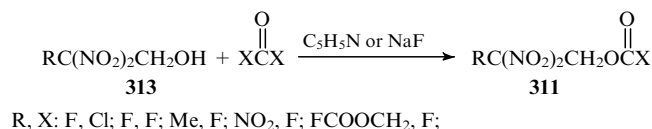
5-Chloromethyl-5-nitro-1,3,2-dioxathian-2-one **310** was synthesised by the reaction of the triol **4** with thionyl chloride in the presence of pyridine.²⁰⁴



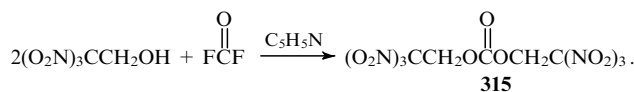
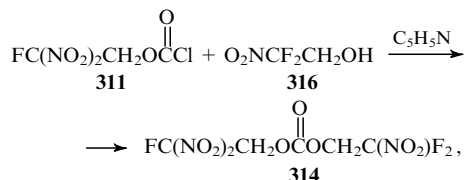
Esters derived from nitro alcohols are usually synthesised either by reactions of nitro alcohols with acid chlorides or anhydrides or by reactions of nitro alcohols with carboxylic acids in the presence of anhydrides of other acids. The preparation

of nitro alcohol acetates has been described in numerous publications. There is no need to consider these studies in detail, because the acetates have been synthesised by conventional procedures, which have been described fairly comprehensively in monographs.^{3, 4}

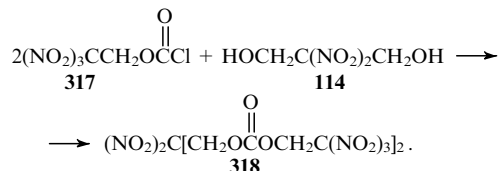
Syntheses of halocarbonates **311** and **312** (yield 91%) by the reactions of nitro alcohols **313** with carbonyl dichloride or difluoride or by the reaction of 2,2-dinitropropane-1,3-diol **114** with carbonyl difluoride have been reported in patents^{205, 206} and papers.^{207, 208}



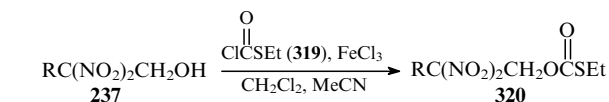
Carbonates **314**²⁰⁵ or **315** (yield 64%)²⁰⁸ were prepared by the reaction of nitro alcohol **316** with the chloroformate **311** (R = F, X = Cl) or of 2,2,2-trinitroethanol with carbonyl difluoride.



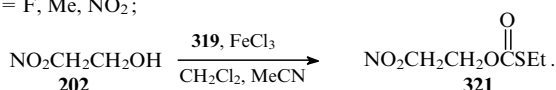
2,2-Dinitropropane-1,3-diol **114** reacts with two molecules of chloroformate **317** giving rise to diester **318** (yield 83%).²⁰⁹



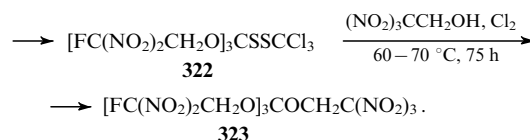
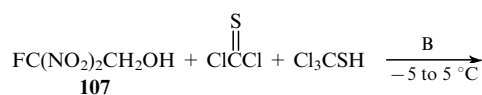
The exothermic reaction of the nitro alcohols **237** or **202** with chloride **319** in the presence of iron(III) chloride has led to the synthesis of *O*-alkyl *S*-ethyl thiocarbonates **320**²¹⁰ or **321**.



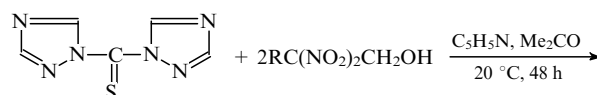
R = F, Me, NO₂;



The three-component reaction involving the nitro alcohol **107**, thiophosgene and Cl₃CSH, taken in a ratio of 3 : 1 : 1, carried out in the presence of a base under conditions of phase transfer catalysis affords compound **322**, which is converted into compound **323** (yield 81%) upon treatment with 1,1,1-trinitroethanol and chlorine.²¹¹

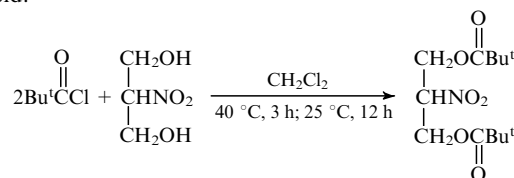


When 2,2-dinitropropanol is made to react with bis(1,2,4-triazol-1-yl) thioketone in acetone in the presence of pyridine at 20 °C, the ester [MeC(NO₂)₂CH₂O]₂C=S is formed in 83% yield over a period of 2 days.²¹² Similarly, the reaction of (O₂N)₃CCH₂OH or the alcohol **107** with bis(1,2,4-triazol-1-yl) sulfoxide yields the corresponding esters.²¹²

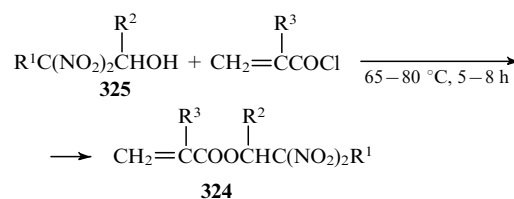


R = F, Me, NO₂.

The reaction of 2-nitropropane-1,3-diol with trimethylacetyl chloride in dichloromethane carried out for 3 h at 40 °C and then for 12 h at 25 °C affords the corresponding bis-ester in 95% yield.¹⁵



Esters **324**, which are of interest as monomers, have been synthesised in 60%–70% yields by the reactions of dinitro alcohols **325** with chlorides of α,β-unsaturated acids.^{213–215}



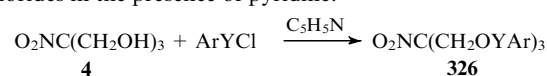
R¹ = H, F, Me; R² = H, Me; R³ = H, Me.

It should be noted that the yield of **324** (R¹ = F, R² = R³ = Me) was as low as 5%.²¹⁴ The reaction of the nitro alcohol **325** (R¹ = Me, R² = H) with acryloyl chloride carried out for 3 h at 20 °C in the presence of TiCl₄ affords the corresponding ester **324** (R¹ = Me, R² = R³ = H) in 93% yield.²¹³

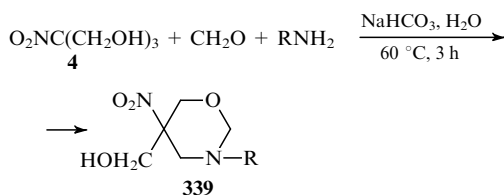
The reaction of perfluoroacryloyl chloride with the nitro alcohol **244** in the presence of triethylamine at –40 to –35 °C follows two competing pathways: esterification of the nitro alcohol giving the ester F₂C=CF₂COOCH₂C(NO₂)₂F₂ (yield 7.9%) and the addition of the nitro alcohol to the double bond of the chloride leading to the ether F₂C(NO₂)CH₂OCF₂–CH(F)COCl (yield 7%).²¹⁶

Esters derived from nitro alcohols and unsaturated dicarboxylic acids have been described in the literature.^{217, 218}

Tris-esters **326** have been prepared by the reactions of the nitro-triol **4** with benzoyl, 4-chlorobenzoyl and toluene-*p*-sulfonyl chlorides in the presence of pyridine.¹⁶⁴



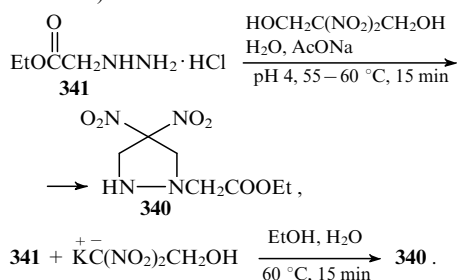
Ar	Y	T / °C	Time / h	Yield (%)
Ph	CO	70	15	51
4-ClC ₆ H ₄	CO	20	30	93
4-MeC ₆ H ₄	SO ₂	0	12	47



R = Me (32%); Prⁱ (22%); Bu^t (77%).

The compounds **339** (R = Me, Et, Pr, Prⁱ, Bu and Bu^t) have also been obtained by another method, namely, the reaction of the nitro-triol **4** with the corresponding 1,3,5-trialkylhexahydro-1,3,5-triazines.²²⁹

The pyrazolidine derivative **340** has been synthesised by the reaction of hydrochloride **341** with 2,2-dinitropropane-1,3-diol **114** (yield 86%) or with the potassium salt of 2,2-dinitroethanol (yield 23.5%).²³⁰



Cyclocondensation of the nitro-diols **302** or **114** with formaldehyde and primary amines leads to hexahydropyrimidine derivatives **342**. The reaction conditions and the yields of reaction products are listed in Table 16.^{200, 231, 232}

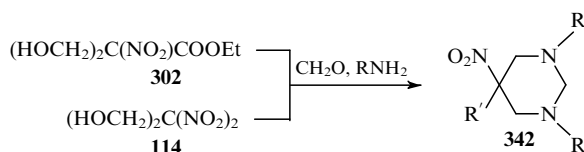
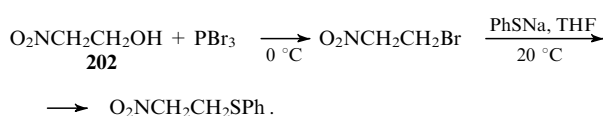


Table 16. Reaction conditions and yields of the compounds **342**.

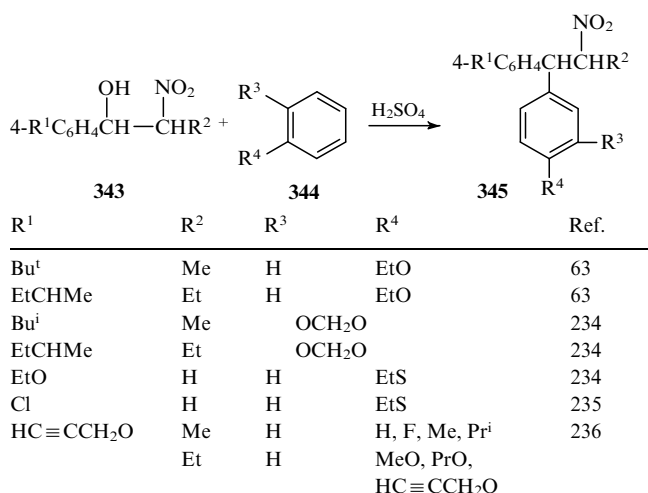
R	R'	Solvent	T / °C	Time / h	Yield (%)	Ref.
Bu ^t	COOEt	EtOH	78	2	25	200
Me	NO ₂	EtOH	5–20		19	231
Bu ^t	NO ₂	MeOH	20	1	29	231
Me ^a	NO ₂	see ^b	20	24	35	232
CH ₂ COOMe ^a	NO ₂	see ^b	20	18	22	232
CH ₂ COOEt ^a	NO ₂	see ^b	20	18	15	232

^a Hydrochlorides of the amines were used; ^b in the presence of AcONa, pH 4.

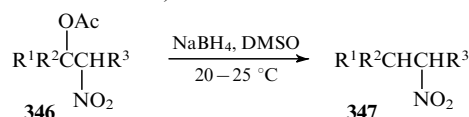
When the nitro alcohol **202** is treated successively with phosphorus tribromide and sodium thiophenoxide, the corresponding thioether is formed in an overall yield of 73%.²³³



The hydroxy group in nitro alcohols **343** is replaced by aryl groups when **343** are treated with arenes **344** in the presence of sulfuric acid; this yields diphenylmethane derivatives **345**.^{63, 234–236}



On treatment of acetates **346** with sodium tetrahydridoborate in DMSO or ethanol at 20–25 °C for 1.5 h, the acetoxy group is substituted by a hydrogen atom giving nitro-compounds **347** (yields 41%–90%).^{27, 237}



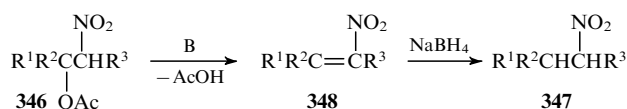
R¹ = C₆H₁₃, C₇H₁₅, ,

Me₂C=CH(CH₂)₂C(Me)=CH(CH₂)₂; R² = R³ = H;²⁷

R¹ = Me, Et, Bu, Ph, MeCH(Et)(CH₂)₃; R² = H, Me;

R³ = H, Me, Et, Pr; R², R³ = (CH₂)₅.²³⁷

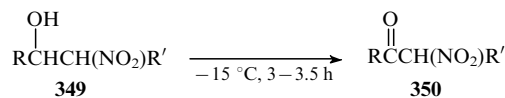
The formation of **347** from the acetates **346** involves the intermediate formation of nitroalkenes **348**.²³⁷



4. Reactions involving several sites

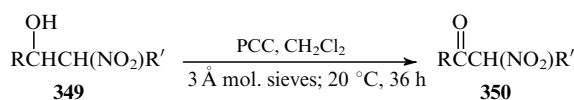
Oxidation of nitro alcohols to nitro-carbonyl derivatives can involve simultaneously two reaction sites, namely, the hydroxy group and the hydrogen atom attached to the carbon atom carrying the hydroxy group.

Nitro alcohols **349** have been converted into nitro ketones **350** by treatment with chromium(VI) oxide supported on montmorillonite at –15 °C accompanied by ultrasonic treatment.⁷²

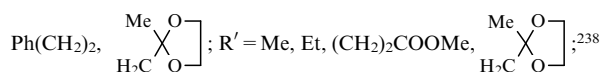


R, R' (yield, %): Me, Me (90); Et, H (76); Prⁱ, Me (93); Prⁱ, Et (90).

Pyridinium chlorochromate has proved to be a good reagent for the transformation of nitro alcohols into nitro ketones. Treatment of nitro alcohols **349** with this reagent in the presence of molecular sieves at 20 °C gave nitro ketones **350** (yields 61%–87%).^{83, 238}



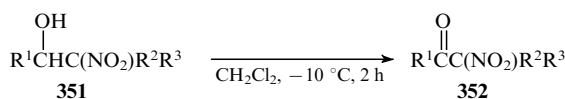
R = Me, CH₂=CH(CH₂)₂; R' = EtCH=CHCH₂; ⁸³ R = Me, Prⁱ,



PCC is pyridinium chlorochromate.

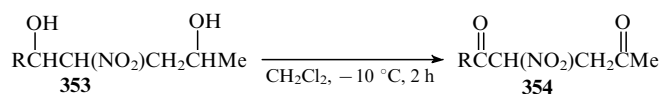
It has been found ²³⁹ that both the rate of the oxidation of EtCH(OH)CH(NO₂)Et with pyridinium chlorochromate on silica gel in CH₂Cl₂ and the yield of the nitro ketone EtCOCH(NO₂)Et formed in this reaction markedly increase upon ultrasonic treatment: without ultrasound the yield of the product is 60% over a period of 1.5–2.5 h at 25 °C, whereas the reaction carried out with sonication is completed over a period of 20 min at –18 °C (yield 71%).

On treatment with K₂Cr₂O₇ or K₂CrO₄ in the presence of Bu₄N⁺HSO₄[–], H₂SO₄ and FeSO₄ at –10 °C, nitro alcohols **351** are readily oxidised to give nitro ketones **352** in high yields (70%–93%), ⁶⁷ and nitro-diols **353** are easily oxidised to nitro diketones **354**. ¹⁵⁵



R¹ = Me, Prⁱ, C₆H₁₃, Ph(CH₂)₂, CH₂=CH(CH₂)₂;

R² = Me, Et, $\begin{array}{c} \text{O} \\ \diagup \quad \diagdown \\ \text{H}_2\text{C} \end{array}$, $\begin{array}{c} \text{Me} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O} \\ \diagdown \quad \diagup \\ \text{H}_2\text{C} \end{array}$, (CH₂)₂COOMe; R³ = H, Me.



R = Me (53%), Prⁱ (45%), C₅H₁₁ (47%), C₁₀H₂₁ (58%), $\text{Cyclo-C}_6\text{H}_{11}$ (58%),

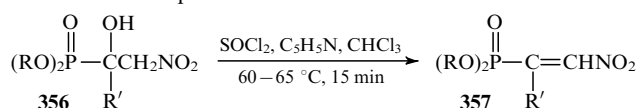
PhCH₂CH₂ (70%), Z-Me(CH₂)₇CH=CH(CH₂)₇ (58%),

Me(CH₂)₄CH(NO₂)(CH₂)₂ (65%).

3-Chloro-6-nitrohexan-2-one has been synthesised in 75% yield by the oxidation of 3-chloro-6-nitrohexan-2-ol with a solution of Na₂Cr₂O₇ in H₂SO₄ at 10–20 °C for 10 h. ⁵⁸

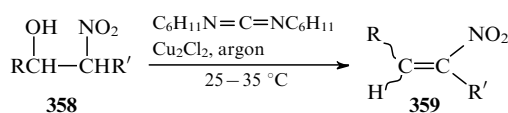
Heating of 1-nitropropan-2-ol with hydrochloric acid (18%–36%) at 95–107 °C for 5–30 h affords lactic acid in 14%–16% yield. ²⁴⁰

Attempts to dehydrate compounds **356** with phthalic anhydride, P₂O₅ or MeCOCl were unsuccessful: the reactions were accompanied by rupture of the C–P bond. Dehydration of these compounds was accomplished by heating them with thionyl chloride in the presence of pyridine. This gave the corresponding unsaturated compounds **357**. ¹²⁷



R, R' (yield, %): Me, Me (58); Me, Et (69); Et, Prⁱ (59); Prⁱ, Et (53).

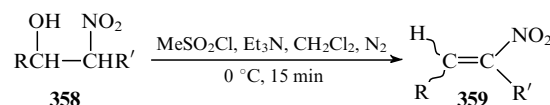
Primary and secondary nitro alcohols **358** are readily dehydrated on treatment with cyclohexylcarbodiimide, being converted into mixtures of diastereoisomeric nitroalkenes **359**. ²⁴¹



R	R'	Time /h	Yield (%)	Isomeric ratio Z/E
H	Me	3.5	35	
Me	Me	17	82	70 : 30
H	C ₆ H ₁₃	2.5	60	
Bu	H	10	90	83 : 17
see ^a	H	14	75	
Bu ^t	H	17	94	
MeCH=CH	H	60	70	
Bu	Me	17	99	55 : 45
2-Furyl	H	24	66	

^a Me₂C=CH(CH₂)₂CH(Me)CH₂.

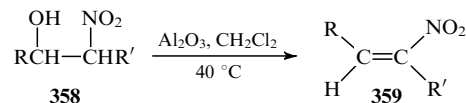
The methanesulfonyl chloride–triethylamine system has also been used for the transformation of nitro alcohols **358** into nitroalkenes **359** (yields 30%–80%). ^{70, 242}



R = Me, Et, R' = Me, Et; ²⁴² R = Me, R' = PhS. ⁷⁵

The nitroalkene Z-MeCH(NO₂)CH₂CH₂CH=C(NO₂)Me is formed in 80% yield when the nitro alcohol MeCH(NO₂)CH₂–CH₂CH(OH)CH(NO₂)Me is refluxed with MeSO₂Cl and Et₃N in dichloromethane under nitrogen. ⁷⁵

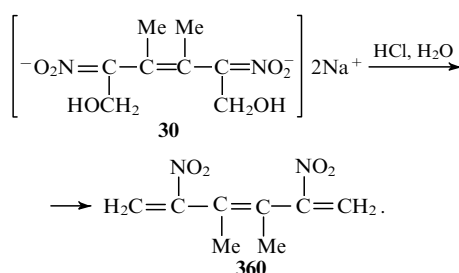
The E-isomers of nitroalkenes **359** were synthesised by dehydration of the nitro alcohols **358** over alumina (Brockmann activity I) at 40 °C. ⁷¹



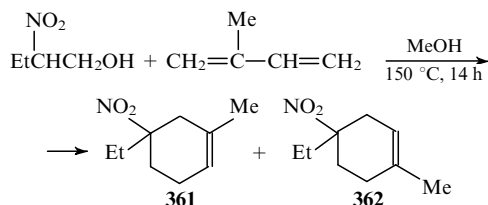
R	R'	Time /h	Yield (%)
Me	Me	8	75
Me	Et	7	77
Me	(CH ₂) ₄ COOMe	7	76
Me	CH ₂ CH(OH)Me	7	73
EtCH=CH(CH ₂) ₂	Me	7	85
Ph(CH ₂) ₂	Me	9	68
Et	H	48	60
C ₆ H ₁₃	H	50	61
Et	(CH ₂) ₆ OH	7	68
cyclo-C ₆ H ₁₁	C ₅ H ₁₁	24	72

The dehydration occurs selectively: when the molecule contains both primary and secondary hydroxy groups, the secondary group is eliminated preferentially. ⁷¹

It is of interest that the dinitro-diol resulting from acidification of the solution of the salt **30** with hydrochloric acid to pH 1 is dehydrated under the reaction conditions to give triene **360** in 26.7% yield. ⁵²



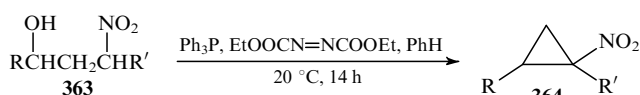
When a mixture of 2-nitrobutan-1-ol and isoprene is kept at 150 °C, the nitro alcohol is dehydrated, and the resulting 2-nitrobut-2-ene reacts *in situ* with isoprene to give a mixture of [4 + 2]-adducts **361** and **362**.²⁴³



On treatment with potassium hydroxide in Et₂O for 2 h at –15 to –20 °C, the nitro alcohol O₂NCH₂CH(OH)CH₂Cl is converted into the aldehyde O₂NCH₂CHCH₂CHO (yield 21 %).²⁴⁴

The reactions of 1,1,1-trinitroethanol or trinitromethane with formaldehyde in the presence of CuSO₄ followed by treatment of the reaction products with ammonia at 100–105 °C for 8–9 h lead to the same product, 2,2-dinitroethylamine.^{98, 245}

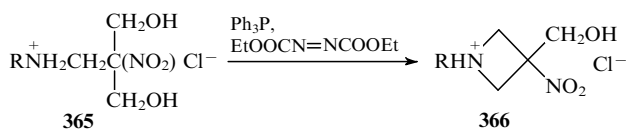
Under conditions of the Mitsunobu reaction (treatment with triphenylphosphine and diethyl azodicarboxylate under an inert atmosphere),²⁴⁶ γ-nitro alcohols **363** are converted into nitroderivatives of cyclopropane **364**.²⁴⁷



R	R'	Yield (%)	Ratio <i>trans</i> : <i>cis</i>
C ₃ H ₁₁	H	82	10 : 1
C ₃ H ₁₁	Me	87	10 : 1
4-PhC ₆ H ₄	H	75	<i>trans</i>
4-MeOC ₆ H ₄	H	92	7 : 1
PhCH ₂ OCH ₂ CH=CH	H	64	<i>trans</i>

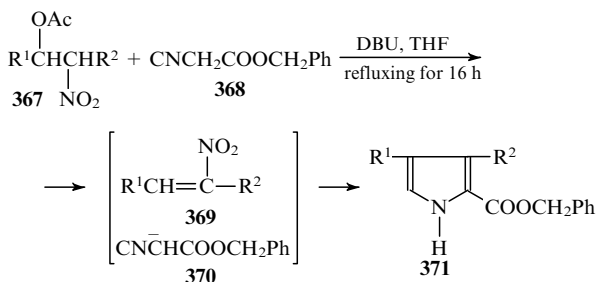
Under the same conditions, PhCH₂OCH₂CH(OH)–CH(CH₂OCH₂Ph)CH₂NO₂ is converted into 1,3-bis(benzyl-oxy)-2-nitrocyclopropane in 98% yield (the ratio of the isomers was not determined).²⁴⁷

When hydrochlorides **365** are introduced into the Mitsunobu reaction, they are converted into hydrochlorides of 1-alkyl-3-hydroxymethyl-3-nitroazetidines **366**.²²⁹



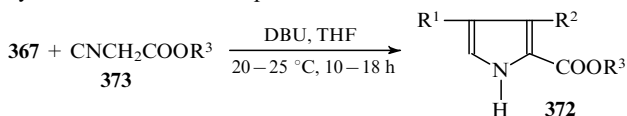
R = Me, Et, Pr, Prⁱ, Bu, Bu^t.

When acetates of nitro alcohols **367** and isonitrile **368** are heated in the presence of DBU, **367** are converted into nitroalkenes **369**, while the isonitrile is deprotonated to give carbanion **370**. The nitroalkenes and the carbanion react to give pyrrole derivatives **371**.²⁴⁸



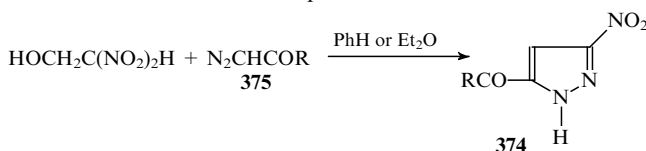
R, R' (yield, %): Me, Me (72); Et, Me (74); Me, Et (76); Et, Et (74); (CH₂)₂COOMe, Me (60); Me, (CH₂)₂COOMe (53).

Pyrrole derivatives **372** have been obtained in high yields (70%–86%) by cyclocondensation of the acetates **367** with alkyl cyanoacetates **373** in the presence of DBU at 20–25 °C.¹⁰⁷



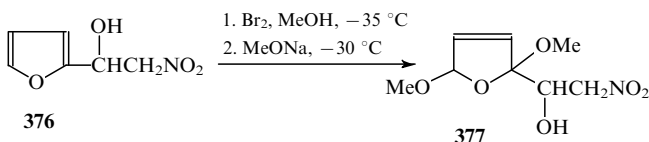
R¹ = Et, (CH₂)₂COOMe; R² = Me, Et, (CH₂)₂COOMe; R³ = Et, Bu^t.

Pyrazole derivatives **374** are formed in the reaction of 2,2-dinitroethanol with diazo compounds **375** in benzene or ether.²⁴⁹



R = OEt (PhH, 50 °C, 6 h, 46%); Me (PhH, 50 °C, 4 h, 64%); Ph (Et₂O, 36 °C, 14 h, 63%).

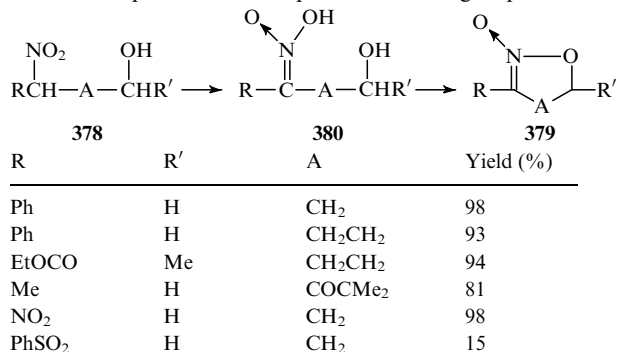
2-(1-Hydroxy-2-nitroethyl)furan **376** reacts with bromine and sodium methoxide to give 2,5-dihydrofuran derivative **377** in 77.5% yield.¹⁴²



2,4,4-Trimethyl-2-nitromethyltetrahydrofuran (yield 30%) is formed when the nitro alcohol BrCH₂CMe₂CH₂C(OH)(Me).CH₂NO₂ is kept over Al₂O₃ in benzene at 25 °C.²⁵⁰

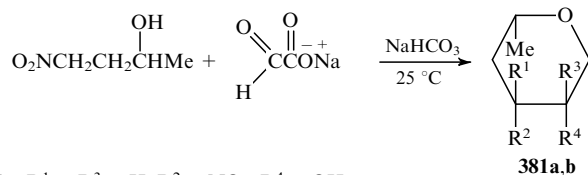
Treatment of (*S*)-1-nitropentan-1-ol with 30% H₂O₂ and K₂CO₃ in methanol (0 °C, 24 h) followed by the addition of hydrochloric acid results in the formation of (*S*)-4,5-dihydro-5-methylfuran-2(3*H*)-one (yield 7%).¹¹¹

Under the conditions of the Mitsunobu reaction, nitro alcohols **378** cyclise to give either isoxazoline *N*-oxides or dihydro-1,2-oxazine *N*-oxides **379** depending on the mutual arrangement of the nitro and hydroxy groups. When R = PhSO₂, the yield of the corresponding isoxazoline is relatively low; in this case, 1-nitro-1-phenylsulfonylcyclopropane is formed as the main reaction product. For the cyclisation products to be formed in high yields, it is necessary that an electron-withdrawing group or a double bond, which stabilise the *aci*-form **380** of the initial compounds, be present in the α-position with respect to the nitro group.²⁵¹



2-Hydroxy-6-methyl-5-nitrotetrahydropyran has been synthesised in 68% yield by cyclocondensation of acrolein with 1-nitropropan-2-ol in the presence of diethylamine and formic acid at 60–62 °C for 20 h.²⁵²

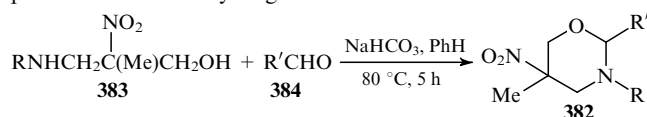
The reaction of 4-nitrobutan-2-ol with sodium glyoxylate in the presence of Na_2CO_3 resulted in the isolation of compound **381** as two isomers (**a** and **b**), their yields being 32% and 10%, respectively.²⁵³



381a: $\text{R}^1 = \text{R}^3 = \text{H}$, $\text{R}^2 = \text{NO}_2$, $\text{R}^4 = \text{OH}$;

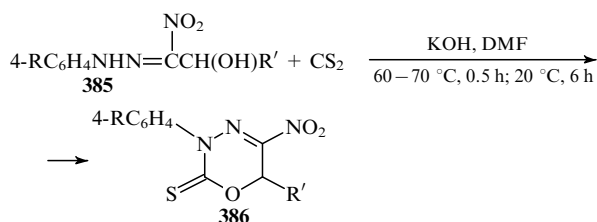
381b: $\text{R}^1 = \text{NO}_2$, $\text{R}^3 = \text{OH}$, $\text{R}^2 = \text{R}^4 = \text{H}$.

Tetrahydro-1,3-oxazine derivatives **382** have been prepared by refluxing compounds **383** with aldehydes **384** in benzene in the presence of sodium hydrogencarbonate.²⁵⁴



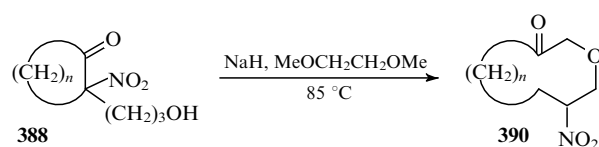
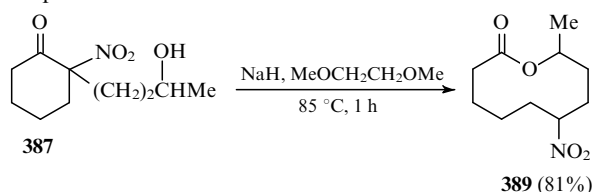
R, R' (yield, %): PhCH_2, Me (80); $\text{cyclo-C}_6\text{H}_{11}, \text{Me}$ (60); PhCH_2, Ph (60).

Hydrazone **385** react with carbon disulfide in the presence of potassium hydroxide to give 1,3,4-oxadiazine-2-thiones **386**.¹⁵⁹



$\text{R} = \text{H}, \text{R}' = \text{Me}$ (71%); $\text{R} = \text{Me}, \text{R}' = \text{H}$ (88%), Me (78%).

On heating with sodium hydride, cyclic ketones **387** or **388** containing nitro and 3-hydroxyalkyl groups in the α -position with respect to the oxo group isomerise with ring expansion giving rise to compounds **389** or **390**.²⁵⁵

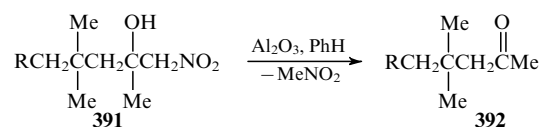


n	Time /min	Yield (%)
4	45	91
10	30	87

5. Cleavage of nitro alcohols

Under certain conditions, β -nitro alcohols (or β -nitro-diols) are cleaved to give the initial carbonyl derivatives and nitro-compounds (or their salts).

In the presence of alumina at ambient temperature, nitro alcohols **391** are cleaved to nitromethane and ketones **392**.^{250, 256}



$\text{R} = \text{Br}$ (20%),²⁵⁰ NO_2 (72%).²⁵⁶

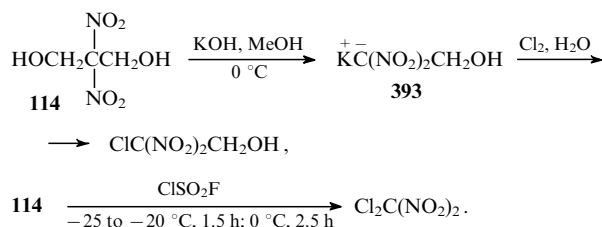
AcONa , BaO or KNaHPO_4 can be used instead of Al_2O_3 .²⁵⁶

Benzyltrimethylammonium hydroxide cleaves the nitro alcohol $\text{Me}_2\text{C}(\text{OH})\text{CH}(\text{NO}_2)(\text{CH}_2)_2\text{NO}_2$ on refluxing in methanol for 6 h to give acetone and 1,3-dinitropropane (yield 50%).²⁵⁷ This process can be carried out in ethanol, dioxane, THF or DMF in the presence of Na_2CO_3 , Na_3BO_3 , MgO or BaCO_3 .²⁵⁷

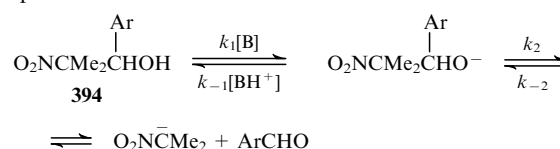
Treatment of the alcohol **107** with sodium dichromate and sulfuric acid results in its cleavage giving formaldehyde and fluorodinitromethane (yield 65%).²⁵⁸

When the dinitro-diol **114**¹⁵⁷ or 2,2-dinitropentane-1,3-diol²⁵⁹ is treated with potassium hydroxide in methanol, the salt $\text{K}^+\text{C}^-(\text{NO}_2)_2\text{CH}_2\text{OH}$ and CH_2O or MeCHO are formed.

The reaction of compound **114** with potassium hydroxide and sodium carbonate yields salt **393**, which reacts with chlorine to give 2-chloro-2,2-dinitroethanol (overall yield 48%).¹⁵⁷ Treatment of the dinitro-diol **114** with chlorine fluorosulfonate affords dichlorodinitromethane (yield 15%).²⁶⁰



The decomposition of nitro alcohols **394** in an aqueous buffer solution with μ 1.0 D and pH 6.5–8.4 has been studied at 25.3 $^\circ\text{C}$ by spectrophotometry. The rate constants for the reaction were determined. It was postulated that deprotonation occurs rapidly, while the rupture of the C–C bond is the rate-determining step of the process.²⁶¹

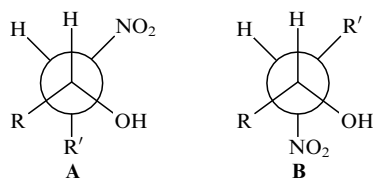


Ar , $10^4 k$ (litre $\text{mol}^{-1} \text{s}^{-1}$): Ph , 3.02 (pH 4.6–8.4); 4-MeC₆H₄, 3.37; 4-MeOC₆H₄, 5.09; 4-ClC₆H₄, 4.22; 4-O₂NC₆H₄, 4.54; 3-ClC₆H₄, 3.79; 3-MeC₆H₄, 3.07.

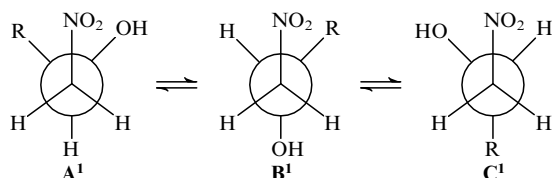
6. Intramolecular hydrogen bonds in nitro alcohols and nitro-diols

Studies discussing the problems concerning intramolecular hydrogen bonding in nitro alcohols and published before 1977 have been surveyed in a review.²⁶²

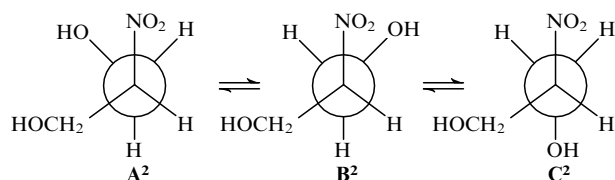
The configurations of the *erythro*- and *threo*-isomers of the nitro alcohols $\text{RCH}(\text{OH})\text{CH}(\text{NO}_2)\text{R}'$ ($\text{R}, \text{R}' = \text{Me}, \text{Me}; \text{Pr}^i, \text{Me}; \text{CF}_3, \text{Me}; \text{CCl}_3, \text{Me}; \text{CBr}_3, \text{Me}; 4\text{-O}_2\text{NC}_6\text{H}_4, \text{Et}; 4\text{-O}_2\text{NC}_6\text{H}_4, \text{Pr}^i$) have been established by IR and ^1H , ^{13}C and ^{15}N NMR spectroscopy. It was found that the *erythro*-isomers occur mostly in the *gauche* conformation **A**, and the *threo*-isomers exist predominantly in the *gauche* conformation **B**. These conformers predominate because they are stabilised by intramolecular hydrogen bonds between OH and NO_2 groups.⁶⁴



The conformation equilibria for the alcohols $RCH(OH)CH_2NO_2$ [$R = H$ (**202**), Me, Ph, CCl_3] and for 2-nitropropane-1,3-diol **3** have been studied. In the case of the alcohols, equilibrium conformations **A**¹, **B**¹ and **C**¹ were considered.²⁶³



For the diol **3**, equilibrium conformations **A**², **B**² and **C**² were discussed.



It was found that the nitro alcohol **202** ($R = H$) exists predominantly in conformations **A**¹ and **C**¹. In other cases ($R = Me, Ph, CCl_3$), conformation **C**¹ predominates. The dihedral angle of $100 - 125^\circ$ is in agreement with the synclinal arrangement of the OH and NO_2 groups and with the formation of a hydrogen bond between them.

In the case of the nitro-diol **3**, conformer **A**² with the synclinal arrangement of the CH_2OH and OH groups predominates in the equilibrium. Thus, the interaction between the two hydroxy groups is stronger than that between the OH and NO_2 groups.²⁶³

IV. Practical use of aliphatic nitro alcohols

Possible applications of aliphatic nitro alcohols have been discussed in a large number of publications. Aliphatic monoatomic and polyatomic nitro alcohols and their derivatives both in a pure state and in various compositions are used most widely as biologically active compounds and as components of rocket fuels or explosives. Other applications of these compounds have also been proposed.

2-Bromo-2-nitropropane-1,3-diol **8** is used most often as a biologically active compound known as 'Biocide'. This nitro-diol as well as nitro alcohols of the general formula $R^1R^2C(OH)CR^3(Br)NO_2$ ($R^1 = H$, alkyl, phenylalkyl; $R^2 = H$; $R^1R^2 =$ cycloalkyl; $R^3 = H, Me, Et, Br$) are active against *Staphylococcus aureus* and *Pseudomonas aeruginosa*.²⁶⁴⁻²⁶⁶ The nitro-diol **8** has been used as an antimicrobial additive²⁶⁷ and as a component of agents controlling the amount of slime in wood pulp during the manufacture of paper,^{265,268} antimicrobial compositions controlling *Chlorella*,²⁶⁹ antiulcer compositions²⁷⁰ and compositions controlling the development of *Cosmarium*.²⁷¹

It has been proposed to use the bis-formate of nitro-diol **8** and 5-bromo-5-nitro-1,3-dioxane and its 2-substituted derivatives, resulting from condensation of **8** with aldehydes, as bactericides and fungicides;^{190,191,220} the mixed ester $4-ClC_6H_4OCH_2-C(NO_2)(Br)CH_2OSO_2Me$ has been used as a component of an agent that fully controls the growth of *Erysiphe gramin*.²¹⁹

The nitro-diol **8** has been patented as a deodorant for the toilets of buses and campers,²⁷² as a deodorant for refuse bins²⁷³

and as a component of compositions removing NH_3 , H_2S and $MeSH$ from aircraft toilet waste waters.²⁷⁴

The use of the nitro-diol **8** and 2-chloro-2-nitropropane-1,3-diol as inhibitors of light- and heat-induced paint changes has been patented.²⁷⁵

The polyester obtained by polycondensation of **8** with terephthaloyl dichloride has been claimed as an agent for cotton processing in order to make cotton fabrics resistant against *Escherichia coli* JFO 3134 and *Staphylococcus aureus* JFO 12732 and more comfortable for wearing.²⁷⁶

The nitro alcohols $R^1C(NO_2)(X)CH(OH)R^2$ ($R^1, R^2 = H$, halogen, substituted alkyl; $X =$ halogen) have been patented as components of microbicide agents, in particular, of those active against *Alternaria tenuis*,⁴⁷ *Pseudomonas aeruginosa*,²⁷⁷ *Plasmidiophora brassicae*²⁷⁸ and *Bacillus subtilis*.²⁷⁹

The nitro alcohols $Cl_3CCH(OH)CH(Br)NO_2$,⁷ 2-nitro-1-(2- and 4-pyridyl)propan-1-ols,²⁸⁰ $EtC(NO_2)(Br)CH_2OH$,³⁵ 2-nitro-1-(2- and 4-quinolyl)propan-1-ols and 2-nitro-1-(2 and 4-quinolyl)propane-1,3-diols²⁸¹ have been used as bactericides and fungicides.

2-Hydroxymethyl-2-nitropropane-1,3-diol **4** has been recommended as an agent for treating water infected with *Streptococcus*.²⁸²

$FC(NO_2)_2CH_2OH$ **107** suppresses the growth of *Escherichia coli* or *Staphylococcus aureus*, while 2-chloro-2,2-dinitroethanol exhibits antispasmodic activity.²⁸³

2-Methyl-4-nitropent-3-en-2-ol has been reported to improve blood circulation.²⁸⁴

A broad spectrum of biological activities is exhibited by the nitro alcohols $R,R'CH(OH)C(NO_2)(X)$ ($R, R', X = CCl_3, Me, Cl; H, Pr, Cl; Me, Cl, Cl; Pr^i, H, Br; Bu, H, Br; C_5H_{11}, H, Br; C_6H_{13}, H, Br; Me, Me, Br; Et, Me, Br; CCl_3, Me, Br; H, Et, Br; Me, Et, Br; Me, Br, Br; Et, Br, Br; Pr^i, Br, Br).⁵⁷$

It has been proposed to use formate, methyl carbonate and some other esters of nitro alcohols $RC(NO_2)_2CH_2OH$ ($R = Cl, Br, Me$) as bactericides and fungicides.^{157,285}

The compounds $R^1ZNHC(S)OCH(R^2)CR^3R^4NO_2$ ($R^1, Z, R^2, R^3, R^4 = Ph, SO_2, H, H, H; Ph, SO_2, H, Br, Me; Ph, CO, H, H, H; 4-O_2NC_6H_4, CO, H, Br, Me; 4-O_2NC_6H_4, CO, Me, H, Et; 4-ClC_6H_4, CO, H, H, H; Ph, CO, H, H, Et; 4-O_2NC_6H_4, CO, Me, H, Me; 2-furyl, CO, H, H, H) have been patented as fungicides and bactericides for deodorants, creams and cleaning compositions,²²⁴ while the esters (2-thienyl) $COOCH(R)CH(R')NO_2$ ($R = H, Me, Pr, Pr^i; R' = H, Me, Et) have been used as fungicides and bactericides for deodorants, soaps and creams.²⁸⁶$$



$R = H, Me, Pr, Pr^i; R' = H, Me, Et.$

The nitro alcohols $RR'C(NO_2)(CH_2)_nOH$ ($R, R' = H, Cl, Br, Br; n = 1-3$) and their acetates have been recommended as components of compositions improving the properties of paper, dyes, cosmetics and adhesives.²⁸⁷

The addition of the nitro-diol **8** to a mixture used for the development of photographic materials inhibits contamination of waste waters.²⁸⁸

The nitro alcohols $RC(NO_2)BrCH(R')OH$ ($R = CH_2OH$, lower alkyls; $R' = H$, lower alkyls) increase the stability of dyes in photographic materials with improved photosensitive layers.²⁸⁹ These nitro alcohols combined with isothiazol-3-one derivatives permit high-quality development of photographic materials even at low pH without decreasing the sensitivity.²⁹⁰

The nitro alcohols $RC(NO_2)(Br)CH(OH)R'$ ($R, R' = H, Me, Et) are added to paper pulp in order to improve the properties of photographic paper.²⁹¹$

A film coated by a composition of polyamide with 2-hydroxymethyl-2-nitropropane-1,3-diol **4** becomes more resistant to abrasive wear.²⁹²

The use of the nitro alcohols $R^1R^2C(NO_2)CH(OH)R^3$ [R^1 , $R^2 = H$, C_{1-5} alkyl, CH_2OH ; $R^3 = H$, alkyl (C_{1-5})] as components of toning agents protecting colloidal photographic materials from X-rays has been patented.²⁹³

The nitro-diol **4** has been used as a stabiliser of developers for colour photography.²⁹⁴ The compound **4** and 2-methyl-2-nitropropane-1,3-diol have been recommended as agents increasing light resistance of dyes.²⁹⁵

2-Methyl-2-nitropropan-1-ol can be used for the preparation of polymerisation inhibitors for esters of unsaturated carboxylic acids.²⁹⁶

The nitro alcohols $XX'C(NO_2)CH(R)OH$ ($X, X' = Hal$; $R = H$, alkyl) are used to prevent fur formation.²⁹⁷

2-Methyl-3-nitropropan-2-ol has been used as a plasticiser for cellulose triacetate.²⁹⁸ The same nitro alcohol blended with the product of condensation of urea and formaldehyde imparts permanent-press and wrinkle-resistant characteristics to cotton textiles.²⁹⁹

The nitro-diols $O_2NC(R)(CH_2OH)_2$ ($R = Me, Et, CH_2OH$) react with melamine at 70 °C and pH 9.5–10 to give adhesive resins that join surfaces under elevated pressures at 250–300 °C.³⁰⁰

2-Methyl-2-nitropropan-1-ol has been used to improve adhesion of rubber to a steel cord.³⁰¹

The product of reaction between 2-ethyl-2-nitropropane-1,3-diol and tetraethylenepentamine, which solidifies over a period of 15 min at room temperature, has been recommended as a coating for steel sheets.³⁰²

The nitro alcohols $RC(NO_2)(X)CH(OH)R'$ ($R = H, CH_2OH$, lower alkyls; $R' = H$, lower alkyls; $X = Hal$) have been patented as agents protecting metal working fluids from bacteria and fungi.^{303, 304}

2-Nitropropan-1-ol increases the covering power, the time of hardening and the strength of cements.³⁰⁵

3-Nitrobutan-2-ol has been used as a selective solvent for dearomatisation of directly distilled petrols.³⁰⁶

The nitrate $MeCH(ONO_2)CH(NO_2)Me$ increases the cetane number of diesel fuels.³⁰⁷

Halo-substituted nitro alcohols of the general formula $R^1[CH(OH)]_nC(NO_2)(X)CR^2R^3OH$ [$R^1, R^2, R^3 = H$, alkyl (C_{1-7}); $X = Cl, Br, I$; $n = 0, 1$], in particular, the nitro-diol **8** have been claimed as antimicrobial agents for hydrocarbon fuels.³⁰⁸

Polynitro alcohols and their derivatives are important components of rocket fuels and explosives.

The compound $(O_2N)_2C(F)CH_2OCOOCH_2CF_3$ has been used as a plasticiser for plastic explosives.²⁰⁵

The formate, methyl carbonate and some other esters of $MeC(NO_2)_2CH_2OH$ have been used as plasticisers for rocket fuels;¹⁵⁷ the compound $[FC(NO_2)_2CH_2]_2NCOOCH_2C(NO_2)_2F$ has been patented as a plasticiser for explosive compositions.³⁰⁹

Among the derivatives of polynitro alcohols proposed as plasticisers for high-energy compositions, the following compounds should be noted: $[EtOCOCH_2C(NO_2)_2F]_2Me$,¹⁸⁷ $(RO)_2CHMe$, $MeCH(OR)OCH_2C(NO_2)_2R'$ [$R = CH_2C(NO_2)_2F$, $R' = F, Me, NO_2$]¹⁸⁶ $[RC(NO_2)_2CH_2O]_2CH_2$ ($R = Me$,^{182, 310} F ,³¹¹ NO_2 ¹⁸²), $[RC(NO_2)_2CH_2O] - CH_2[OCH_2C(NO_2)_2R']$ ($R, R' = NO_2, Me$,¹⁸² Me, Et ³¹⁰), $RC(NO_2)_2CH_2OC[CHCOOCH_2C(NO_2)_2R]COOCH_2(NO_2)_2$. $R' (R = R' = H, F, Me, NO_2)$.²¹⁸

The use of the orthoester $[FC(NO_2)_2CH_2O]_2CH - [OCH(Me)C(NO_2)_2F]$ as a co-plasticiser in high-energy compositions has been patented,³¹² the orthocarbonate $[FC(NO_2)_2CH_2O]_3COCH_2C(NO_2)_3$ has been used as a plasticiser and as an energetic explosive.²¹¹

2-Fluoro-2,2-dinitroethanol **107** can be used as a plasticiser and a binding agent for rocket fuels and explosive compositions;⁹¹ the ether $(O_2N)_3CCH_2OC(NF_2)_3$ can be used as a plasticiser and an oxidant for rocket fuels.¹⁸⁰

The following compounds have been patented as energetic binding agents for high-energy compositions: the vinyl ethers $RC(NO_2)_2CH_2OCH=CH_2$ ($R = F, NO_2$)³¹³ and $FC(NO_2)_2 - CH_2C(NF_2)_2CH_2OCH=CH_2$,²¹³ nitroformals synthesised by polycondensation of the tetranitro-diol $[HOCH_2C(NO_2)_2CH_2]_2$ with formaldehyde¹⁸⁵ or by polymerisation of the epoxide $FC(NO_2)_2CH_2OCH_2CHOCH_2$,^{314 314} and esters formed by 2,2-dinitropropane-1,3-diol **114** with oxalic, malonic or fumaric acids.³¹⁵

The polyester resulting from the reaction of the dichloride $[ClCOCH_2CH_2]_2C(NO_2)_2$ with the diol $[HOCH_2C(NO_2)_2CH_2]_2O$ has been patented as a component of energy-producing compositions.³¹⁶

The nitro-derivatives $[RC(NO_2)_2CH_2O]_2C=S$ ($R = F, Me, NO_2$) have been used as intermediate compounds in the synthesis of energetic explosives.²¹²

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Interaction of alloys and intermetallic compounds obtained by mechanochemical methods with hydrogen

I G Konstanchuk, E Yu Ivanov, V V Boldyrev

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Abstract. Data on hydrogenation of mechanical alloys and intermetallic compounds formed in the course of mechanical alloying and mechanical milling are generalised. It is shown that mechanochemical methods make it possible to solve a number of problems arising in the hydrogenation of metals and alloys and to synthesise novel hydrides and nanocomposite materials. The mechanism of hydrogenation of mechanical alloys is discussed. The bibliography includes 98 references.

I. Introduction

The diversity of practical tasks associated with the accumulation of hydrogen and the use of metal hydrides and intermetallic compounds (IMC) in various technologies stimulate the development of research directed to the search for novel metal–hydrogen systems with definite structural, kinetic, and thermodynamical characteristics.

This type of research consists of the use of alloys and solid solutions based on the known hydride-forming metals, IMC and composite materials obtained from hydride-forming components containing binders that are inert with respect to hydrogen.¹ LaNi₅, TiFe, and magnesium and its alloys are considered to be the most promising from the viewpoint of the accumulation of hydrogen.^{2,3} These materials are traditionally prepared by alloying and by the methods of powder metallurgy. One substantial problem is the activation of these materials which are usually covered by a layer of oxides and hydroxides, thus preventing the chemisorption of hydrogen at the surface and resulting in long induction periods and low reaction rates in the initial hydrogenation. To achieve the highest reaction rate it is necessary to perform several cycles of hydrogenation and dehydrogenation (cycling), which result in the dispersion of the alloy and the development of its microstructure. The microstructure plays a significant role in further cycling and affects considerably the reaction rate and the amount of absorbed hydrogen.

I G Konstanchuk, V V Boldyrev Institute of Solid State Chemistry and Processing of Mineral Raw Materials, Siberian Branch of the Russian Academy of Sciences, ul. Kutateladze 18, 630128 Novosibirsk, Russian Federation. Fax (7-383) 232 28 47. Tel. (7-383) 232 96 00

(I G Konstanchuk), (7-383) 232 15 50 (V V Boldyrev)

E Yu Ivanov TOSOH SMD, 3515 Grove City Road, Grove City, OH 43123, USA. Fax (1-614) 875 00 31. Tel. (1-614) 875 79 12

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In addition, traditional methods of preparation of alloys are mainly restricted by thermodynamically stable compounds and solid solutions.

Mechanochemical methods (mechanical alloying, mechanical milling, *etc.*) consist in mechanical treatment of metal powders in high-energy planetary ball mills. This treatment results mainly in plastic deformation of the material under conditions that fix its metastable state. These methods can be applied to the synthesis of metastable phases: amorphous phases,⁴ supersaturated solid solutions, non-stoichiometric intermetallic compounds,⁵ quasi-crystals,^{6,7} and composites with different microstructure and composition including those with non-interacting components.⁸ These phases often exhibit unusual physicochemical properties and enhanced reactivity.^{8,9} Mechanical alloying, as shown in the present review, can be a promising method for the preparation of materials with high reactivity with respect to hydrogen.

II. Magnesium systems

1. Problems arising in the hydrogenation of magnesium and its alloys

Magnesium and its alloys are promising materials for the accumulation of hydrogen. The stoichiometric hydrogen content in magnesium hydride is 7.6 mass % (Table 1), which exceeds its content in other known hydrides and also in gas cylinders.^{10,11} However, the relatively high thermal stability of magnesium hydride (equilibrium hydrogen pressure of 0.1 MPa is achieved at ~560 K), insufficiently high rates of hydrogenation of magnesium and dehydrogenation of MgH₂, long-lasting activation, and incomplete conversion of magnesium into the hydride (which decreases the hydrogen content to 5 mass %) have stimulated the appearance of research projects aimed at the possibility of improving the above-mentioned characteristics.

It has been established to date that the formation of magnesium hydride is connected with the processes of formation and growth of MgH₂ nuclei. For the majority of metal–hydrogen systems, the first stage of the interaction of hydrogen with a metal is characterised by the formation of a solid solution of hydrogen in a metal, in which nuclei of the hydride phase are crystallised.¹² The formation of solid solutions of hydrogen is not typical of magnesium, or more precisely, their concentrations are low.^{13–15} The hydride nuclei appear at the surface of magnesium particles; when the nuclei overlap, the reaction rate is controlled by diffusion processes. ‘Diffusion retardation’ then occurs, which prevents the complete conversion of magnesium into the hydride. In the first cycle of hydrogenation, the extent of conversion does

Table 1. Characteristics of hydrogen storage systems.^{10, 11}

Method of storage	Hydrogen content		Hydride density /g cm ⁻³	Accumulated energy		Hydrogenation rate
	(mass %)	/10 ²² at cm ⁻³		/kJ g ⁻¹	/kJ cm ⁻³	
H ₂ , gas 20 MPa, 300 K	1.2 ^a	0.9	—	142.7	2.13	—
H ₂ , liquid	≤ 12 ^a	4.2	—	142.7	9.96	—
LaNi ₅ H ₆	1.4	5.5	6.2	2.0	13.04	High
TiFeH ₂	1.9	6.3	5.5	2.7	14.93	"
MgH ₂	7.6	6.6	1.5	10.8	15.64	Low
MgNiH ₄	3.6	5.8	2.7	5.1	13.75	High
Gasoline	—	—	—	48	38	—

^a With account of the mass of the storage system.

not usually exceed 0.9, in subsequent cycles it does not exceed 0.6–0.7.^{16–18}

Kinetic characteristics of hydrogenation processes in the first cycle differ substantially from those in the later cycles. The surface layer of magnesium oxide, which is always present on the original metal particles before the first hydrogenation, inhibits the formation of magnesium hydride nuclei, because no dissociative adsorption of hydrogen on this layer occurs.¹⁹ Therefore, the rate of hydrogenation of magnesium in the first cycle is determined by the processes of destruction of the oxide film and formation of a metallic surface with hydrogen chemisorption ability.^{19–21} A model of the first cycle of hydrogenation of magnesium taking into account the dynamics of the destruction of the oxide film and kinetics of the nucleus growth has been proposed.²²

During activation through cycling, exfoliation of the oxide film occurs. The initial reaction rate is determined by the dissociative chemisorption of hydrogen on a pure metal surface, and the nucleus growth occurs due to the surface diffusion within the layer of the chemisorbed hydrogen.²³ An increase in the number of nuclei with an increase of ΔP (the difference between the pressure in the reactor and the hydrogen equilibrium pressure for magnesium hydride at the temperature of the experiment), which is a driving force of the reaction, or the introduction of catalysts accelerates the initial stage of hydrogenation, leads to the faster formation of the continuous layer of the hydride, and to a change over to diffusion conditions at lower conversion rates.²⁴ It was shown by experiments on the movement of the Kirkendall mark that hydrogen atoms or ions are the diffusing species.²⁵

The rate of decomposition of magnesium hydride depends on the dynamics of the formation and growth of nuclei of magnesium metal.²³ The desorption of hydrogen from the surface of the solid reaction product, metallic magnesium, is the limiting stage of the reaction; for this reason, the size of the Mg/MgH₂ interface plays a significant role.

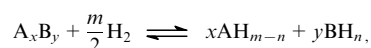
Thus, the rate of magnesium hydrogenation in the first stage and the rate of decomposition of magnesium hydride are determined by the processes of adsorption (or desorption) of hydrogen on the metal surface (in the first hydrogenation, by the formation of the metal surface), by the rates of formation and growth of nuclei of the reaction product, and after the creation of the continuous layer of MgH₂ in the hydrogenation, by the rate of diffusion of hydrogen through the hydride. Hence, changes in the kinetics of hydrogenation and dehydrogenation can be achieved by controlling these stages.

In the majority of studies dealing with the improvement of kinetic and thermodynamic characteristics of magnesium in the interaction with hydrogen, its alloys with other metals have been used. However, it should be noted that in the case of magnesium, the choice of these metals is rather limited for the enthalpy of mixing of magnesium with many elements of the Periodic Table is positive.

To date, only two magnesium intermetallic compounds are known that absorb hydrogen reversibly, *viz.*, Mg₂Ni and

Mg₅₁Zn₂₀, and the corresponding hydrides, MgNiH₄ (Ref. 26) and Mg₅₁Zn₂₀H_{*y*} (*y* = 90–95).²⁷ The hydride Mg₂NiH₄ is regarded as a promising one for the accumulation of hydrogen, because it interacts with hydrogen at a high rate at temperatures of about 473–573 K and $P_{H_2} \approx 0.5–1.0$ MPa,²⁸ although its hydrogen capacity is less than that of magnesium (see Table 1). At the first stage of hydrogenation of Mg₂Ni under the conditions ensuring fast heat removal and at rather high hydrogen pressures, chemisorption of hydrogen on the surface of IMC with an effective activation energy of 14.0 ± 0.8 kJ mol⁻¹ is the limiting stage.²⁹ However, due to high rates of hydrogenation and dehydrogenation, the processes of heat and mass transfer play a significant role and may become limiting, especially if this IMC is used on a technological scale. The creation of composite materials containing inert metallic fillers is the way to solve the problems of heat and mass transfer,³⁰ but this further decreases the hydrogen capacity of an accumulator.

The interaction of IMC of magnesium and of some other elements, such as rare earth metals, Cu, Al, Ca, with hydrogen leads to the decomposition of the intermetallic compound to form a mixture of two hydrides or a hydride and a metal (or another IMC). This process was termed hydrogenolysis,^{31, 32} in general it can be represented by the equation



where A, B are elements constituting the IMC; *n* = 0 if the second element does not give a hydride.

Hydrogenolysis can be reversible, as in the case of Mg₂Cu,³³ and irreversible, as for most IMC of magnesium with rare earth metals and Al.^{11, 32, 34–40} The reversibility is determined by the relationship between the values of the heat of formation of the binary hydride and the initial IMC. The mechanism of hydrogenolysis has not been studied in detail. No complete separation of hydrides or a hydride and a metal (IMC) resulted from hydrogenolysis occurs. The material obtained is composed of particles with a developed interface between its constituents^{35, 36} which determines the reactivity of these particles in further hydrogenation–dehydrogenation cycles.

Of the systems that undergo hydrogenolysis, the main attention has been paid to IMC of magnesium with rare earth metals. Hydrogenolysis results in a non-stoichiometric hydride LnH_{*x*}, which plays the role of a ‘hydrogen pump’, which facilitates the delivery of hydrogen to the magnesium surface and thus accelerates hydrogenation.^{35–37, 41} However, no significant enhancement of the kinetics of dehydrogenation of these reaction mixtures occurs in comparison with pure MgH₂.^{34–36, 40} In order to accelerate dehydrogenation, it is necessary to introduce elements that facilitate the processes of hydrogen desorption and the formation of the metallic phase nuclei, for example, *d*-metals.^{34, 37, 42–44} These additives form a separate phase as a result of cycling. After hydrogenolysis the material is a virtually multi-phase system, its features being typical of those for multi-phase alloys.

Two- and multi-phase systems are alloys of magnesium with other elements, the composition of which does not correspond to the stoichiometric composition of intermetallic compounds. These can be alloys with Ni, Cu, rare earth, and some other metals.

Hydrogenation of alloys of magnesium with rare earth metals yields a mixture of binary hydrides, as in the case of hydrogenolysis of IMC. The compositions formed differ, first of all, in specific features of the microstructure and in the size of the magnesium/lanthanide hydride interface. In the decomposition of a non-stoichiometric alloy, the interface is, as a rule, smaller than that in hydrogenolysis of IMC, which results in a decrease in the rates of the interaction of these systems with hydrogen.

The alloys Mg–Ni and Mg–Cu are two-phase systems containing magnesium and IMC Mg₂Ni or Mg₂Cu. Hydrogenation of these alloys can be carried out in two versions: under conditions where both phases are hydrogenated and under conditions where only magnesium is hydrogenated and the intermetallic compound serves only as a catalyst. However, in both cases dissociative hydrogen adsorption takes place on clusters of the *d*-element resulting from segregation occurring in the course of hydrogenation–dehydrogenation.[†] Studies of the surface of alloys by ferromagnetic resonance,⁴⁵ X-ray photoelectron and Auger spectroscopy^{46,47} gave reason to adopt a model of the structure of the surface of the alloy and the scheme of the initial stage of hydrogenation, which accounts for the catalytic activity of transition metals.^{47–49} The essence of the model is as follows:

1. Activation of the material in hydrogenation–dehydrogenation cycles leads to dispersion of the sample, that is, to the formation of a new clean surface.
2. In the interaction with traces of oxygen and water, clusters of a *d*-element are formed on this surface (the so-called oxidative segregation).
3. Dissociative chemisorption of hydrogen takes place on the clusters of the *d*-element.
4. The hydrogen atoms formed diffuse into the bulk of the material along the metal/oxide interface.

The course of the reaction, as was mentioned above, depends largely on the size of the magnesium/catalyst interface and accordingly, on the size of magnesium particles in the alloy.

The size of magnesium crystallites determines the degree of its conversion into the hydride. The process of nucleation is accelerated under the action of catalytic additives, which leads to faster formation of a continuous layer of the hydride and to a change to the diffusion control of the reaction.²⁴ In the case of larger magnesium particles, these processes slow down and practically completely stop the reaction long before complete conversion. The portion of magnesium that does not enter the reaction decreases and the hydrogen content increases with a decrease in the size of particles in the alloy.

Hence, the main problems in the creation of two- and multi-component materials for accumulation of hydrogen are, first, the choice of a catalyst and determination of its optimum concentration at which the maximum hydrogen content is achieved over a given time and second, the creation of the microstructure of the sample ensuring the maximum magnesium/catalyst interface.

In addition, the problem of activation exists for all the alloys. The rate of the first hydrogenation is determined by the rate of the rupture of the oxide film, by the rates of the formation and growth of magnesium hydride nuclei. The effect of additives reduces most commonly to a decrease in the induction period and to an increase in the rate of the first hydrogenation as compared to analogous characteristics for pure magnesium,^{17,24,50,51} however, the duration of the first cycle remains too high.

[†] Segregation processes occur due to the presence of traces of oxygen and water in the hydrogen.

2. The interaction of mechanical alloys of magnesium with hydrogen

A new approach to the creation of two- and multi-component systems interacting with hydrogen has been proposed.^{52–55} It is based on the use of mechanical alloying. In the initial stage of processing of a mixture of metal powders (in ~5 min) in centrifugal planetary mills, composites are formed with a considerable interface similar to those resulting from hydrogenolysis of IMC, but the hydrogenolysis stage is excluded. These composites were termed mechanical alloys (MA). A typical (rather porous) structure of a particle of a mechanical alloy with uniformly distributed particles of a metal catalyst within the magnesium matrix is shown in Fig. 1.⁵⁵ Wide angle X-ray scattering (WAXS) of these materials did not reveal the formation of either intermetallic compounds or solid solutions.

The processes of hydrogenation and dehydrogenation have been studied for the systems Mg–Ce;⁵⁶ Mg–Fe, Mg–Co, Mg–Ti, Mg–V, Mg–Nb, Mg–Cr, Mg–C, Mg–Si;^{52–54,57–59} Mg–Ni;^{29,52,53,60–63} Mg–TiO₂;^{64–66} Mg–V₂O₅, Mg–Cr₂O₃;⁶⁶ Mg–MnO₂; Mg–Fe₂O₃, Mg–NiO;⁶⁷ Mg–MmM'₅ (MM'₅ is IMC of the type LaNi₅, Mm is a mischmetal, M' is Ni with admixtures of Al, Co, and Mn),^{68,69} Mg–FeTi,⁷⁰ etc.

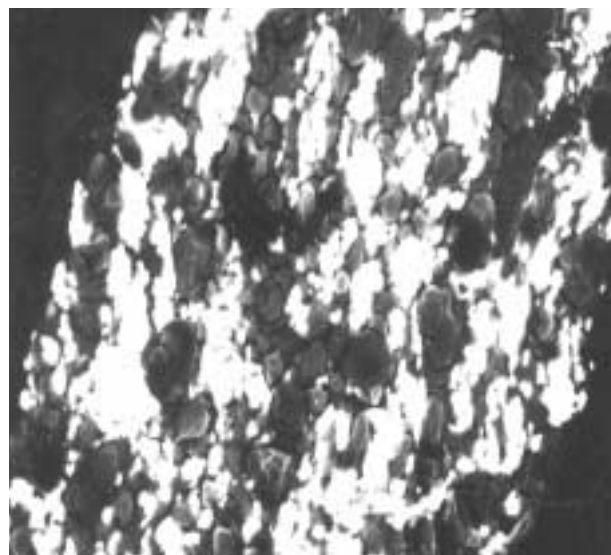


Figure 1. A particle of mechanical alloy Mg–Ni at a fracture; the image in the Ni *K_α* radiation.

Thus, mechanical alloying allows the considerable extension of the range of systems under study including mixtures that could not be alloyed by traditional methods, such as Mg–Fe, Mg–Ti, Mg–Nb, and Mg–Cr with positive enthalpy of mixing of the components, or mixtures of magnesium with oxides. It is also very difficult to prepare from the latter composites with homogeneous distribution of the components by traditional alloying methods.

The additives to magnesium used in mechanical alloys differ in their nature. Thus the above-mentioned additives can be divided into six groups.

1. Ni forms with magnesium the intermetallic compound Mg₂Ni, which can absorb and liberate hydrogen.
2. Ce, Nb, and Ti form hydrides CeH₃, NbH₂, and TiH₂, which can serve as 'hydrogen pumps' due to the change in stoichiometry.
3. MmM' and FeTi are intermetallic compounds, which absorb hydrogen reversibly under milder conditions compared to magnesium.
4. Fe, Co, and Cr are metal catalysts, which do not form hydrides themselves under the conditions studied.

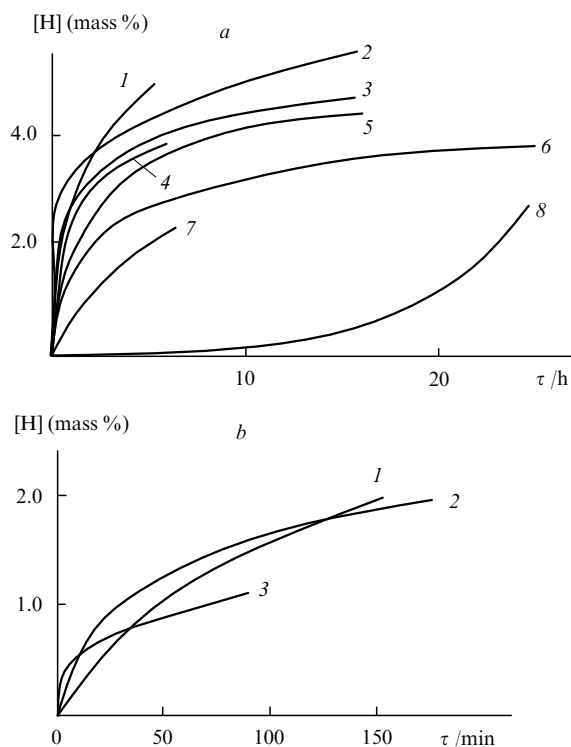


Figure 2. Kinetics of the first hydrogenation of magnesium and its mechanical alloys.

(a): $T = 625 \text{ K}$ and $P_{\text{H}_2} = 1.5 \text{ MPa}$; (1) Mg + 5 mass % of Co; (2) Mg + 5 mass % of Nb; (3) Mg + 5 mass % of Fe; (4) Mg + 5 mass % of C; (5) Mg + 8 mass % of Ce; (6) Mg + 5 mass % of Ti; (7) Mg + 5 mass % of Si; (8) metallic magnesium, particle size is 20 μm ;
(b): $T = 615 \text{ K}$, $P_{\text{H}_2} = 1.5 \text{ MPa}$; (1) Mg + 8 mass % of Fe; (2) Mg + 10 mass % of Fe_2O_3 ; (3) Mg + 10 mass % of NiO .

5. Si and C form with magnesium compounds with predominantly covalent bonds.

6. Metal oxides.

All the types of catalytic additives accelerate remarkably the first hydrogenation as compared to that of pure magnesium^{52,67} (Fig. 2). The character of the action of additives (except for Si and C) seems to be the same and consists in the acceleration of the stage of chemisorption of hydrogen on the surface of a catalyst. It is of note that mechanical alloys Mg–Ni are hydrogenated during the first cycle faster than the corresponding ordinary alloys Mg–Ni (Fig. 3).⁶¹

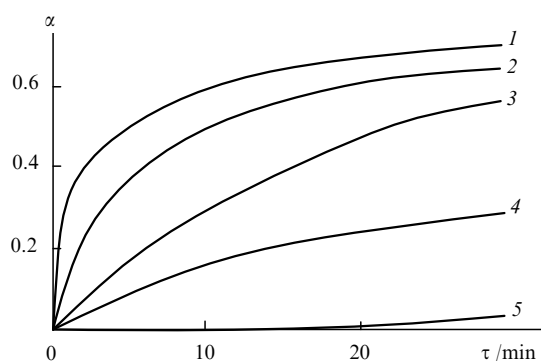


Figure 3. Kinetics of the first hydrogenation of mechanical alloys of magnesium with nickel.

[Ni] (mass %): (1) 60, (2) 53, (3) 35, (4) 1; (1–4) at $P_{\text{H}_2} = 1.8 \text{ MPa}$, $T = 583–593 \text{ K}$; (5) ordinary alloy of Mg with 25 mass % of Ni at $P_{\text{H}_2} = 2.1 \text{ MPa}$, $T = 673 \text{ K}$.

The rate of the first hydrogenation depends on the nature and concentration of the catalyst, but in almost all the systems examined, the reaction begins at the maximum rate (see Figs 2, 3). This means that the surface of the catalyst in mechanical alloys, unlike that in traditional alloys, is accessible to hydrogen.

X-ray photoelectron spectroscopic studies^{29,71} of the surface of MA have shown that it is covered with a layer of organic impurities and oxygen-containing magnesium compounds. The thickness of this layer is small, and it does not seem to affect the hydrogenation process. The profiles of concentration of the elements for magnesium MA containing 50 mass % Ni are shown in Fig. 4. The surface layer (3–5 nm) contained neither metallic magnesium, which appeared at a depth of 40 nm, nor nickel, which appeared at a depth of $\sim 4–10 \text{ nm}$ in the oxidised state and at a depth of 40 nm in the metallic state. The presence of oxygen throughout the entire layer provides evidence for the destruction of the surface MgO film and its dispersion in the matrix. Carbon-containing impurities also penetrate into the bulk upon mechanical alloying.

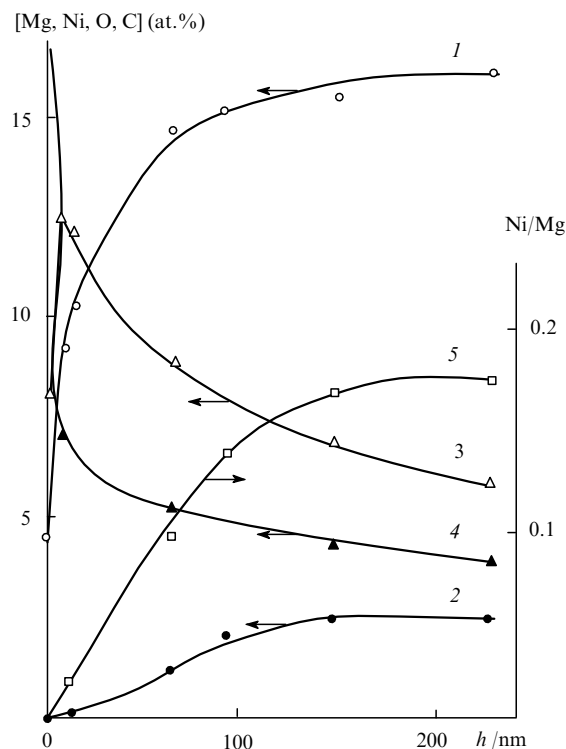


Figure 4. The dependence of the chemical composition on the etching depth (h) for a mechanical alloy of Mg with 50 mass % of Ni. (1) Mg, (2) Ni, (3) O, (4) C, (5) Ni/Mg.

The chemical state of the elements in the near-surface layer of MA differs significantly from that in the original metals. The contour of the nickel $2p_{3/2}$ line at a depth of 40 nm corresponds to metallic nickel and to the nickel implanted into an inert matrix as isolated atoms. In addition, charge transfer from magnesium to non-bonding levels of the nickel atoms has been observed. In this case, a portion of magnesium is in the state to which the formal oxidation degree of +1 can be ascribed. The chemical state of oxygen also differs from that in the original metals and MgO , which might be due to defectiveness of the surface layer of MA.^{29,71} The nickel atoms resulting from the chemical interaction between Mg and Ni in the course of mechanical alloying bear an excessive electron density and are active catalysts of hydrogen dissociation. The nickel atoms are, probably, present not only in the surface layer, but also in the bulk of the sample forming a

supersaturated solid solution around the nickel particles upon dispersion of nickel within the matrix.

Other MA of magnesium with metals and IMC, even those having a positive enthalpy of mixing, seem to have a similar structure. This can be indirectly proved by the fact that the initial hydrogenation rate of mechanical alloys Mg–Fe and Mg–Ni depends linearly on the square of the concentration of the catalyst in MA.⁵⁹

Hence, disordering of the surface layer, the rupture of the oxide film, and dispersion of the catalyst take place in mechanical alloys. Disorder of the surface layer makes the catalyst accessible to hydrogen, which is the main reason for the rapid first hydrogenation of MA as compared to that of alloys and mixtures of the same composition.^{29, 71}

It should be noted that this surface structure is quite stable over a long period: the initial rate of hydrogenation of MA that have been stored in air for 9–12 months did not differ from that of freshly prepared samples.²⁹

The high reactivity (with respect to hydrogen) of mechanical alloys of magnesium with transition metal oxides may also be accounted for by the presence of metallic particles and partially reduced metal oxides at the surface formed in the course of mechanical processing.^{64–67} The efficiency of the action of metal oxides as catalysts depends on the ease of their reduction.⁶⁶

For the majority of systems examined (except for Mg–Ce and, under special experimental conditions that will be considered below, Mg–Fe and Mg–Co), magnesium hydride (the second phase, catalyst) is the product of the first hydrogenation. The degree of conversion of magnesium into the hydride, as in two-phase systems, in these MA depends on their microstructures. A model of a microstructure reflecting qualitatively the initial stage of hydrogenation is presented in Fig. 5: MgH_2 is formed around the catalyst particles. It is difficult for hydrogen to penetrate through the layer of hydride; that is why the reaction slows down with an increase in the thickness of the layer. The thickness of the hydride layer, which depends on the distance between particles of the catalyst, decreases with an increase in the concentration of the catalyst, and the degree of conversion also increases. However, the hydrogen content (mass %) in the alloy decreases due to the large mass of catalyst. It has been found experimentally^{59, 63} that the optimum catalyst content was in the range of 2 mass %–25 mass %.

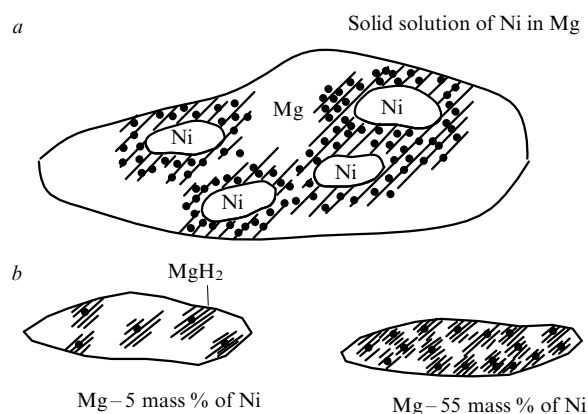
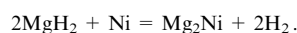


Figure 5. A model of the microstructure of mechanical alloy Mg–Ni (a) and the illustration of the effect of the Ni concentration on the degree of conversion (b).

In subsequent cycles, MA retain high rates of hydrogenation and dehydrogenation (Figs 6, 7) and rather high hydrogen capacity.⁵²

In the case of the Mg–Ni mechanical alloy, the intermetallic compound Mg_2Ni is formed after 3–4 cycles of hydrogenation–dehydrogenation, mainly according to the equation⁶¹



Further, kinetic characteristics of the system do not differ from those of the ordinary two-phase system Mg–Ni or the intermetallic compound Mg_2Ni .^{29, 63}

Kinetic characteristics of the mechanical alloy Mg–Ce in the cycling are also comparable with those of hydrogenation and dehydrogenation obtained in the hydrogenolysis of Mg– CeH_x mixtures (Fig. 8).⁵⁶ This shows that the size of the interface in MA has the same order of magnitude as the interface in the mixtures obtained in the hydrogenolysis.

As for MA composed of thermodynamically immiscible components, one could expect rapid destruction of a sample in repeating hydrogenation–dehydrogenation cycles due to exfoliation of the system. However, these systems appeared to be rather stable in cycling. A mechanical alloy Mg–Fe retains its hydrogen capacity for ~ 70 cycles, and the rate of hydrogenation even

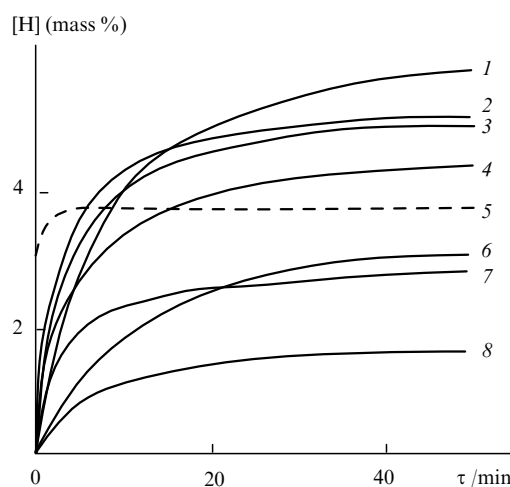


Figure 6. Kinetics of hydrogenation for the fifth cycle, $P_{\text{H}_2} = 1.5$ MPa, $T = 625$ K.

(1) Mg, particle size is 20 μm , mechanical alloy; (2) Mg + 5 mass % of Nb, (3) Mg + 5 mass % of Fe, Co or Ni, (4) Mg + 5 mass % of Ti, (7) Mg + 5 mass % of Si, (8) Mg + 50 mass % of C; (5) intermetallic compound Mg_2Ni ; (6) Mg, particle size is equal to the size of particles of the mechanical alloy ($P = 0.7$ MPa, $T = 583$ K).

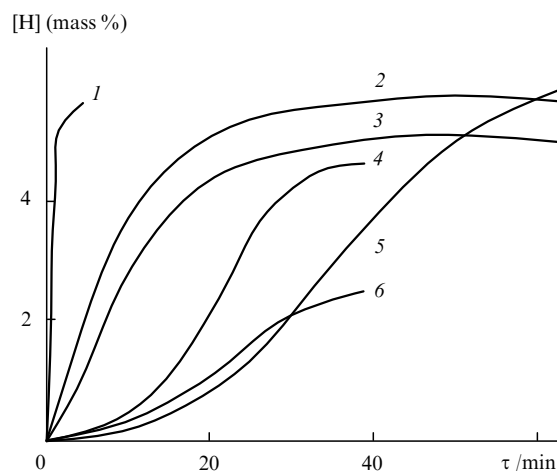


Figure 7. Kinetics of dehydrogenation, $P = 0.1$ MPa.

Mechanical alloy: (1) Mg + 5 mass % of Ni, $T = 615$ K; (2) Mg + 5 mass % of Fe, $T = 625$ K; (3) Mg + 5 mass % of Nb, $T = 625$ K; (4) Mg + 5 mass % of Ti, $T = 625$ K; (6) Mg + 5 mass % of Si, $T = 621$ K; (5) Mg, particle size is 20 μm , $T = 625$ K.

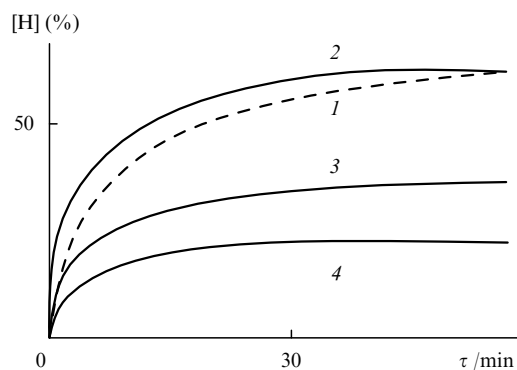
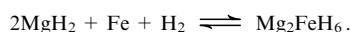


Figure 8. Kinetics of hydrogenation at $T = 603$ K and $P_{H_2} = 1.9$ MPa. (1) mechanical alloy Ce + 25Mg; (2) CeMg₁₂; mixture: (3) Mg + 10 mass % of LaNi₅; (4) Ce + 12Mg.

gradually increases;⁵⁹ a mechanical alloy Mg–TiO₂ retains its kinetic characteristics at least up to the 39th cycle⁶⁴ (there are no data on longer cycling).

It was shown^{59, 72} that complex competing processes including sintering and dispersion of the sample occur in a Mg–Fe system in the hydrogenation–dehydrogenation. Hydrogen undergoes dissociation on iron and it further diffuses into the bulk of the sample along the interface and grain boundaries to form an Mg/Fe adsorption layer at the interface in which rather high mobility of both hydrogen and metals is observed. Some experiments on the annealing of a contact pair Mg/Fe using a microprobe analysis have shown that the principal possibility is for iron to diffuse along the surface of magnesium in a hydrogen atmosphere.^{59, 72} This favours an increase in the Mg/Fe contact area and in the hydrogenation rate. When a definite hydrogen concentration in the adsorption layer at the interface Mg/Fe is achieved, a ternary hydride of the composition Mg₂FeH₆ crystallises at a noticeable rate, which was observed at $T \geq 615$ K. At hydrogen pressures exceeding the equilibrium pressure over MgH₂, catalytic hydrogenation of magnesium occurs in parallel, often at a higher rate; the synthesis of Mg₂FeH₆ can also occur according to the equation



However, since the equilibrium hydrogen pressure for Mg₂FeH₆ is lower than that for magnesium hydride⁵⁷ (Fig. 9), the synthesis of the latter was successfully accomplished directly from the elements. This reaction has been described in detail.^{59, 72}

Analogous processes seem to occur in the hydrogenation of a mechanical alloy Mg–Co. This system does not belong to immiscible ones; however, for this system only one intermetallic compound MgCo₂ is known, which does not absorb hydrogen under ordinary hydrogenation conditions. In the hydrogenation of mechanical alloys in this system, two hydrides, *viz.*, Mg₂CoH_x ($x = 4-5$) and Mg₃CoH₅, were detected^{58, 59} which, like Mg₂FeH₆, can be synthesised from the elements (without the intermediate stage of formation of magnesium hydride). Decomposition of ternary magnesium–cobalt hydrides gave a previously unknown IMC with composition close to Mg₂Co and having a cubic structure. This compound interacts with hydrogen even at room temperature to form solid solutions and at elevated temperatures to form ternary hydrides (Table 2).

It should be noted that ternary magnesium–iron and magnesium–cobalt hydrides could not be detected for a long time due to the lack of hydride-forming IMC in the systems Mg–Fe and Mg–Co. Yvon *et al.*⁷³ considered the hydride Mg₂NiH₄ as a complex compound composed of the Mg²⁺ cation and the [NiH₄]⁴⁻ anion. Assuming that the 18 electron rule, which determines the content of a ligand (H in this case), is valid for these complexes, they have predicted the possibility that hydrides Mg₂FeH₆ and Mg₂CoH₅ exist. Research by these authors in

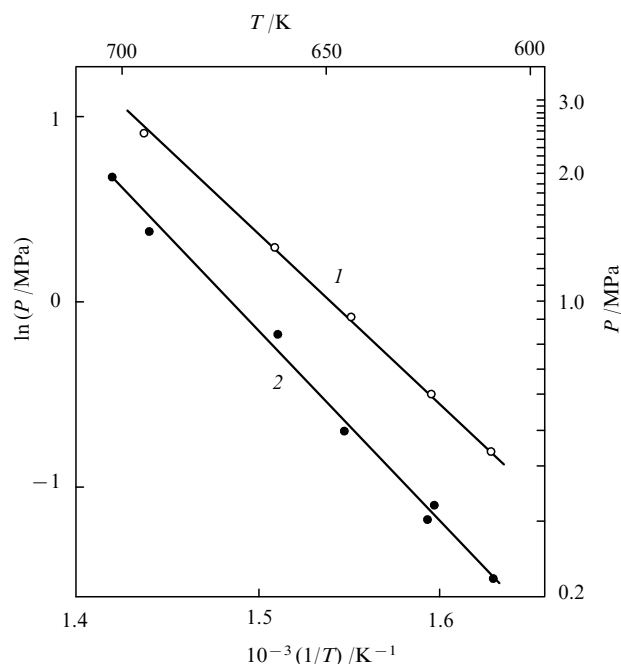


Figure 9. Temperature dependence of equilibrium pressures of hydrogen over the hydride phases MgH₂ (1) and Mg₂FeH₆ (2).

Table 2. Crystallographic data for novel ternary hydrides and intermetallic compounds.

Compound	Unit cell	Cell parameters /nm	Ref.
Mg ₂ FeH ₆	Cubic, <i>Fm</i> 3 <i>m</i>	$a = 0.6443$ $a = 0.6442 \pm 0.0002$	74 59
Mg ₂ CoH _x , (low-temperature modification) ^a	Tetragonal	$a = 0.4477 \pm 0.0001$, $c = 0.6612 \pm 0.0001$, $a = 0.4480(2)$ $c = 0.6619(3)$	59 75
Mg ₂ CoH _x , (high-temperature modification)	Cubic	$a = 0.644$ at ~ 480 K	59
Mg ₃ CoH ₅	Orthorhombic	$a = 0.4675 + 0.0002$, $b = 0.8073 + 0.0003$, $c = 1.0091 \pm 0.0003$, $Z = 4$	59
'Mg ₂ Co'	Cubic	$a = 1.143 + 0.001$	58, 59

^a The temperature of a reversible phase transition of Mg₂CoH_x from the low-temperature modification to the high-temperature one is 470 K, ΔH for the phase transition is ~ 2 kJ mol⁻¹.^{58, 59}

1984–1985 aimed at synthesising these hydrides was successful.^{74, 75} At the same period, the hydrides were found in the hydrogenation of mechanical alloys.⁷⁶ The lack of a method for the preparation of a material with a large Mg/Fe and Mg/Co interface caused the authors^{74, 75} to use a mixture of pressed metal powders. The reaction had to be conducted for weeks under drastic conditions, nevertheless, complete conversion of these mixtures into the hydrides was not achieved. Neither the second hydride Mg₃CoH₅ existing in the Mg–Co system nor the intermetallic compound Mg₂Co could be isolated and identified.

The magnesium–iron and magnesium–cobalt ternary hydrides were examined as catalysts for the hydrogenation of unsaturated hydrocarbons. These catalysts manifested catalytic activity comparable with that of catalysts based on platinum-group metals, and high selectivity in processes of partial reduction

Table 3. Catalytic characteristics of ternary hydrides and traditional catalysts.⁵⁹

Catalyst	Degree of conversion (%)	Selectivity (%)
Compound to be hydrogenated is acetylene		
Mg ₂ CoH _x	44	100 (with respect to C ₂ H ₄)
Pd/Al ₂ O ₃	21	90
Compound to be hydrogenated is butadiene		
Mg ₂ FeH ₆	51–55	99.2–99.7
Pt–S/Al ₂ O ₃	23	100
Pd–S/Al ₂ O ₃	36	72

of acetylene derivatives and compounds with several double bonds (Table 3).^{59, 77}

Hydrogenation and dehydrogenation of MA containing, for example, two or more IMC can be more complicated. Depending on the composition of MA, cycling can result in the interaction between the components, their decomposition, and the formation of other phases, which can be both hydride-forming and hydride-non-forming. Thus a study of hydrogenation of a MA containing 66.6 mass % of La₂Mg₁₇ and 33.3 mass % of LaNi₅ has shown⁷⁸ that several hydrogenation–dehydrogenation cycles result in their decomposition and the formation of Mg, Mg₂Ni, and LaH_x ($x = 2.00–2.99$). Then, depending on the temperature and hydrogen pressure used in hydrogenation, hydrogen is absorbed either by magnesium or by magnesium and Mg₂Ni, and LaH_x serves as a ‘hydrogen pump’. After 20 cycles, the sample was a conglomerate of all the phases with a granule size of $\sim 0.2 \mu\text{m}$. Although these MA have lower hydrogen capacity as compared to that of pure La₅Mg₁₇, the rates of their hydrogenation and dehydrogenation are higher in the first cycles and depend, other conditions being the same, on the duration and intensity of mechanical processing. Thus MA obtained under the most drastic conditions (at an acceleration of 130 m s^{-2} for 25 min) absorbs 3.5 mass % of hydrogen (90% of full capacity) in less than 1 min at 523 K and liberates the same amount in 6 min, whereas under the same conditions it takes 2.5 h for pure La₅Mg₁₇ to absorb 4.9 mass % of hydrogen (also 90% of its full capacity) and 3 h to desorb it.⁷⁸ This was explained⁷⁸ by the small size of MA particles ($\sim 10 \mu\text{m}$), their multi-phase composition and catalytic activity of one or two components. It was thus concluded that a solution of the problem of improvement of the kinetic characteristics of hydrogenation and dehydrogenation lies in the creation of analogous composite materials.

3. Hydrogenation of Mg₂Ni obtained by mechanical alloying and mechanical milling

The intermetallic compound Mg₂Ni interacts with hydrogen at a high rate at 473–573 K and a hydrogen pressures of 0.5–1.0 MPa; however, a problem of activation exists. From 10 to 20 cycles of hydrogenation–dehydrogenation are necessary for activation⁷⁹ in the course of which dispersion of the material and the formation of a metallic surface occur. These difficulties can be avoided if Mg₂Ni is subjected to mechanical milling or is synthesised by mechanical alloying using the same procedure as for the synthesis of MA but increasing the duration of the treatment. It was shown^{80, 81} that mechanical alloying of a mixture of Mg and Ni powders gives nanocrystalline Mg₂Ni with the size of crystallites of about 20–30 nm. This material interacts rapidly with hydrogen, and reproducible rates of hydrogenation are achieved even by the second cycle (Fig. 10). If a small amount of palladium (less than 1 mass %) is added to the reaction mixture during mechanical alloying, the thus modified Mg₂Ni absorbs hydrogen at room temperature (Fig. 11).^{80–83} An analogous result was obtained without addition of palladium.⁸⁴ However, in this case

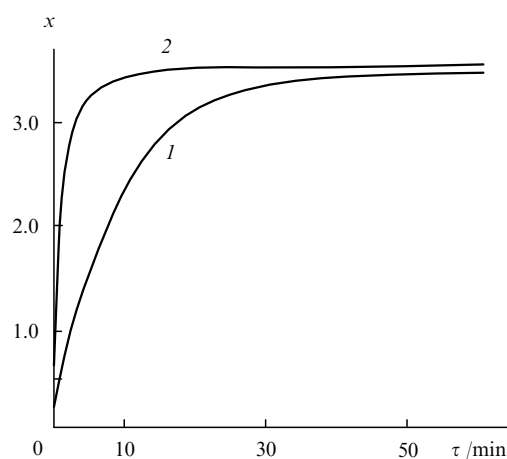


Figure 10. Kinetics of hydrogenation of nanocrystalline Mg₂Ni prepared by mechanical alloying at $T = 573 \text{ K}$, $P_{\text{H}_2} = 1.16 \text{ MPa}$; (1) the first cycle; (2) the second and subsequent cycles. The x values in the formula Mg₂NiH_x are shown in the y-axis.

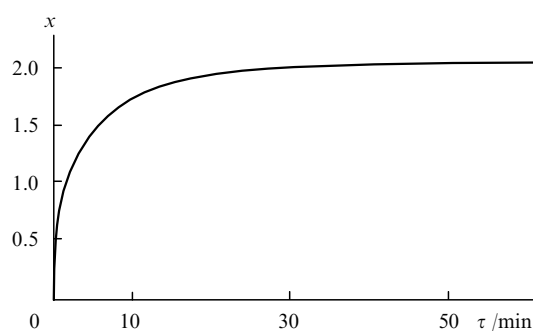


Figure 11. Kinetics of hydrogen sorption by nanocrystalline Mg₂Ni modified with palladium during mechanical alloying (room temperature, $P_{\text{H}_2} = 1.2 \text{ MPa}$, without activation). The x values in the formula Mg₂NiH_x are shown in the y-axis.

hydrogenation of Mg₂Ni was performed immediately after its mechanical milling without exposure to air (Fig. 12). Mechanical milling implies practically the same procedure as mechanical alloying except that the initial material is not a mixture of metal powders but an intermetallic compound obtained by traditional alloying. As is shown by Fig. 12, the reaction rate and the amount of absorbed hydrogen increase as the duration of mechanical

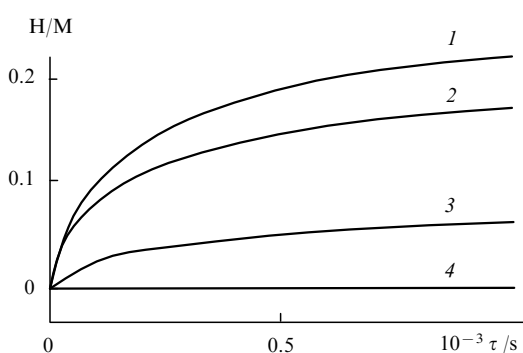


Figure 12. Kinetics of hydrogen sorption for Mg₂Ni (285 K, $P_{\text{H}_2} = 2 \text{ MPa}$) after its mechanical milling in an argon atmosphere for 30 (1), 5 (2), 1 min (3), and without milling (4). The ratio of hydrogen atoms to metal atoms in Mg₂NiH_x is shown in the y-axis.

milling is increased, which can be due to gradual dispersion of the sample and the formation of pure metal surface during this milling. However, at room temperature hydrogenation does not go to completion; the hydrogen content corresponds to the formula Mg_2NiH_x ($x \approx 2$). This might be connected with the fact that as the temperature decreases, following the formation of a hydride layer on the surface of particles, the diffusion of hydrogen through this layer, the rate of which can be small at room temperature, becomes the limiting stage. The 'diffusion retardation' occurs similarly to that observed in the hydrogenation of magnesium. Moreover, at $T < 515 \text{ K}$ Mg_2NiH_4 exists as a low-temperature modification, the structure of which is the monoclinic distortion of a cubic high-temperature modification.⁸⁵ The latter normally results from hydrogenation at temperatures above the temperature of phase transition. The explanation of this fact calls for additional studies.

III. Hydrogenation of FeTi and LaNi_5 undergoing mechanical milling

As compared to magnesium systems, LaNi_5 and FeTi are low-temperature accumulators of hydrogen. They absorb hydrogen at room temperature. However, commercial polycrystalline samples covered with oxygen-containing compounds require, as a rule, preliminary activation. For instance, the procedure for activation of FeTi consists of heating the sample in a vacuum to 673–723 K and subsequent annealing in hydrogen at a pressure of $\sim 0.7 \text{ MPa}$ followed by cooling to room temperature and increase in the hydrogen pressure to 3.5–6.5 MPa.⁸⁶ This procedure is repeated several times so that hydrogenation is reproducible.

Activation of LaNi_5 proceeds much more easily than in the case of FeTi, but this is still required and consists of a prolonged exposure of the sample at high hydrogen pressure (about 5.0 MPa) at room⁸⁷ or elevated ($\sim 623 \text{ K}$) temperatures in vacuum.⁸⁸

Mechanical milling of these intermetallic compounds in ball mills allows omission or simplification of the activation procedure. The kinetic curves of hydrogen sorption for mechanically milled FeTi are presented in Fig. 13.⁸⁴ After mechanical milling, contact of the sample with air was excluded. It is seen that in this case hydrogenation starts at the maximum rate, and the degree of conversion depends on the duration of the treatment. If the sample was exposed to air after mechanical milling and prior to hydrogenation, activation was necessary, but it occurred much more easily than for ordinary alloys: it is sufficient to heat the sample at 673 K in vacuum for 30 min.⁸⁹

If FeTi is modified with a small amount of palladium, which is added during mechanical milling, neither annealing of the sample nor preliminary exposure of the sample to hydrogen are required.

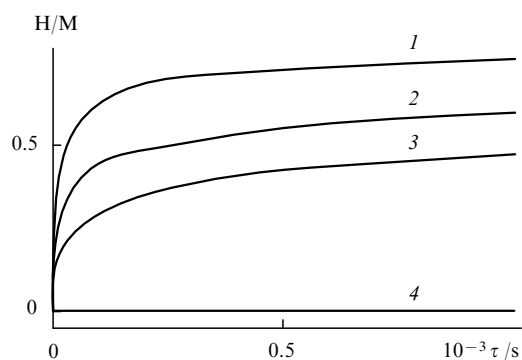


Figure 13. Kinetics of hydrogen sorption for FeTi (283 K, $P_{\text{H}_2} = 2 \text{ MPa}$) after its mechanical processing in an argon atmosphere for 24 (1), 3 h (2), 30 min (3), and without processing (4). The ratio of hydrogen atoms to metal atoms in FeTiH_x is shown in the y-axis.

This sample immediately absorbs hydrogen at room temperature.^{81, 83, 90}

Isotherms of 'pressure–composition' at room temperature without preliminary activation of samples were obtained⁹¹ for amorphous and nanocrystalline FeTi formed upon mechanical alloying. It was shown that the shape of the isotherms is very 'sensitive' to the microstructure of the samples and changes significantly after their annealing. The relaxation of structural defects and mechanical strains upon annealing leads to a decrease in the solubility of hydrogen in both cases and to a change in the length and slope of the plateau in the isotherm of nanocrystalline FeTi. The shape of the adsorption isotherm of the initial nanocrystalline powder indicates the significant contribution of an amorphous component. This fact together with the electron microscopy and WAXS data allowed the authors⁹¹ to draw the following conclusion: the microstructure of particles of nanocrystalline FeTi formed upon mechanical alloying is nanocrystallites with a highly disordered intercrystallite region; the portion of this structure in the bulk material is 20%–30%. It should be emphasised that these data give direct evidence that the degree of disorder and mechanical strains affect the character of the hydrogen absorption in the sample. During preliminary activation, which is required for hydrogenation of intermetallic compounds not doped with palladium the relaxation processes have, as a rule, already occurred, which prevents the unambiguous interpretation of the results.

Analogous kinetic data have been obtained for LaNi_5 .^{81, 83} The kinetic curves for hydrogenation of mechanically milled samples of LaNi_5 — one of which was hydrogenated immediately after mechanical milling, another was kept in air for a long period, and the third was prepared with the addition of palladium — are presented in Fig. 14.

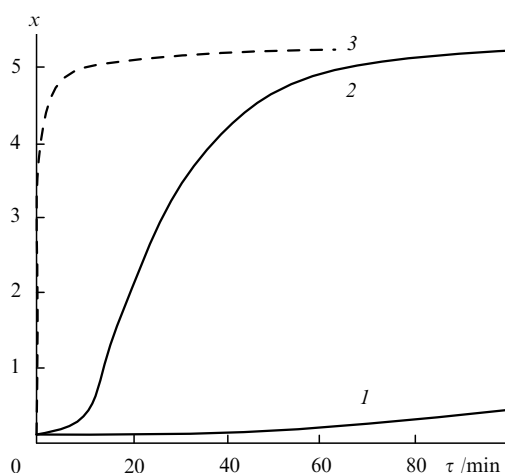


Figure 14. Kinetics of hydrogenation of LaNi_5 milled mechanically at $T = 313 \text{ K}$ and $P_{\text{H}_2} = 1.5 \text{ MPa}$;

(1) the sample kept in air for several months; (2) the sample immediately after mechanical activation; (3) the sample modified with palladium. The x values in the formula LaNi_3H_x are shown in the y-axis.

Hence, mechanical milling of intermetallic compounds Mg_2Ni , FeTi, and LaNi_5 yields a metallic surface, on which dissociative adsorption of hydrogen occurs. However, upon contact of these samples with air the surface is rapidly oxidised and the kinetic characteristics of hydrogenation are impaired. Modification with palladium (one of the best catalysts for the dissociative adsorption of hydrogen) during mechanical milling of these intermetallic compounds allows hydrogenation to be carried out at room temperature without preliminary activation.

IV. The direct formation of hydrides during mechanical milling

The formation of metal hydrides is possible during mechanical milling.^{92–96} To this end, mechanical milling is run in a hydrogen atmosphere at elevated pressure. In this way, binary hydrides of the compositions $\text{TiH}_{1.9}$, $\text{ZrH}_{1.66}$ and MgH_2 have been prepared and characterised by WAXS analysis, differential thermal analysis, and electron microscopy.^{92–95} It is remarkable that magnesium usually absorbs hydrogen in noticeable amounts only at temperatures above 573 K, whereas hydrogenation concurrent with mechanical milling yields magnesium hydride without heating. To date it remains unclear which factor is determining in the formation of hydrides during mechanical milling in a hydrogen atmosphere. It might be crushing, plastic deformation, the formation of a fresh metal surface, local increase in temperature upon collision of grinding bodies, *etc.* Most likely, all these processes contribute to the formation of hydrides.

Mechanochemical processes are known to be non-equilibrium ones and often occur *via* metastable states. This is the case in the hydrogenation of ZrNi during its mechanical milling in a hydrogen atmosphere.⁹⁶ This process includes the stages differing from those in the traditional hydrogenation, namely, the consecutive formation of the hydride phases ZrNiH and/or ZrNiH_3 followed by their amorphisation, and then the decomposition of the amorphous phase to ZrH_2 and metastable hydride $\alpha\text{-Zr}_{1-\delta}\text{NiH}_x$. As a result, composite particles composed of amorphous ($\alpha\text{-Zr}_{1-\delta}\text{NiH}_x$) and crystalline ($\alpha\text{-ZrNiH}_3$ and/or ZrH_2) hydride phases are formed according to the hydrogen pressure used, which varies from 0.1 to 1.0 MPa. Particles resulting from mechanical processing in a hydrogen atmosphere appeared to be much smaller in size (0.5–1.0 μm at a hydrogen pressure of 1.0 MPa) than those obtained under similar conditions in an argon atmosphere (50 μm) due to the higher fragility of the hydride phases as compared to that of ZrNi .

Taking this into account, it was concluded⁹⁶ that mechanical processing in a hydrogen atmosphere can be a promising method for the creation of hydrogen-accumulating materials with a very large interface between the amorphous and crystalline phases and for the creation of hard magnets with anisotropic nanosized grains, which can be obtained by consecutive hydrogenation, amorphisation, and dehydrogenation with simultaneous crystallisation.

When mechanical milling of Mg_2Ni was carried out in a hydrogen atmosphere at a pressure of 1.0 MPa in a 'Fritsch P7' ball planetary mill at a rotation rate of 400 rev min^{-1} , the sorption of hydrogen was also detected.⁹⁷ According to the WAXS data, the samples obtained corresponded to the α -phase, a solid solution of hydrogen in the intermetallic compound $\text{Mg}_2\text{NiH}_{0.3}$. The latter is usually formed in the initial stages of hydrogenation and at higher hydrogen concentrations, the formation of Mg_2NiH_4 begins.⁹⁸ However, upon hydrogenation during mechanical milling, the amount of hydrogen absorbed exceeded significantly that corresponding to the formula $\text{Mg}_2\text{NiH}_{0.3}$. For instance, after processing for 80 h this amount achieved 1.6 mass % ($\text{Mg}_2\text{NiH}_{1.8}$) without noticeable changes in X-ray patterns. In this case, a correlation between the value of specific surface of the sample and the hydrogen content in the sample was observed (Fig. 15). The authors⁹⁷ associate this fact not only with the disintegration of the sample, but also with the formation of a nanocrystalline composite material during mechanical milling composed of crystalline particles with this phase disordered at the grain interface where hydrogen can occupy more sites than in the crystalline phase. The thickness of this disordered phase might be only several nanometers and is not observed in X-ray patterns.

In our opinion, the data given in Ref. 97 do not rule out the principal possibility for the formation of the hydride Mg_2NiH_4 during mechanical milling since the investigations were performed in a low-energy 'Fritsch P7' apparatus. Under more drastic

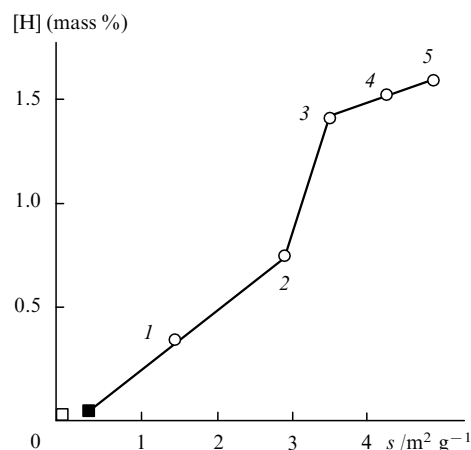


Figure 15. The correlation between the specific surface of the samples (s) prepared by hydrogenation of Mg_2Ni during mechanical milling and the hydrogen content in the samples.

τ / min: (1) 5, (2) 15, (3) 60, (4) 300, (5) 7800.

conditions (more powerful mills, higher hydrogen pressure), hydrogenation can occur to reach the stage of formation of the ternary hydride, which, probably, would be a metastable phase. In any case, the formation of a solid supersaturated solution of hydrogen in Mg_2Ni at the grain interface⁹⁷ indicates that the processes of traditional hydrogenation and hydrogenation during mechanical milling differ in the initial stages.

V. Conclusion

The above review of published data on the interaction between hydrogen and mechanical alloys and intermetallic compounds undergoing mechanical milling allows the following conclusions to be drawn.

Mechanical alloying is a promising method for the preparation of materials with high reactivity with respect to hydrogen.

As compared to traditional methods for the preparation of alloys and intermetallic compounds, mechanical alloying is substantially less time- and energy-consuming. There is no need for high temperatures. Depending on the apparatus design, the process of mechanical alloying takes from several minutes to several hours to yield homogeneous materials or composites with a sufficiently uniform phase distribution, while in the case of traditional alloying, as a rule, special prolonged homogenising annealing is necessary. This is especially important for obtaining alloys of metals differing considerably in their specific densities.

Mechanical alloys formed in the early stages of mechanical alloying are metastable systems with a large interface where the 'atomic' contact of metals occurs and their chemical interaction is possible. This interaction consists of both electron transfer from one element to another thus increasing the catalytic activity of the metal-catalyst and the reduction of oxides used as the second phase in magnesium systems thus creating centres of hydrogen adsorption.

A highly disordered specific structure of the MA surface with a catalyst dispersed in the form of atoms in the near-surface layer is responsible for the high hydrogenation rate in the first cycle. This structure is stable to oxygen and the operation with the sample in air does not require any special conditions.

The possibility to vary the microstructure during mechanical alloying allows the reaction rate and hydrogen capacity of MA to be varied.

The method of mechanical alloying provides a possibility to create composites from non-interacting components, which favours the synthesis of novel hydrides and IMC in the reaction of these MA with hydrogen.

Mechanochemical synthesis or mechanical processing of intermetallic compounds results in a material with nanosized particles and a pure metal surface, which excludes the necessity for its activation before hydrogenation. Despite the fact that this surface is prone to rapid oxidation, the activation of these materials after their contact with air still proceeds much more easily than that of ordinary IMC. If catalytic centres of hydrogen adsorption are created at the surface of IMC, for example, by the introduction of a small amount of palladium during mechanical alloying, high hydrogenation rates can be achieved at room temperature without preliminary activation, as in the case of Mg_2Ni , FeTi , and LaNi_5 .

Some hydrides can be formed directly during mechanical processing in a hydrogen atmosphere. In this case, due to the non-equilibrium character of mechanochemical processes, metastable hydride phases and nanocomposites can be formed, which opens up new prospects for the synthesis of novel materials.

Of course, mechanical alloying does not solve all the problems associated with the hydrogenation of metals and alloys; all the potentialities of mechanical alloying have not been exhausted. The major part of the investigations dealt with magnesium systems for which mechanical alloying is the efficient method of preparation of materials with high reactivity towards hydrogen, and which has practically no alternative in the case of immiscible components. Examination of other systems has only just started, though for these systems the possibility of solving the problem of activation by means of mechanical processing has already been shown. Studies of the synthesis of nanocomposites that could possess high reactivity and high hydrogen capacity by mechanical processing seem to be promising. Unfortunately, it should be noticed that by now the problems concerning cycling of MA and IMC milled mechanically have not been sufficiently covered in the literature; little attention has been paid to processes of dehydrogenation, etc. We hope that these problems will find their researchers in the future.

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Gas hydrates, a new class of impurities in high purity gases and gas – vapour mixtures

V M Vorotyntsev, V M Malyshev

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Abstract. The conditions of formation and structural features of gas hydrates are considered. The existing physicochemical models of formation of gas hydrates are analysed and an algorithm for calculating the parameters which influence the efficiency of gas purification is proposed. Theoretical values of dissociation pressure and water vapour pressure over the surface of mixed hydrates in mixtures of volatile inorganic hydrides are given as well as the distribution coefficients of the components between phases in the process of their formation. It is shown that the appearance of impurities in the form of gas hydrates in hydrides can markedly affect the efficiency of their refinement. The bibliography includes 43 references.

I. Introduction

The chemical nature of impurities determines their behaviour in the processes of separation and refinement of substances. In studies of suspended particles of submicro-size it was established that the transition of the same compound from the molecular to the heterogeneous form substantially alters its behaviour as an impurity in these processes. Therefore, suspended particles of submicro-size are regarded as a new class of impurities in substances of high purity. The interaction of impurity components (especially, water) with the main substance yielding donor–acceptor complexes or new chemical compounds substantially broadens the array of impurities in the substance under purification. At the same time, the appearance of a ‘new’ impurity component may be due to the formation of molecular complexes, that are bound only by van der Waals forces. Certain complexes of this kind known as gas hydrates and suspended submicro-size particles may also be attributed to a new class of impurities in ultrapure substances. It is interesting to study their structure, the formation conditions, and behaviour in the process of gas refinement. The aim of this paper is to analyse the existing physicochemical models of gas hydrate formation and to devise algorithms for calculating their parameters which affect the efficiency of gas refinement: the pressure of saturated water

vapour over the surface of hydrates and dissociation pressure as well as distribution coefficients of gas mixture components between the gas and solid phases.

Gas hydrates were first detected and given this name as early as 1810 when Davy synthesised a chlorine gas hydrate. Nikitin suggested¹ that gas hydrates are solid solutions. Several reviews and monographs have been published^{2–7} which present in detail both historical aspects and physicochemical data on gas hydrates.

At present, over 120 gas hydrates are known. Many of them have found practical uses: for example, gas hydrates of Freon 12 are applied to desalinating sea water and in the concentration of heavy water.⁸

Gas hydrates formed in gas mains can block the transportation of natural gas resulting in pipeline failures.⁵ In addition, gas hydrates can be formed in the process of purification of volatile substances under high pressure and change the solubility of the water impurity in such substances.⁹

Clathrate compounds are formed by the inclusion of one species of molecules called ‘guests’ into the cavities of a crystalline network built of molecules of another species called ‘hosts’. The term ‘inclusion compounds’ was introduced by Schlenk, and the term ‘clathrate compounds’ was proposed by Powell.¹⁰ Originally, only compounds with cellular cavities were regarded as clathrates. Nowadays, both terms are synonyms defining the compounds in question irrespective of the type of cavities. Their major difference from common chemical compounds consists in their reacting components (‘host’ and ‘guest’) being generally coordinatively saturated compounds and their interaction is, as a rule, based on van der Waals forces. Therefore, the clathration is accompanied by a slight gain of energy and plays a crucial role only when no chemical reactions take place. The crystalline lattice of the ‘host’ per se is thermodynamically unstable if it is not filled with a minimum number of gas molecules, and thus cannot exist in the ‘pure’ form. This peculiarity distinguishes it from the crystalline lattice of ice.

II. Structure of gas hydrates

All the known gas hydrates have basically one of the following structures: I, II and H. The structures I and II are characterised respectively by a cubic symmetry (space group $Pm\bar{3}n$, $Fd\bar{3}m$) and the structure H, by hexagonal (space group $P6/mmm$) symmetry. Structure H was discovered in 1987.² Some compounds possess a different structure; for example, Br_2 and Me_2O have tetragonal (space group $P4_2/mnm$) symmetry, while Me_3CNH_2 has cubic (space group $I\bar{4}3d$) symmetry.

V M Vorotyntsev, V M Malyshev Institute of Chemistry of High Purity Substances, Russian Academy of Sciences, ul. Tropinina 49, 603600 Nizhnii Novgorod, Russian Federation. Fax (7-831) 266 86 66. Tel. (7-831) 266 47 64 (V M Vorotyntsev)

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There are five fundamental types of cavities in the crystalline network of which structures I, II, and H are constructed. The basic characteristics of these cavities are presented in Table 1.

Table 1. Structural properties of clathrate hydrates.²

Parameter	Structure I	Structure II	Structure H
Space group	<i>Pm3n</i>	<i>Fd3m</i>	<i>P6/mmm</i>
Unit cell parameters / Å			
<i>a</i>	12.03	17.31	12.26
<i>c</i>	—	—	10.17
Number of water molecules per unit cell	46	136	34
Number of cavities in the unit cell with D_{mean} / Å			
7.8	2	16	3
8.7	6	0	0
9.4	0	8	0
7.8	0	0	2
10.7	0	0	1
Composition of the structure			
all cells are occupied	$M \cdot \frac{23}{4} \text{H}_2\text{O}$	$M \cdot \frac{17}{3} \text{H}_2\text{O}$	see ^a
large cells are occupied	$M \cdot \frac{23}{3} \text{H}_2\text{O}$	$M \cdot 17 \text{H}_2\text{O}$	$M \cdot 34 \text{H}_2\text{O}$

^a Structure H is stabilised only due to filling of the smallest cavities with xenon and hydrogen sulfide.

Gas molecules intercalating into structures I, II, and H differ substantially in size and shape. There is a relationship between the maximum van der Waals diameter of gas molecules and the lattice structure. Gas molecules will not occupy the cavities if their van der Waals diameter is larger than the free diameter of these cavities. The latter is roughly equal to the difference between the geometric size of the cavity indicated in Table 1 and the van der Waals diameter of the oxygen molecule (2.8 Å). For example, when the van der Waals diameter of a gas (d_g) is in the range from 4.2 to 5.5 Å, the gas hydrate with structure I is formed; when $3.8 < d_g < 4.0$ Å or $5.6 < d_g < 7.0$ Å, structure II is formed, and when $d_g = 8.2$ –8.3 Å, structure H is formed.²

Certain gas hydrates include more than one substance as their ‘guests’. If different compounds occupy cavities randomly, a mixed gas hydrate is formed. When large cavities are filled with gas molecules of large size and small cavities are occupied by those of small size, double hydrates are formed. All hydrates with structures H and II for relatively large gas molecules (> 6.8 Å) are of the double type. In such hydrates, the ‘auxiliary’ gases, xenon and hydrogen sulfide, occupy small cavities and stabilise the crystal.

III. Physicochemical models of gas hydrate formation

1. An ideal solution model

First, a model of ideal solutions has been used by van der Waals for a description of the non-stoichiometric nature of clathrate crystals.¹¹ Initially, it was used for clathrates of hydroquinone with cavities of only one type. However, the equations derived for this molecule had to be modified considerably because of the specificity of gas hydrates (the presence of cavities of different size and shape in structures I and II, crystalline lattices of water molecules, *etc.*). The modifications were first done by Barrer and Stuart¹² and then by van der Waals and Platteeuw.¹³

By assuming that only one molecule occupies each cavity, van der Waals obtained the following expression for the distribution function for an ensemble of molecules of water W and gas M forming a clathrate crystal:

$$Z = \exp\left(-\frac{F_0}{kT}\right) \sum_{N_{M_1}} \prod_{i=1}^2 \left[N_{M_i} B_{M_i} A_M \frac{N_i!}{(N_i - N_{M_i})! N_{M_i}!} \right], \quad (1)$$

where F_0 is the free energy of water molecules in an empty clathrate lattice; N_{M_1} and N_{M_2} are the numbers of gas molecules in the respective cavities; B_{M_i} is the molecular distribution function of molecules M in cavities i ; A_M is the absolute activity; and N_1 and N_2 are the numbers of large and small cavities, respectively. For Eqn (1), it is assumed that, first, F_0 is independent of the extent of cavity filling and the nature of gas M and, second, the value of B_{M_i} is the same for each cavity of the i th type and is independent of whether or not the cavity is occupied. The first condition is not strictly true for large gas molecules nor is the second condition, for strongly polarised gas molecules.

In the case of an equilibrium distribution of gas molecules M over cavities, all the known thermodynamic functions are included in Z in accordance with the following equation:

$$kT d(\ln Z) = \frac{U}{T} dT + PdV + N_M kT d(\ln A_M) - \mu_W dN_W, \quad (2)$$

where U is the internal energy, $N_M = N_{M_1} + N_{M_2}$ is the equilibrium number of intercalated gas molecules with activity A_M , μ_W is the chemical potential and N_W is the number of water molecules in the clathrate lattice.

Using the method of molecular dynamics, Rodger has attempted to establish how far the assumptions underlying the cellular theory of gas hydrates are valid.¹⁴ It was shown that one of the approximations, according to which the free energy of the ‘water crystal’ is independent of the presence of ‘guest’ molecules in the cell structure, does not hold for gas hydrates. Analysis of the results obtained suggested that the conditions of gas hydrate formation may equally depend on kinetic and thermodynamic factors.

Disregarding the kinetic factors, Eqns (1) and (2) may be transformed to yield an expression for the determination of the chemical potential of water molecules in the equilibrium distribution of ‘guest’ molecules over the cavities of a gas hydrate:^{12, 13}

$$\mu_W = \mu_W^0 + kT \sum_i n_i \ln(1 - Q_i), \quad (3)$$

where μ_W^0 is the chemical potential of an empty hydrate lattice, n_i is the ratio of the number of i -type cavities in the elementary cell to the number of its constituent water molecules, Q_i is the fraction of gas-filled cavities calculated using the known Langmuir formula:

$$Q_i = \frac{C_{M_i} f_M}{1 + C_{M_i} f_M}, \quad (4)$$

where, C_{M_i} are the Langmuir coefficients depending on temperature and pressure (the latter dependence is very weak), f_M is the gas fugacity.

It was shown¹⁵ that one should take into account the fugacity of gas molecules in calculations. Sufficient accuracy in the calculation of this parameter is achieved using the Redlich–Quong equation.

Equation (3) makes it possible to determine the minimum value of the fraction of filled cavities, and in combination with Eqn (4), it allows the estimation of the minimum pressure of gas M (dissociation pressure P_{dis}) necessary for the hydrate stabilisation at a given temperature.

The results of studies^{16–18} demonstrate that there is also a maximum pressure under which gas hydrates may exist in a steady state (15 000–20 000 atm). With hydrates of tetrahydrofuran and SF₆ as examples it was shown¹⁸ that at 77 K and 10 000–20 000 atm they are transformed to a denser modification with a 19% decrease in volume.

Barrer and Stuart¹² have derived an expression for the determination of the saturated vapour pressure over the surface of gas hydrate for the case of thermodynamic equilibrium of a gas hydrate with water vapour:

$$P_W = P_W^0 - \sum_i n_i \ln(1 + C_{M_i} f_i), \quad (5)$$

where P_W^0 is the saturated vapour pressure (dependent on temperature and the structural type) over an empty clathrate lattice. Using the experimental data for the most thoroughly studied hydrates of methane (structure I) and propane (structure II), the authors of Ref. 19 showed that the dependence $P_W^{0(I,II)}$ is satisfactorily (with an error of $\sim 3.5\%$) described by two three-membered equations for the temperature range 260–290 K

$$\ln P_W^{0(I)} P = -128.0009 + 22.0937 \ln T - \frac{193.6439}{T}, \quad (6)$$

$$\ln P_W^{0(II)} P = -111.0433 + 20.2241 \ln T - \frac{690.3979}{T}. \quad (7)$$

Thus, if the Langmuir coefficients are known, Eqns (5)–(7) permit us to calculate the pressure (or fugacity) of gas hydrate dissociation or the saturated water vapour pressure above its surface.

In recent years, more accurate models for the thermodynamic description of gas hydrates have been developed.^{7,10} It has been shown that the most important factors to be taken into account in the construction of such models are the interactions of intercalated molecules (interaction of a ‘guest–guest’ type). The refinement of a thermodynamic description of gas hydrates is made in a way analogous to that used in the theory of solutions when a model of a regular solution is considered instead of a model of an ideal solution. The model thus obtained is called the ‘regular clathrate model’. It should be emphasised that at higher degrees of filling of cavities in the hydrate network and similarity of parameters characterising the ‘guest–guest’ interactions for different gases (*e.g.*, in narrow groups of gas mixtures such as natural gas, hydrides, *etc.*), their contributions to the formulae describing the interaction of intercalated molecules are virtually constant and independent of the gas phase composition. In this case, the ‘guest–guest’ interaction may formally be included in μ_0 (Ref. 7). It is for this reason that the possibilities of practical application of the ideal gas hydrate model are noticeably extended. Therefore, this paper discusses in sufficient detail the model of an ideal gas hydrate rather than a model of a regular clathrate, which is more complex and cumbersome for practical calculations.

2. Calculation of Langmuir coefficients

In order to determine the Langmuir coefficients, van der Waals and Platteeuw²⁰ used a spherical cell model. By substituting the mean cavity radius R_i formed by Z_i water molecules for the mean cell radius formed by the neighbouring molecules in liquid, these authors obtained the equation

$$C_{M_i} = \frac{4\pi}{kT} \int_0^{R_i} \exp\left(-\frac{W(r)}{kT}\right) r^2 dr, \quad (8)$$

where $W(r)$ is the radial potential function derived using the interaction potential of the gas molecules with the surrounding water molecules and r is the radial distance of the intercalated gas molecule from the cavity centre.

The energy of gas–water interaction is usually determined by the Lennard-Jones potential. The interaction between gas molecules in the hydrate cavities may be disregarded, as it is insignificant compared to the gas–water interaction and the accuracy of its determination is low (20%–40%).²¹

Calculations of the dissociation pressure by Eqns (3) and (8) using Kihara’s potential (*e.g.*, in studies^{22,23} for methane, nitrogen, ethane, and propane) agree well with the experimental values

of dissociation pressure of the corresponding gas hydrates. As regards the parameters of Kihara’s potential, preference was given to those values which gave the best fit of the μ_W values calculated by Eqns (3) and (4) and found in experiments. The model for calculating the Langmuir coefficients was further improved in studies^{24–27} to allow a more adequate description of experimental data.

To calculate the Langmuir coefficients of a spherical gas molecule in a real non-spherical hydrate cavity, the following equation was proposed:²⁴

$$C_{M_i} = \frac{1}{kT} \int_0^{2\pi} \int_0^\pi \int_0^{R_i} \exp\left(-\frac{W}{kT}\right) r^2 \sin \theta dr d\theta d\varphi, \quad (9)$$

where $W = W(r, \theta, \varphi)$ is the interaction potential in the cavity. To estimate it, the spherical Kihara potential was used, because this potential is believed to permit a better prediction of hydrate equilibria than other potentials do.^{24,25} Kihara’s potential has the following form:

$$F(x) = \infty \quad \text{at } x < 2a, \\ F(x) = 4\epsilon \left[\left(\frac{\sigma}{x-2a} \right)^{12} - \left(\frac{\sigma}{x-2a} \right)^6 \right] \quad \text{at } x > 2a, \quad (10)$$

where $F(x)$ is the potential energy of a binary interaction for a distance x between the water and gas molecules, ϵ is the potential well depth, σ is the distance between molecular centres for which $F(x) = 0$ and a is the nuclear radius of interaction between water and gas molecules. When the distribution of cavity-forming water molecules is known, the summation of binary interactions of a gas molecule with each water molecule allows the estimation of the interaction potential in the cavity $W(r, \theta, \varphi)$ for selected coordinates of the gas molecule.

The spherically symmetrical, smoothed potential derived from the cell model, $\langle W(r) \rangle$, is expressed through Kihara’s parameters in the following manner:

$$\langle W(r) \rangle = 2Ze \left[\frac{\sigma^{12}}{R^{11}r} \left(B^{10} + \frac{a}{R} B^{11} \right) - \frac{\sigma^6}{R^5 r} \left(B^4 + \frac{a}{R} B^5 \right) \right], \quad (11)$$

where Z is the coordination number and R is the radius of the cavity.

$$B^n = \frac{1}{n} \left[\left(1 - \frac{r}{R} - \frac{a}{R} \right)^{-n} - \left(1 + \frac{r}{R} - \frac{a}{R} \right)^{-n} \right],$$

n is 4, 5, 10 and 11.

By comparing the results of calculations using Eqns (9), (10), and (11), the radius and coordination number were determined for each cavity,²⁴ which allow the use of $\langle W(r) \rangle$ for the approximation of the interaction potential in a cavity for all distances at which the potential is negative or ‘slightly positive’. In this case, the coordination number of an equivalent spherical cavity is not necessarily equal to the real coordination number of the cavity (Table 2).

The effects of the second and third layers of water molecules in the hydrate lattice on the accuracy of calculation of Langmuir constants were studied.²⁵ It is assumed that the binary interaction between a gas and a water molecule is described by the quasi-spherical Kihara potential (10). The characteristics of smoothed potential in the form of Eqn (11) were obtained, as before,²³ by comparing the results of calculations by Eqn (11) with the results of the summation of the binary interactions. The data reported in Ref. 28 on the distribution of water molecules in a hydrate cell were used for the estimation of the effects of the second and third levels of water molecules. When the effective radius and coordination number of the second and third levels of water molecules were introduced, it was assumed that the gas and water molecules interact only due to the attractive forces. To determine the effective radius of the second level (R_{2i}), the following expression was used:

Table 2. Effective radii of shells of water molecules for various types of cavities in gas hydrates.

Cavity	First shell ²²		First shell ²³		Second shell		Third shell	
	$R_i, \text{\AA}$	Z	$R_i, \text{\AA}$	Z	$R_i, \text{\AA}$	Z	$R_i, \text{\AA}$	Z
Structure I								
Small cavity	3.95	20	3.875	20	6.593	20	8.056	50
Large cavity	4.3	24	4.152	21	7.078	24	8.285	50
Structure II								
Small cavity	3.91	20	3.870	20	6.667	20	8.079	50
Large cavity	4.73	28	4.703	28	7.464	28	8.782	50

$$\frac{Z}{(R_{2i})^6} = \sum_j \frac{Z_j}{(r_j)^6}, \quad (12)$$

where Z_j is the number of the second level molecules at the distance r_j from the cavity centre. The effective radius of water molecules at the third level R_{3i} was determined similarly. However, whereas the second layer of water molecules may be correctly described using the crystallographic data, it is not always possible to distinguish the third and subsequent layers. Therefore, the contribution from the third level is determined by those from the subsequent layers of water molecules. The results of calculation of the effective radius for the second and third layers are presented in Table 2. The calculation of the smoothed interaction potential between gas and water molecules by Eqn (11) for the three water layers has shown²⁵ that although the contributions from the molecules of more distant layers are small compared to that of the first-layer molecules and make up only a few percent, nonetheless their consideration leads to a nearly tenfold increase in the Langmuir constant. Consequently, accurate calculation of the Langmuir constants requires consideration of no less than three layers of water molecules.²⁵

To make it possible to use the parameters of Kihara's potential obtained by independent calculations based on the data on viscosity and the second virial coefficient in Eqn (11), it was proposed^{26,27} to introduce a correction factor into Eqn (8) to account for the irregularity of the shape of gas molecules and the cavity. To this end, it was proposed to calculate the Langmuir constant by the following equation:

$$C_0 = CQ, \quad (13)$$

$$Q = \exp \left\{ -A_0 \left[U \left(\frac{\sigma}{R-a} \right) \frac{\varepsilon}{rT} \right]^n \right\}, \quad (14)$$

where C is calculated by Eqn (8), A_0 and n are empirical constants depending on the cavity type, and U is the empirical parameter taking into account the shape of the gas molecules. For small and spherical molecules, $U = 0$. The largest deviation of the coefficient Q from 1 is observed for the gas molecules localised in large cavities of structure I, which are the most asymmetrical. The results of calculations of the dissociation pressure for a number of substances based on the above model agree well with the reported experimental data.^{26,27} The Q value may also be larger than 1. Relatively high Q values are observed for small Langmuir constants (for large gas molecules). This may be explained by strong fluctuations of the cell potential $W(r, \theta, \varphi)$.²⁶

The method of molecular dynamics was used²⁹ to study the potential field in a small cavity of type I gas hydrate. The thermal motion of 'host' molecules of the lattice was found to change the natural potential in the cavity and to result in its substantial anisotropy and temperature dependence. An equation for the potential in the form of a polynomial of the sixth power was proposed and its parameters were determined for methane. It was shown that Kihara's potential may also be applied using the dependence of parameters a and R on angles θ and φ . The form of these dependences can be determined from the results of simulation by the method of molecular dynamics.

Thus, a system of Eqns (8), (11), (13), and (14) makes it possible to calculate the Langmuir constants necessary for determination of the conditions for the existence of gas hydrates by the Eqns (3)–(5).

3. Calculation of gas hydrate parameters for argon, krypton and xenon

Using the model of ideal solutions for the calculation of the conditions for the existence of gas hydrates and the spherical cell model for the determination of the Langmuir constants, an algorithm for the computation of parameters of gas hydrates in the separation and refinement of gases was derived and the corresponding programs for an IBM PC were developed.³⁰

To check the applicability of Eqns (8) and (11)–(14) for the determination of the Langmuir constants, these were calculated³⁰ for the gas hydrates of argon, krypton, and xenon because of the availability of experimental data on these compounds.³¹

The calculation of the Langmuir constants within the framework of the above model requires that the parameters of Kihara's potential for the substances under study be known. The literature data on these parameters are contradictory; in some cases, the discrepancy reaches 50%–100%. The authors of Ref. 32 have used the parameters of Kihara's potential reported in Ref. 27, whereas in another study,³¹ double hydrates were used for the experimental determination of the Langmuir constants. In the latter work, the absorption of the above-mentioned gases in structure II of CHCl_3 hydrate under different gas pressures was investigated. All large cavities were occupied by CHCl_3 , while the inert gas filled the small cavities. The linear dependence obtained between the pressure and the volume of the gas absorbed confirmed once again the applicability of the Langmuir isotherm. Figure 1 shows the plots of the dependence of the logarithm of the Langmuir constant for argon, krypton, and xenon on $1/T$. All the

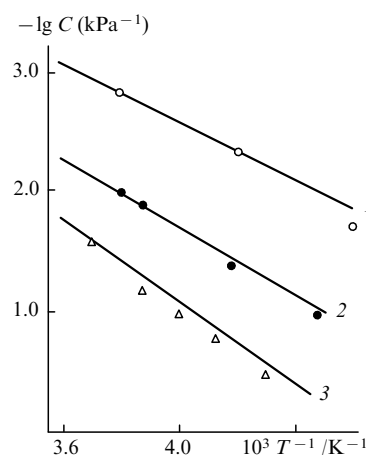


Figure 1. The temperature dependence of the Langmuir constants for argon (1), krypton (2), and xenon (3). The solid line corresponds to the theoretical calculations, the points represent the experimental data.

dependences proved to be linear thus allowing the determination of the enthalpy of dissociation for each gas in 12 water cavities, and the results obtained coincided with the theoretical data.³¹ Figure 1 also shows the results of calculations based on the above model. However, the parameters of Kihara's potential differ from those reported²⁷ (Table 3) by the magnitude of the error of their determination (5%–7%). The use of accurate ε and σ values results in underestimation of the Langmuir constants for krypton and xenon by more than an order of magnitude.

To check the applicability of Eqns (5)–(7) for the calculation

Table 3. Parameters of Kihara's potential used to calculate the Langmuir constants.

Parameter	Ar	Kr	Xe
$\sigma/\text{\AA}$	<u>3.29</u> 3.29	<u>3.53</u> 3.3	<u>3.65</u> 3.43
$\varepsilon/k/\text{K}$	<u>156.08</u> 156.08	<u>216.4</u> 230.0	<u>314.51</u> 340.0
$a/\text{\AA}$	<u>0.217</u> 0.217	<u>0.232</u> 0.217	<u>0.252</u> 0.252

Note. Numbers above the line are potential parameters given in Ref. 26, those below the stroke are parameters used by us. For all gases in all cases we assumed $U = 0$.

of the vapour pressure of water above the surface of hydrates, calculations were performed³⁰ for the hydrates of the same inert gases under their dissociation pressure. As follows from the above-mentioned theory of gas hydrate formation, under the pressure of hydrate dissociation, the pressure of water vapour above its surface is equal to that above the ice surface at the same temperature. For example, at 273 K the pressure of water vapour calculated by the algorithm mentioned is 0.54, 0.53, and 0.57 kPa for argon, krypton, and xenon, respectively. The literature data value for the same parameter for ice is 0.6 kPa,³² i.e. fairly good agreement is observed between the theoretical and experimental results.

Thus, the theoretical model of gas hydrate formation allows an accurate calculation of the dissociation pressure of a hydrate-forming gas and the minimum content of water at which the formation of hydrates is still possible. In the refinement of some substances, e.g., Freons and volatile inorganic compounds capable of forming gas hydrates in the vapour phase, their effect on the efficiency of this process may be substantial.^{33–36}

IV. Vapour pressure of water over the surface of gas hydrates in mixtures of volatile inorganic hydrides

In volatile inorganic hydrides, the content of water and some other impurities should not exceed a certain level. Demands for higher purity of substances and a larger set of impurities to be controlled make it necessary to consider the possible presence of different forms of water.

Under elevated pressures, the impurity of water can form finely dispersed, solid gas hydrates with some volatile inorganic hydrides.¹⁵ The presence of gas hydrates in the vapour phase may lead to incorrect determination of the water concentration in a given gas.³⁴

Using the algorithm for the calculation of the parameters of gas hydrates,³⁰ the pressure of water vapour above the surface of methane and hydrogen sulfide hydrates for different temperatures and gas pressures was calculated³⁴ (Table 4). For these compounds, the temperature dependences of dissociation pressure of

gas hydrates and the parameters of Kihara's potential have been studied in sufficient detail.²⁷

Analogous calculations for other hydrides are problematic due to the absence of the respective parameters of Kihara's potential. Therefore, the Lennard-Jones potential was used³⁴ to calculate the Langmuir constants by Eqn (4).

To check the applicability of the Lennard-Jones potential for this purpose, the Langmuir constants were calculated for the gas hydrates of argon, krypton, and xenon, because the experimental values of the constants are known.² The parameters of the Lennard-Jones potential necessary for such calculations are presented in Table 5. The use of literature values of ε and σ leads to the underestimation of the Langmuir constants for all gases by more than one order of magnitude. Therefore, to calculate the Langmuir constants, preference was given to the values of ε and σ , which are within the range of their error estimates. For water, the following parameters were used: $\varepsilon_{\text{W}}/k = 102.1$ K, $\sigma_{\text{W}} = 3.564$ \AA.²⁷ When calculating ε and σ for the cases of cross-interaction of water molecules with molecules of hydrides, the Lorentz–Berthelot rule was used:³⁴

$$\varepsilon_0 = (\varepsilon_{\text{W}}\varepsilon)^{1/2}; \sigma_0 = \frac{1}{2}(\sigma_{\text{W}} + \sigma),$$

where ε_0 and σ_0 are parameters describing the gas–water interaction.

Analogous formulae were also used for the calculation of the vapour pressure of water above the surface of hydrates of some volatile inorganic hydrides. The results of calculations for gas hydrates of arsine, hydrogen selenide, and phosphine, as well as methane, characterised by structure I are given in Table 4 as examples.³⁴ Comparison of the results of calculations for hydrogen sulfide and methane shows that the deviation of values derived using the interaction potentials of Kihara and Lennard-Jones does not exceed 10%. The percentage of water in gas given in the table, which is equal to the ratio of water vapour and gas pressures, determines the minimum content of water in the molecular form at which the formation of gas hydrates is possible under given conditions. If the concentration of molecular water exceeds the indicated value, it is decreased owing to the formation of hydrates and tends to reach the level given in the table. Consequently, the given value of water concentration determines the maximum concentration of water in the molecular form for specified conditions.

The results of calculations presented in the tables indicate that if one disregards the formation of hydrates and takes into account only the condensation of water to form ice, then the value of the vapour pressure of water and hence the concentration of molecular water may be overestimated by a factor of 1.5 or more. With a decrease in temperature, the ratio of the vapour pressure of water above the ice surface to that of gas hydrate increases (Table 6) with a concomitant increase in the scatter of values of this parameter for different hydrides (except for arsine and hydrogen sulfide), which becomes significant at temperatures below 273 K. It seems so far impossible to calculate this parameter for a wider temperature range since the required initial data are unavailable. Nonetheless, this parameter may be estimated using the equations given in Ref. 34 by approximating the data shown in Table 6 by the least-squares method.

For arsine and hydrogen sulfide at $T < 273$ K

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{189.1}{T} - 0.328, \quad (15)$$

for phosphine at $T < 273$ K

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{613.4}{T} - 1.879, \quad (16)$$

for hydrogen selenide at $T < 273$ K

$$\ln\left(\frac{P_2}{P_1}\right) = -\frac{49.5}{T} + 0.587, \quad (17)$$

Table 4. Results of the calculations of water vapour pressure over the surface of various hydrates.

T/K	Methane hydrate ^a					Hydrogen sulfide hydrate ^b					Arsine hydrate			Phosphine hydrate			Hydrogen selenide hydrate				
	P'_{dis}	P'_{W}	$c'_{\text{H}_2\text{O}}$ (%)		P_{dis}	P_{W}	$c_{\text{H}_2\text{O}}$ (%)	P'_{dis}	P'_{W}	$c'_{\text{H}_2\text{O}}$ (%)		P_{dis}	P_{W}	$c_{\text{H}_2\text{O}}$ (%)	P_{dis}	P_{W}	$c_{\text{H}_2\text{O}}$ (%)	P_{dis}	P_{W}	$c_{\text{H}_2\text{O}}$ (%)	
P_{dis}	P_{W}	$c_{\text{H}_2\text{O}}$ (%)																			
252	—	—	—	1130	0.09	0.80	42	0.10	0.24	42	0.09	0.21	32	0.09	0.29	31	0.09	0.30	28	0.09	0.32
	—	—	—	10000	0.07	0.07	300	0.08	0.03	300	0.06	0.02	200	0.07	0.04	500	0.06	0.01	100	0.08	0.08
	—	—	—	20000	0.06	0.03	515	0.07	0.01	517	0.05	0.01	485	0.06	0.01	1022.7	0.05	0.005	231	0.07	0.03
259	1550	0.19	1.23	1550	0.17	1.10	55	0.19	0.35	55	0.17	0.30	45	0.18	0.40	55	0.17	0.31	33	0.18	0.54
	10000	0.15	0.15	10000	0.13	0.13	300	0.15	0.05	300	0.13	0.04	300	0.13	0.05	600	0.12	0.02	150	0.14	0.10
	20000	0.13	0.07	20000	0.12	0.06	650	0.13	0.02	653	0.11	0.02	602	0.12	0.02	1242	0.11	0.01	301	0.13	0.04
	2030	0.35	1.74	2030	0.32	1.55	71	0.36	0.51	72	0.32	0.44	60	0.34	0.55	91	0.31	0.35	38	0.34	0.88
266	10000	0.28	0.28	10000	0.25	0.25	400	0.28	0.07	400	0.24	0.06	350	0.26	0.07	700	0.23	0.03	200	0.27	0.13
	20000	0.25	0.13	20000	0.23	0.12	815	0.25	0.03	818	0.22	0.03	740	0.23	0.03	1493	0.20	0.01	387	0.24	0.06
	2620	0.64	2.44	2620	0.58	2.19	92	0.67	0.72	92	0.58	0.63	83	0.61	0.74	160	0.55	0.35	45	0.64	1.41
273	10000	0.53	0.53	10000	0.48	0.48	500	0.52	0.10	500	0.45	0.09	400	0.49	0.12	800	0.43	0.05	250	0.50	0.20
	20000	0.48	0.24	20000	0.44	0.22	1010	0.46	0.05	1012	0.40	0.04	900	0.43	0.05	1778	0.38	0.02	490	0.45	0.09
	5940	1.07	1.80	5940	0.93	1.34	204	1.12	0.55	204	0.98	0.48	190	1.02	0.54	319	0.94	0.30	90	1.09	1.21
280	10000	0.99	0.99	10000	0.88	0.88	600	0.95	0.16	600	0.83	0.14	500	0.89	0.18	900	0.80	0.09	300	0.92	0.31
	20000	0.89	0.45	20000	0.81	0.40	1240	0.84	0.07	1240	0.74	0.06	1081.1	0.790	0.073	2100	0.71	0.03	614	0.82	0.13
	12800	1.75	1.37	12800	1.56	1.22	436	1.84	0.42	437	1.61	0.37	415	1.69	0.41	612	1.57	0.26	175	1.84	1.05
287	20000	1.64	0.82	20000	1.47	0.74	1000	1.62	0.16	1000	1.42	0.14	600	1.60	0.27	1000	1.46	0.15	350	1.66	0.48
	40000	1.46	0.37	30000	1.39	0.46	1500	1.51	0.10	1505	1.34	0.09	1290	1.43	0.11	2457	1.28	0.05	761	1.48	0.20
	26100	2.84	1.09	26100	2.54	0.98	865	3.00	0.35	865	2.65	0.31	880	2.75	0.31	1140	2.61	0.23	327	3.06	0.94
294	35000	2.71	0.78	30000	2.49	0.83	1200	2.85	0.24	1200	2.53	0.21	1000	2.70	0.27	1400	2.53	0.18	450	2.92	0.65
	50000	2.56	0.51	35000	2.42	0.69	1800	2.66	0.15	1809	2.38	0.13	1524	2.55	0.17	2856	2.29	0.08	933	2.63	0.28

Note. The following designations are used: P'_{dis} , P'_{W} , and $C'_{\text{H}_2\text{O}}$ are values obtained using Kihara's potential, P_{dis} , P_{W} , and $C_{\text{H}_2\text{O}}$ are those obtained with the Lennard-Jones potential (the gas pressures P'_{dis} , P_{dis} and water pressure P_{W} are given in kPa).

The following parameters of Kihara's potential were used: ^a $\epsilon/k = 197.39 \text{ K}$, $\sigma = 3.501 \text{ \AA}$, $a = 0.13 \text{ \AA}$, $U = 0$; ^b $\epsilon/k = 414.88 \text{ K}$, $\sigma = 2.747 \text{ \AA}$, $a = 0.36 \text{ \AA}$, $U = 0$.

Table 5. Parameters of the Lennard-Jones potential used to calculate the Langmuir constant.

Substance	ε/k /K			σ /Å		
	I	II	III	I	II	III
H ₂ S	301	309	290	3.623	3.722	3.8
H ₂ Se	320	334	310	3.86	3.876	3.86
PH ₃	270	260	275	3.897	3.992	3.77
AsH ₃	277	293	280	4.06	4.069	3.8
CH ₄	148.6	153.4	148.6	3.758	3.413	3.6
Ar	93.3	117.2	100	3.542	3.405	3.3
Kr	178.9	—	185	3.655	—	3.55
Xe	231	—	250	4.047	—	3.75

Note. The following designations are used: I — the data from Refs 37 and 38; II — calculation by the procedure proposed in Ref. 39, III — our results.

Table 6. Ratios of the vapour pressure of water over hydrates at the dissociation pressure to that at the saturated vapour pressure for some hydrides.

T /K	AsH ₃	PH ₃	H ₂ Se	H ₂ S
252	1.53	1.74	1.39	1.52
259	1.50	1.63	1.40	1.49
266	1.46	1.54	1.41	1.47
273	1.43	1.44	1.41	1.45
280	1.29	1.33	1.32	1.32
287	1.18	1.22	1.24	1.21
294	1.08	1.11	1.16	1.11

for all hydrides at $T > 273$ K

$$\ln\left(\frac{P_2}{P_1}\right) = \frac{940.6}{T} - 3.089, \quad (18)$$

where P_1 and P_2 are the pressures of water vapour above the gas hydrate surface at the pressure of saturated hydride vapour and at the pressure of dissociation, respectively. Thus, for phosphine at 200 K, this parameter and hence the ratio of the real concentration to its theoretical value is 3.28.

In addition, the presence of water in the form of a finely dispersed phase requires the use of an appropriate purification technique. Specifically, this concerns the formation of double or mixed hydrates, when other hydrides or gases may be intercalated as impurities into the crystalline lattice of gas hydrates.

Thus, the above data indicate that the appearance of impurities in hydrides in the form of gas hydrates can substantially affect the process of their refinement.

V. The formation of mixed hydrates in inorganic hydrides and atmospheric air

A large contribution to the development of theory and experimental techniques for studying mixed gas hydrates was made by Nikitin¹ who proposed and developed a method of isomorphous co-precipitation in mixed hydrates of rare components from the gas phase irrespective of their concentration. It was shown that there is no need to apply high pressures to form gas hydrates of a large number of gases, since the gas in question under a partial pressure lower than the pressure of its hydrate dissociation, can form a gas hydrate in the form of an isomorphous mixture with hydrates of other gases. Based on the results obtained and general theoretical concepts, Nikitin formulated the ‘analogy rule’, according to which two substances having the same van der Waals forces and commensurable molecules should form with a third substance analogous molecular compounds possessing similar stability and the ability to form mixed crystals with each other.

Thus, taking into account the ‘analogy rule’ and the law of isomorphous co-precipitation, it may be inferred that a mixed hydrate can contain different quantities of the all gas phase components that can form isomorphous structures.

Let us consider the methods employed for the quantitative assessment of the conditions for formation of mixed gas hydrates.

1. The effect of gas mixture composition on conditions of gas hydrate formation and vapour pressure of water above its surface

One of the critical parameters characterising the process of gas hydrate formation at a given temperature is its dissociation pressure P_{dis} . The dissociation pressure determines the minimum pressure of a gas mixture at which the hydrate is thermodynamically stable. To carry out processes of refinement of substances that form gas hydrates, one should know the dependence of the dissociation pressure of gas hydrates and the vapour pressure of water over their surface on the composition of gas mixture. This dependence may be determined using the model proposed by Barrer and Stuart.¹²

The application of the model of ideal solutions for the case of thermodynamic equilibrium yielded an equation for the calculation of the pressure of saturated water vapour over the surface of a gas hydrate formed by a mixture of gases $M_1, M_2, \dots, M_i$.¹²

$$\ln\left(\frac{P_W}{P_W^0}\right) = \frac{1}{m(n+1)} \left[n \ln\left(1 - \sum_i Q_{1i}\right) + \ln\left(1 - \sum_i Q_{2i}\right) \right], \quad (19)$$

where P_W is the pressure of saturated vapour over the hydrate surface; P_W^0 is the pressure of saturated vapour above an empty clathrate lattice (which depends on the structural type and temperature; these may be found in Ref. 32); m is the number of water molecules per cavity; n is the ratio of large-to-small cavities in the elementary crystalline hydrate cell ($n = 3, m = 5.75$ for structure I hydrates and $n = 2$ and $m = 5.67$ for structure II hydrates³²); Q_{1i} and Q_{2i} are the fractions of small and large cavities filled with gas M_i .

The filling of cavities in gas hydrates is well described by the Langmuir adsorption isotherm:¹⁵

$$Q_{ji} = \frac{C_{ij}f_i}{1 + \sum_i C_{ij}f_i}, \quad (20)$$

where $f_i = \phi_i P_i$ is the fugacity of gas M_i , ϕ_i is the fugacity coefficient, P_i is its pressure and C_{ij} are the Langmuir coefficients calculated using the spherical cell model.³²

The model used for calculating the fraction of filled cavities in mixed gas hydrates describes well the experimentally found (most probably, derived in an indirect way)⁵ compositions of equilibrium phases formed by hydrates of natural gas (Table 7).

Table 7. Composition of the equilibrium phases formed by natural gas ($T = 269.5$ K; $P = 4150$, $P_W^h = 0.455$, $P_W^h = 0.367$ kPa).

Natural gas		Q_i		c_i	
components	percentage	calculation	calculation	experiment	
CH ₄	82.50	51.42	56.93	56.95	
C ₂ H ₆	5.99	13.44	14.88	5.66	
C ₃ H ₈	3.26	20.67	22.88	24.97	
iso-C ₄ H ₁₀	0.30	2.75	3.05	4.69	
N ₂	7.19	1.07	1.18	0.46	
CO ₂	0.20	0.23	0.25	0.44	
Other	0.56	0.75 ^a	0.83 ^a	0.83	
Σ	100	90.33	100	94.0	

^a Found experimentally.

Since an empty hydrate lattice cannot be formed directly from water or ice, the following relation² is valid: $P_W^0 > P_W^{l,s}$, where $P_W^{l,s}$ is the pressure of saturated water vapour above the surface of liquid (l) or ice (s). It follows from Eqn (19) that the intercalation of the gas forming the hydrate into the hydrate lattice cavities reduces the pressure of water vapour above the hydrate surface. As soon as it becomes equal to or lower than $P_W^{l,s}$, crystalline lattice formation becomes possible. Thus, the dissociation pressure is determined from the condition

$$P_W = P_W^{l,s}. \quad (21)$$

By substituting (19) and (20) into (21), one obtains an expression for the calculation of the dissociation pressure:³⁵

$$\ln\left(\frac{P_W^{l,s}}{P_W^0}\right) = \frac{1}{m(n+1)} \left[n \ln\left(1 + \sum_i C_{li}f_i\right) + \ln\left(1 + \sum_i C_{2i}f_i\right) \right]. \quad (22)$$

Equation (22) was solved for the dissociation pressure by numerical methods on a PC. The computations were performed for gas mixtures of different composition containing hydrides of arsenic, phosphorus, sulfur, and selenium, as well as krypton at different temperatures of hydrate formation. In the calculations by Eqn (22), it was assumed that $P_W^{l,s} = 2.52$ kPa at $T = 294$ K and $P_W^{l,s} = 0.092$ kPa at $T = 252$ K.³² The results of calculations are presented in Fig. 2.

As is seen from the Figures showing a ternary gas mixture (two hydrides and water), in all cases when values of P_{dis} of individual components are different, the dissociation pressure depends substantially on the fraction of the main substance and the temperature of hydrate formation. With the decrease in the amount of the main component, P_{dis} varies monotonically from the value of dissociation pressure of a pure major component to that of a pure component, which serves as an impurity (Fig. 2a, curves 1–4; Fig. 2b, curve 1).

For four-component systems, the content of the second component was arbitrarily taken to be equal to 10% of that of the main substance, and this ratio was maintained constant. The portion of the major component varied in the same way as in the case of ternary systems, though at the expense of the fourth component. The character of changes in the dissociation pressure was analogous to that in the first case, though at definite ratios of concentrations of the second and the fourth components (this ratio varies for different systems and depends on the temperature and P_{dis} of each component) extrema may appear in the curve of dependence of P_{dis} on composition (Fig. 2a, curve 2).

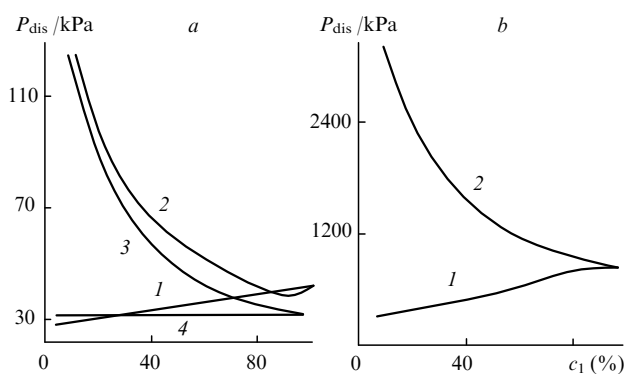


Figure 2. Dissociation pressure of gas hydrates vs. concentration of the main component of a gas mixture for different systems at 252 K (a) and 294 K (b).

(a): (1) $H_2S + H_2Se + H_2O$; (2) $H_2S + H_2Se + H_2O + Kr$; (3) $AsH_3 + PH_3 + H_2O + Kr$; (4) $AsH_3 + PH_3 + H_2O$;
(b): (1) $H_2S + H_2Se + H_2O$; (2) $H_2S + H_2Se + H_2O + Kr$.

Thus, the presence in a gas mixture of components with lower and higher values of dissociation pressure than that of the main substance under purification may substantially alter the conditions of formation of hydrates and in some cases prevent their formation in the process of purification.

The maximum concentration of water in a gas mixture containing gas hydrates is determined by the pressure of saturated water vapour above the hydrate surface.³⁴ Let us consider the influence of gas mixture composition on the pressure of water vapour above the surface of a gas hydrate.

Under real conditions, the composition of a gas mixture changes due to changes in the partial pressures of its components.^{33, 35, 36}

Let us consider first a ternary gas system comprising two hydrides and water. The variation of partial pressures occurs in the following manner:^{35, 36} first, the pressure of a major component, equal to the pressure of its saturated vapour at a given temperature, is assumed to be constant, while the partial pressure of an impurity component increases from zero to a maximum value equal to the pressure of its saturated vapour at this temperature. After the maximum partial pressure of impurity is reached, further decrease in the proportion of the major substance is possible only owing to the reduction of its partial pressure. In this situation, the pressure of the impurity component is maintained constant. As a result, the total pressure of the gas mixture first increases and then decreases. The vapour pressures of water above the hydrate surface calculated for this case by Eqn (19) are presented in Fig. 3.³⁶

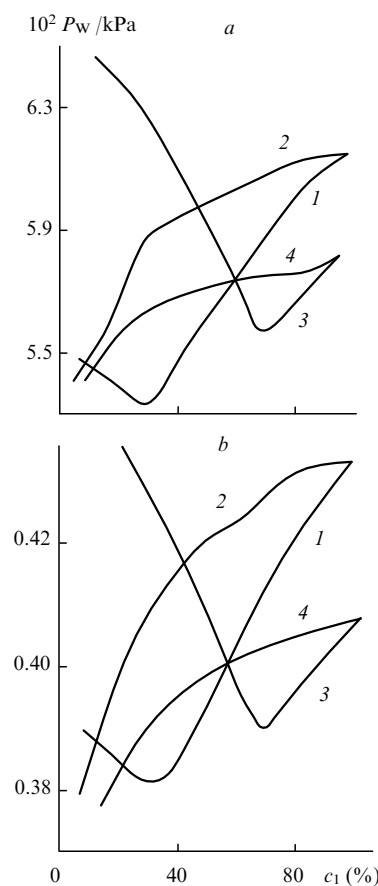


Figure 3. Pressure of water vapour above the surface of gas hydrates vs. concentration of the main component of a gas mixture at 252 K (a) and 273 K (b).

(a): (1) $AsH_3 + PH_3 + H_2O$; (2) $AsH_3 + PH_3 + H_2O + Kr$; (3) $H_2S + H_2Se + H_2O$; (4) $H_2S + H_2Se + H_2O + Kr$;
(b): (1) $AsH_3 + PH_3 + H_2O$; (2) $AsH_3 + PH_3 + H_2O + Kr$; (3) $H_2S + H_2Se + H_2O$; (4) $H_2S + H_2Se + H_2O + Kr$.

As seen from the Figures, there is a minimum in P_W corresponding to the maximum value of the total pressure of the gas mixture. This is due to the maximum filling of hydrate cavities by gas molecules resulting in higher stability of the clathrate lattice and a lower pressure of water vapour above its surface.

In the calculations of four-component systems, the content of the second component was also arbitrarily assumed to be equal to 10% of the content of the main substance (see above), and this ratio was maintained constant.³⁵ As the temperature of the gas mixture was higher than the critical temperature of the fourth component (krypton), the total pressure increased monotonically with the decrease in the level of the major component, and the vapour pressure of water over the surface of mixed hydrate was substantially decreased (Figs 3 *a* and 3 *b*, curves 2 and 4).

Thus, the increase in the pressure of a gas mixture due to the addition to it of a component which does not condense at a given temperature, allows a significant decrease in the content of molecular water in the gas mixture.

2. Distribution coefficients of constituent molecules of a gas mixture in the cavities of mixed hydrates

In the process of separation and refinement of multicomponent systems $M_1, M_2, \dots, M_i$, mixed hydrates may be formed at appropriate temperatures and pressures. This is accompanied by redistribution of gas mixture components between the gas hydrate and the gas mixture. The gas hydrate (or the gas mixture) is enriched or depleted in one or several components because of differences in the composition of equilibrium phases: gas phase and solid phase (on an anhydrous base).³⁰ In order to estimate the purification efficiency, it is necessary to know the composition of gas hydrates, which is determined by distribution of molecules of the major substance and impurities in the cavities.

The distribution of the hydrate-forming molecules in the cavities of a gas hydrate is characterised by the distribution coefficient^{33, 36}

$$K_i = \frac{Q_i P_s}{P_i \sum_i Q_i}, \quad (23)$$

where Q_i is the fraction of hydrate cavities filled with molecules M_i , P_s is the total pressure of the gas mixture, and P_i is the partial pressure of M_i molecules in the gas phase.

The fraction of filled cavities is determined from the Langmuir isotherm [Eqn (20)]. If n_j is the fraction of type j cavities in the gas hydrate, then

$$Q_i = \sum_j n_j Q_{ij}. \quad (24)$$

To characterise the redistribution of gas mixture components upon formation of gas hydrates, it is convenient to use the relative distribution coefficient^{33, 36}

$$K_{i1} = \frac{K_i}{K_1}, \quad (25)$$

where the mixture component with $i = 1$ is arbitrarily assumed to be the major substance (the one to be purified).

By substituting Eqn (23) into Eqn (25) the following relation is obtained:

$$K_{i1} = \frac{Q_i P_1}{Q_1 P_i}. \quad (26)$$

The relative distribution coefficient makes it possible to assess whether the gas hydrate will be enriched (when $K_{i1} > 1$) or depleted (when $K_{i1} < 1$) in impurities from the substance subject to purification. It follows from Eqns (24) and (26) that the relative distribution coefficient may substantially depend on the conditions of hydrate formation and the impurity concentration in the gas mixture.

The dependences of relative distribution coefficient on the conditions of gas hydrate formation were studied³⁶ in mixtures containing inorganic hydrides of arsenic, sulfur, selenium, phosphorus and antimony, as well as methane and nitrogen.

Under real conditions, the composition of a gas mixture changes as a result of changes in the partial pressures of the components of a mixture.

Let us consider first a ternary gas mixture containing two hydrides and water. In the temperature range studied (250–290 K), the pressure of water vapour is negligible in comparison with the total pressure of the gases³⁴ and hence may be disregarded. Thus, the total gas pressure is determined by the partial pressures of the hydrides. If the partial pressure of the major component (equal to the pressure of its saturated vapour at a given temperature) is assumed to be constant, then the decrease of its fraction in the mixture may occur at the expense of an increase in the partial pressure of the impurity component, up to its maximum level (equal to the pressure of its saturated vapour at a given temperature). This results in an increase in the total pressure of the gas mixture. The increase in the partial pressure of impurity above its maximum level leads to condensation of the impurity component. Thus, further decrease in the fraction of the major substance is possible only at the expense of a decrease in its partial pressure, the pressure of the impurity component being maintained constant. This results in the reduction of the total pressure of the gas mixture. The relative distribution coefficients calculated for this case by Eqn (26) are presented in Fig. 4 *a, b*. The

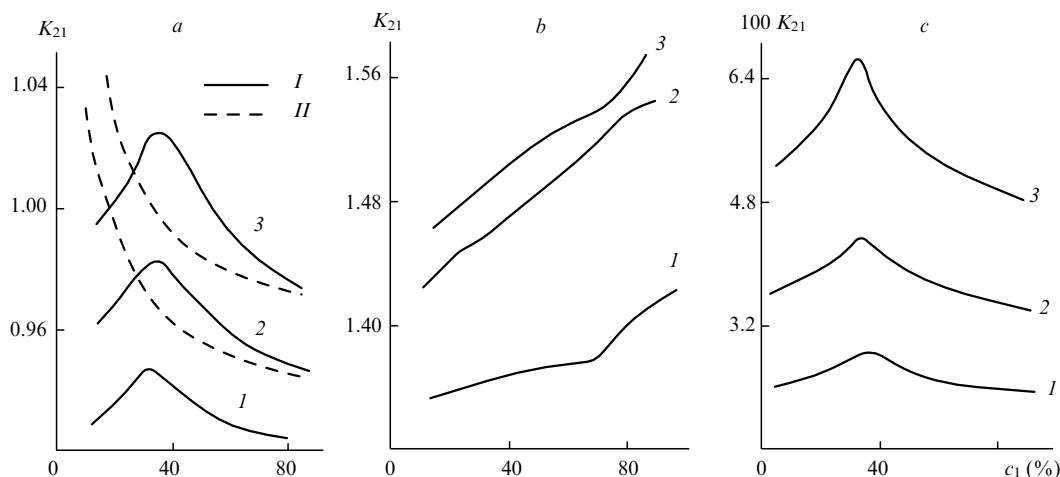


Figure 4. Relative distribution coefficient vs. concentration of principal (*I*) and the second (*II*) components of gas mixture for the systems: $\text{AsH}_3 + \text{PH}_3 + \text{H}_2\text{O}$ (*a*), $\text{H}_2\text{S} + \text{H}_2\text{Se} + \text{H}_2\text{O}$ (*b*), $\text{AsH}_3 + \text{CH}_4 + \text{H}_2\text{O} + \text{PH}_3$ (*c*) at 252 K (*I*), 273 K (*2*) and 294 K (*3*).

Langmuir constants, which are required for the determination of the fraction of the cavities filled from Eqn (20), were calculated using the spherical cell model.³²

As is seen from these figures, in all cases the relative distribution coefficient depends substantially on the fraction of the main substance. This is due to the fact that changes in the partial pressures (fugacity) of the components of the gas mixture result in redistribution of molecules of different gases between the gas hydrate cavities according to Eqn (20). The presence of extrema in curves 1–3 shown in Fig. 4a and inflection points in all curves of Fig. 4b may be explained by non-monotonic changes in the fugacity of the components of the mixture upon the non-monotonic changes in the total pressure of the gas mixture.³⁷ Incidentally, depending on the fraction of the components of the mixture, the relative distribution coefficient of the second component may be either > 1 , *i.e.* the hydrates accumulate predominantly the impurity from the substance subject to purification, or < 1 , *i.e.* the hydrates accumulate mostly the major substance.

In calculations of four-component systems, the content of the second component was arbitrarily assumed to be equal to 10% of that of the main substance, and this proportion was maintained constant. The fraction of the main component varied in the same manner as in the case of ternary systems, though at the expense of changes in the concentration of the fourth component. If the temperature of the gas mixture is below the critical temperature of the third component, then the total pressure is first increased and then decreased as the fraction of the main component is increased. This leads to the formation of extrema in curves 1–3 (Fig. 4c). If the temperature of the gas mixture is above the critical temperature of the fourth component, the total pressure of the mixture grows monotonically with the decrease in the fraction of the main component. In this case, the relative distribution coefficient of the second component changes monotonically (Fig. 4a, curves II). Figure 4a shows that in this case, too, K_{21} may be either > 1 or < 1 , depending on the fractions of the gas mixture components.

If the total pressure of the gas mixture remains invariant despite changes in its composition, the partial pressure of each component is subject to variation. Then, the dependence of the relative distribution coefficient of the second component on the fraction of the main component in the gas phase is virtually linear for different mixture compositions and conditions of hydrate formation (Fig. 5).

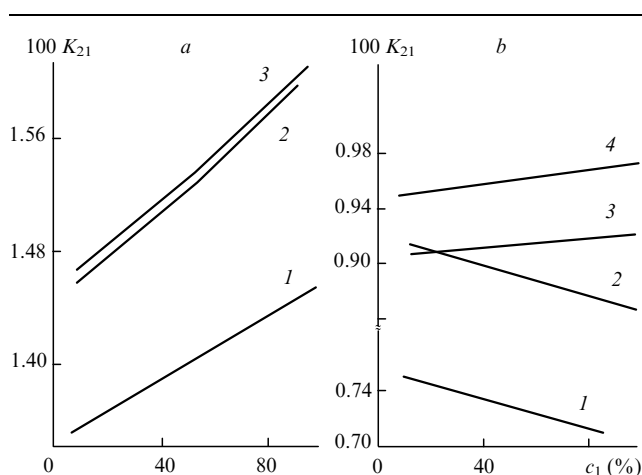


Figure 5. Relative distribution coefficient *vs.* concentration of the main component of a gas mixture for the systems: $\text{H}_2\text{S} + \text{H}_2\text{Se} + \text{H}_2\text{O}$ (a), $\text{AsH}_3 + \text{SbH}_3 + \text{H}_2\text{O} + \text{PH}_3$ (b, 1, 2), and $\text{AsH}_3 + \text{SbH}_3 + \text{H}_2\text{O}$ (b, 3, 4).

(a)	1	2	3	(b)	1	2	3	4
T/K	294	252	294	T/K	294	252	294	252
P_s/kPa	930	230	150	P_s/kPa	1520	500	1520	500

The above data indicate that under the same conditions of hydrate formation the relative distribution coefficient depends substantially on the ratio of components in gas mixtures, and in some cases it may differ greatly from unity (see, *e.g.*, Fig. 4b). Hence, substantial enrichment or depletion of the main component in the impurities present may already occur at the stage of hydrate formation. Separation of gas hydrates from the gas mixture allows additional purification of the main substance or air–gas mixtures.

3. Concentration of technogenic impurities in atmospheric gas hydrates

The atmosphere continuously receives strong fluxes of gases containing deleterious compounds, such as sulfur and carbon dioxides, carbon and nitrogen monoxides, chlorinated organic compounds, *etc.* Such noxious compounds are released by natural and industrial sources. Nowadays, the natural and anthropogenic fluxes are commensurable, though in some instances the latter may dominate.⁴⁰ Such compounds are either uniformly dispersed in space or concentrated on some carriers (aerosols, various colloidal particles, *etc.*). Concentration of hazardous impurities on specific carriers may lead, on the one hand, to environmental cleaning by the ‘storage’ of such impurities in relatively small quantities of microparticles. On the other hand, these ‘stores’ are a serious threat to biosystems, since such a redistribution of minor components in atmospheric air may radically affect various physicochemical processes in the biosphere.⁴¹ The role of carriers in which the components of gas mixtures can be concentrated may be played by water molecules, water-based clusters, or gas hydrates.^{35, 41}

When technogenic impurities are released into the atmosphere in quantities sufficient for the formation of gas hydrates, it is necessary to know their composition and the conditions of their stability at a given temperature.

The use of Eqn (22) makes it possible to determine whether or not gas hydrates are formed under given conditions.

Knowing the fraction of cavities filled with molecules of a gas mixture, one can determine their concentration in the gas hydrate. Since, on average, there are 5.75 water molecules per cavity in structure I hydrate and 5.67 water molecules per cavity in structure II hydrate,⁵ then we obtain for structure I

$$c_i = \frac{Q_i}{5.75}, \quad (27)$$

and for structure II

$$c_i = \frac{Q_i}{5.67}. \quad (28)$$

Let us consider an air mixture (with nitrogen and oxygen as the main components) containing sulfur and carbon dioxides, nitrogen monoxide, Freon 12 and chloroform as impurities.^{42, 43} The results of calculations performed using the above equations allowing the determination of relative distribution coefficients and the concentrations of impurities in gas hydrates are presented in Table 8.

For the temperature range under study, $P_W^s = 0.2566$ kPa at 263 K and $P_W^s = 0.6067$ at 273 K. The gas mixtures indicated above do not form any gas hydrates at 273 K, because condition (21) is not fulfilled, whereas in all other cases the formation of gas hydrates is possible. When the temperature increases, the probability of hydrate formation decreases. It is of note that the hydrates formed will contain predominantly the impurity components. Gas hydrates concentrate preferentially the compounds with minimum dissociation pressures at given temperature. For example, at 273 K the dissociation pressures of nitrogen, sulfur dioxide, and chloroform are 11 000, 18.7, and 3.5 kPa, respectively. In addition, the extent of concentration of individual impurity in a hydrate or the relative distribution coefficient (relative to the coefficient of nitrogen distribution) depends substantially on the composition of a gas mixture, temperature,

Table 8. Relative distribution coefficients and concentration of an impurity in the gas hydrates.

Gas	P_i /kPa	P_i/P_s (%)	$T = 263\text{ K}$			$T = 273\text{ K}$		
			Q_i (%)	c_i (%)	K_{il}	Q_i (%)	c_i (%)	K_{il}
Structure I; $P_s = 159\text{ kPa}$								
			$P_W = 0.2446\text{ kPa}$			$P_W = 0.6184\text{ kPa}$		
N ₂	78	49.1	0.31	0.05	1	0.34	0.06	1
O ₂	21	13.2	0.11	0.02	1.32	0.12	0.02	1.30
CO ₂	15	9.44	1.0	0.17	16.7	1.08	0.19	16.5
N ₂ O	20	12.6	12.8	2.23	160	13.1	2.28	151
SO ₂	25	15.7	77.9	13.6	778	73.9	12.9	679
Structure I; $P_s = 219\text{ kPa}$								
			$P_W = 0.2223\text{ kPa}$			$P_W = 0.5675\text{ kPa}$		
N ₂	78	35.6	0.18	0.03	1	0.21	0.04	1
O ₂	21	9.59	0.06	0.01	1.30	0.07	0.01	1.28
CO ₂	30	13.7	1.08	0.19	15.2	1.18	0.21	14.3
N ₂ O	40	18.3	12.9	2.26	137	13.3	2.31	121
SO ₂	50	22.8	81.0	14.1	686	77.9	13.6	567
Structure II; $P_s = 112.1\text{ kPa}$								
			$P_W = 0.2435\text{ kPa}$			$P_W = 0.6103\text{ kPa}$		
N ₂	78	69.6	1.42	0.25	1	1.26	0.22	1
O ₂	21	18.7	0.44	0.08	1.17	0.39	0.07	1.14
CO ₂	0.1	0.09	0.01	0.002	6.90	0.01	0.002	6.80
CHCl ₃	2.0	1.78	22.6	3.98	623	20.0	3.52	642
CF ₂ Cl ₂	10	8.92	33.1	5.83	182	27.0	4.75	168
SO ₂	1.0	0.89	3.67	0.65	203	3.00	0.53	186
Structure II; $P_s = 122.1\text{ kPa}$								
			$P_W = 0.2223\text{ kPa}$			$P_W = 0.5675\text{ kPa}$		
N ₂	78	63.9	1.13	0.20	1	1.07	0.19	1
O ₂	21	17.2	0.35	0.06	1.16	0.32	0.06	1.13
CO ₂	0.1	0.08	0.009	0.002	6.35	0.008	0.001	5.97
CHCl ₃	5.0	4.10	25.4	4.47	350	23.0	4.05	346
CF ₂ Cl ₂	15	12.3	34.5	6.07	159	28.0	4.93	136
SO ₂	3.0	2.45	7.65	1.35	177	6.00	1.06	151

and pressure. This is due to the redistribution of gas mixture molecules among hydrate cavities according to the Langmuir coefficients determined by the character of the van der Waals interaction.

Thus, gas hydrates may be formed under the conditions of the environmental presence of technogenic impurities over a wide range of ambient temperatures (the temperate climate zone). Such gas hydrates become sites of predominant concentration of typical technogenic impurities.

VI. Conclusion

The appearance of impurities in the form of gas hydrates in gases undergoing cleaning may significantly influence the process of their refinement: at the stage of hydrate formation the content of water in the gas phase decreases accompanied by changes in its composition due to redistribution of components between the solid and gas phase.

The presence in a gas mixture of components with higher or lower values of dissociation pressure than that of the principal substance subject to purification may change substantially the conditions of gas hydrate formation and in some instances even prevent their formation in the process of purification.

The relative distribution coefficient for the same conditions of hydrate formation depends appreciably on the ratio of the components in the gas mixture and in some cases it differs markedly from unity. Therefore, even at the stage of hydrate formation, the substance can be considerably enriched or depleted

in impurities. Thus, the separation of gas hydrates from the gas mixture may provide additional purification of the major substance or air–gas mixtures.

The existing models which simulate gas hydrate formation allow an accurate determination of the dissociation pressure of a hydrate-forming gas, the minimum water content at which the formation of hydrates is still possible, as well as the distribution coefficients of molecules of a gas mixture over the cavities of gas hydrates.

The computational results provide evidence that gas hydrates can be formed under environmental conditions (in the range of temperatures characteristic of the temperate climate zone). Under these conditions, they predominantly accumulate deleterious impurities released into the atmosphere from technogenic exhausts. Concentration of such impurities becomes hazardous for biological systems.

Thus, the gas hydrates formed in the vapour phase in the process of refinement of gases (Freons, volatile inorganic hydrides, *etc.*) as well as the suspended particles of submicro-size form a new class of impurities in ultrapure substances, and it is necessary to account for their influence on the processes of refinement of gases.

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Computer simulation of electrochemical processes on interfaces

G V Khaldeev, S N Petrov

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Abstract. The basic problems of computer simulation of mass and charge transfer in electrochemical processes such as electrocrystallisation and corrosion of metals are analysed. Three main approaches to the simulation of electrochemical problems are considered: the Ising (lattice gas) model, molecular dynamics (MD) and Monte Carlo (MC) methods. The principal equations used in simulation techniques and examples of the simulation of particular systems are presented. The bibliography includes 136 references.

I. Introduction

Computer simulation plays an important role in the solution of many physical problems. Certainly, the use of graphical two- (2D) and three-dimensional (3D) models obtained by computer simulation is interesting not only for physicists but also for chemists.¹ Primarily, these are simulation of phase transitions in chemical systems, construction of 'phase portraits' changing in time for these systems, and predictive assessment of the evolution of hierarchic near-the-surface crystal-electrolyte structures exposed to external factors. In computer simulation of electrochemical problems, reactions involving charge transfer are included in kinetic schemes along with chemical steps. The prerequisite for concentration and charge gradients to appear is the formation of fluctuations of the material density in the vicinity of reaction sites on the surface, where chemical reactions occur. Therefore, simulation of a metal–electrolyte interface is done taking account of the collective local degrees of freedom of a system.^{2,3} Computer simulations of the dynamics of surface electrochemical processes are based on the lattice gas model (the Ising model) as well as on molecular dynamics (MD) and Monte Carlo (MC) methods. The simulation techniques are well developed and the corresponding application software is available.⁴

II. Lattice gas models

Corrosion-electrochemical systems described by computer simulations can be tentatively divided in two groups: processes involving the formation of a new crystalline phase on the

substrate — crystallisation (i) and processes of dissolution — decrystallisation (ii).

Gilmer's approach is quite sufficient if the 'rigid' 2D-lattice Ising kinetic model is used for the computer-assisted description of the formal kinetics of growth and dissolution of ideal crystal lattices.^{5,6} The following assumptions are made: (1) the atoms removed from the surface can only enter multi-centre adsorption states with maximum stability (S-positions); (2) the order of occupying the adsorption cells is fulfilled according to which cell can contain no more than one atom; (3) the van der Waals metal–metal (M–M) interaction is approximated by a pair Mie potential of the type $U(r) = A/r^n - B/r^m$, where A and B are constants characterising the attractive and repulsive forces, respectively, r is the distance between the particles, and $n > m > 0$. The Hamiltonian for a simple cubic Ising lattice taking account of interaction between the closest neighbours (NN) has the form:⁷

$$H = -J \sum_{\langle ij \rangle} \sigma_i \sigma_j, \quad (1)$$

where J is the exchange energy; σ_i and σ_j are variables of the occupancy of cells i and j , respectively; the term $\sigma_i = \pm 1$ 'controls' the second assumption of the Ising model, and the symbol $\langle ij \rangle$ shows that summation is carried out over pairs of the closest neighbours. The formation of a step on this lattice (Fig. 1) is always accompanied by the formation of centres possessing excess charge and deficiency of mass, kinks, which are the most adsorption-active cells on a crystal surface (the TLK-model, from terrace T, step L, kink K). In these models, the solid is a Kossel–Stransky crystal.⁸

The pair potential can be written in a form convenient for practical use:

$$U(r_{ij}) = \frac{E_1 [a(B_a/r_{ij})^m - b(C_{lat}/r_{ij})^n]}{b - a}, \quad (2)$$

where E_1 is the depth of the potential well; the a and b constants are the degrees of 'far-range action' and 'hardness' of the potential, respectively; B_a and C_{lat} are constants of attraction and repulsion interaction, respectively; and r_{ij} is the distance between the reacting particles i and j . The potential most commonly used for computer simulation of electrochemical systems is the Lennard-Jones potential, while the Buckingham potential

G V Khaldeev, S N Petrov A M Gorkii Perm University, Department of Chemistry, ul. Bukireva 15, 614600 Perm, Russian Federation.
Fax: (7-342) 233 80 14. Tel. (7-342) 239 64 68. E-mail: mvm@pgu.perm.ru

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[†] A defect-free crystal constructed according to Drude–Sommerfeld⁹ (from ions oscillating in equilibrium positions with a Debye frequency of $\mu_D = 10^{13} \text{ s}^{-1}$ near the equilibrium positions, and an electron subsystem).

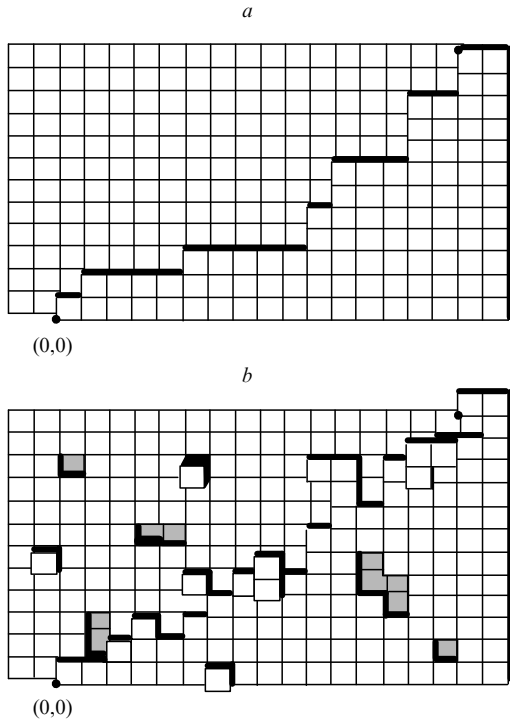


Figure 1. Typical stepped configurations on the (100) face of a simple cubic lattice; (a) $T = 0$ K; (b) $T > 0$ K.

and the anharmonic Morse potential are used more rarely. These potentials are written as follows:
the Lennard-Jones potential (pair potential 6–12)

$$U_{LJ}(r_{ij}) = 4E_1 \left[-\left(\frac{C_{lat}}{r_{ij}}\right)^6 + \left(\frac{B_a}{r_{ij}}\right)^{12} \right], \quad (2a)$$

the three-parameter Buckingham potential (if repulsion is determined by overlapping of wave functions)

$$U_B(r_{ij}) = 4E_1 \left[-\left(\frac{C_{lat}}{r_{ij}}\right)^6 + B_a \exp\left(-\frac{C_{lat}}{r_{ij}}\right) \right], \quad (2b)$$

and the Morse potential

$$U_M(r_{ij}) = \delta \{ \exp[-2\alpha(r_{ij} - C_{lat})] - 2\exp[-\alpha(r_{ij} - B_a)] \}, \quad (2c)$$

where δ and α are empirical constants. The energy E_1 is determined by the nature of interaction of particles and is as high as ~ 10 eV for the ionic bond, $\sim 1-5$ eV for the metal bond, ~ 0.5 eV for the hydrogen bond and ~ 0.1 eV for the van der Waals interaction.

The pair interaction potentials (2a) and (2b) are used in the case of nonspecific physical adsorption, when $E_1 < 0.5$ eV. The adsorption energy E_{ads} can be calculated from a relation obtained by integration of the Lennard-Jones potential (2a) assuming that atoms (the number of which in unit volume of a crystal equals the Avogadro number, N_A) form an averaged ‘jelly’-background with mean parameters E_1 and C_{lat}

$$E_{ads} = \frac{\pi}{3} N_A E_1 B_a^3 \left[\left(\frac{C_{lat}}{r_{ij}}\right)^3 - \frac{1}{15} \left(\frac{C_{lat}}{r_{ij}}\right)^9 \right]. \quad (3)$$

Models of the liquid mercury surface in contact with an electrolyte are in satisfactory agreement with the relationship (3).¹⁰ An ideal flat condenser is formed in this case. The minimal distances between the particles

$$l \equiv r_{ij \min} \simeq \frac{C_{lat}}{\sqrt[6]{5}}$$

have to be smaller for flat condenser models than for an actual surface M. Hence, it is necessary to take into account both the crystallographic features of adsorption and changes in the electronic structure of an adsorbate–adsorbent system (mixing of wave functions of valence electrons of the adsorbed particles with those of the metal adsorbent occurs).

The stability of two-dimensional lattices (usually, tetragonal, trigonal and hexagonal lattices incorporating 32×32 , 64×64 , 128×128 , 256×256 etc. cells are analysed) depends on the total energy of the system. The dynamically unstable tetragonal lattice is transformed into the trigonal lattice, which is more energetically stable.¹¹ Dimers of a tetragonal lattice with antiparallel spins oriented along a particular crystallographic direction are rearranged in a simultaneous cooperative act¹² into a more stable Ising structure (Fig. 2). As a result, the density of dimers increases.

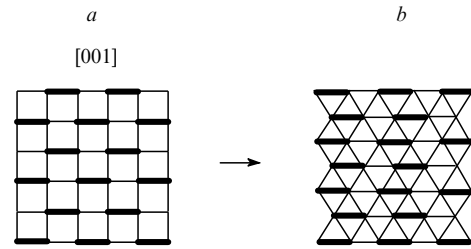


Figure 2. Transformation of simple tetragonal lattice (a) into triangular lattice (b).

The rearrangement occurs in the sequence: self-organising $\rightarrow$ high order $\rightarrow$ low entropy^{13,14} and results in the generation of a low-entropy surface structure. The kinetics of destruction of two-dimensional lattices can follow their reversible nature, i.e., transition of rows or separate intermediates into solution with restoration of the coverage provided that the concentration of the surfactant in solution is sufficient. The equation for the destruction rate (current I) has the ‘Arrhenius form’ determined by the degree of coverage of the crystal with surfactant particles, θ_{surf} , which in turn depends on the external factors and internal state of the crystal surface – electrolyte system:

$$I = v_i(\theta_{surf}) \theta_{surf}^n \exp \left[-\frac{E_a(\theta_{surf})}{kT} \right], \quad (4)$$

where $v_i(\theta_{surf})$ is the pre-exponential frequency factor (vibration frequency of i th metal surface particles, $10^{13}-10^{14}$ s⁻¹), n is the order of the reaction between the adsorbed particles, and $E_a(\theta_{surf})$ is the activation energy of interaction of passivating particles in 2D-structures. The $E_a(\theta_{surf})$ dependence is nonlinear: at $\theta \leq 0.2$, the interaction of the surfactant particles in the adsorbed layer can be neglected, but at $\theta > 0.8$ (under conditions of rapid increase in the B_a constant), an attraction correction should be made to determine $E_a(\theta_{surf})$. Usually, $E_a(\theta_{surf}) = E_b - \Delta H_{ads}$, where E_b is the bonding energy of the surfactant particles and ΔH_{ads} is their heat of adsorption on the crystal surface. The pre-exponential terms of kinetic equation (4) take account of the adsorption isotherm of a surfactant on the crystal surface, that is calculated within the scope of the Ising lattice model.¹⁵ This determines changes in the rate of reorganisation of surface intermediates and, as a result, the current I across the interface.

Further, it is worthwhile to consider, within classical concepts, the interaction of a 2D-film with a substrate leading to the formation of some new phases (layers). For example, this interaction is typical of the inhibition of metal dissolution.¹⁶ If only the potentials of pair interactions ‘a particle in film – a particle in substrate’ are taken into account additively, then, according to Heitler and London,¹⁷ the pair potential is expressed as:

$$U(r) = \sum_i U_i(r) = -\frac{K_L}{r^6}, \quad (5)$$

where $K_L = (3/4)\hbar v_0 \varepsilon^2$ is the London constant, $\hbar = h/2\pi$ is the Planck constant, v_0 is the characteristic frequency of vibration of charged particles, and ε is the polarisability of particles. Then, according to Ref. 18, one can write:

$$U(r) = - \int K_L r_{ij}^{-6} N_A dV, \quad (5a)$$

where N_A is the number of particles per unit molar volume of the metal, dV is an element of the solid phase volume (in a particular case, the volume of the adsorbed particle) at a distance r_{ij} from a particle given by the r coordinate in the first near-surface layer of the substrate. If $N_A = \text{const}$, then

$$U(r) = -\frac{N_A \pi K_L}{6l^3}, \quad (5b)$$

where l is the shortest distance between the adsorbate and adsorbent particles. In the flat condenser model, the adsorbate and adsorbent are independent layers, and if the surfactant layer penetrates into the substrate, then to estimate $U(r)$ it is necessary to integrate over the depth l of the substrate. Integration gives

$$U(r) = -\frac{\Gamma_{\text{surf}, M}}{12\pi l^2}, \quad (5c)$$

where $\Gamma_{\text{surf}, M} = \pi^2 N_A^2 K_L$ is the Hamaker constant.¹⁹ For example, such penetration occurs in the case of hydrogen adsorption. The size of the cell is close to that of the adsorbed hydrogen atom, that is, the use of the Ising model for the estimation of hydrogen adsorption is substantiated. If an electrical double layer appears and charges are transferred between the inhibiting surfactant film and the substrate, $\Gamma_{\text{surf}, M}$ can be calculated by summing pair potentials for three-dimensional elements

$$\Gamma_1 = \frac{3}{4} \pi^2 N_{A, \text{surf}}^2 \varepsilon_{\text{surf}}^2 E_{i, \text{surf}}, \quad (6)$$

where $N_{A, \text{surf}}$ is the number of surfactant particles in unit molar volume of the film and $\varepsilon_{\text{surf}}$ and $E_{i, \text{surf}}$ are the polarisability of surfactant particles and the ionisation potential in the surfactant film, respectively. After the film–substrate interaction has occurred, the Hamaker constant in equation (5c) is determined by a superposition of constants for the film (Γ_{surf}) and the metal (Γ_M)

$$\Gamma_{\text{surf}, M} = \Gamma_{\text{surf}} - 2\sqrt{\Gamma_{\text{surf}} \Gamma_M} \left(\frac{2\sqrt{E_{i, \text{surf}} E_i}}{E_{i, \text{surf}} + E_i} \right) + \Gamma_M, \quad (7)$$

where E_i is the ionisation energy of the metal.

If the ionisation energies in the inhibiting film and in the metal become equal, $E_{i, \text{surf}} \simeq E_i$, relation (7) can be simplified

$$\Gamma_{\text{surf}, M} = (\sqrt{\Gamma_{\text{surf}}} - \sqrt{\Gamma_M})^2. \quad (8)$$

According to Frumkin,²⁰ the lateral interactions of adsorbed particles

$$E_a(T, \theta_{\text{surf}}) = E_b + \Delta E_{\text{lat}}(T, \theta_{\text{surf}})$$

in a two-dimensional adsorption structure can also be of chemical or physical nature, and $E_a(T, \theta_{\text{surf}})$ can be > 0.5 eV or < 0.5 eV. The Frumkin's correction factor $\Delta E_{\text{lat}}(T, \theta_{\text{surf}})$ decreases with an increase in temperature and increases for $\theta_{\text{surf}} \geq 0.2$. Interactions in 'surfactant particles in solution – a surfactant in an inhibiting film' and 'surfactant particles in solution – substrate atoms' systems result in the formation of defects in the covering surfactant film because of the non-equivalence of energetic positions of the substrate atoms.

The interaction of particles in the 2D-structure of the covering film determines a hierarchy of defects and 3D-islands of the surfactant, which depends strongly on the structural features of

the substrate. Within the scope of the linear elasticity theory, the contact of films with metal surfaces is considered taking account mostly of two parameters: the module of elasticity and the differences in the crystallographic parameters of film and substrate lattices. If the lattice parameter of an adsorbed covering 3D-film is larger than that of the substrate, the relaxation of strain in the film ends with the formation of discrepancy dislocations, and it is not deteriorated; in the absence of strain relaxation, the film is deteriorated.

Computer simulations use models that combine simultaneous formation of 2D- and 3D-structures on heterogeneous substrates. Analytical solutions of equations that describe inhibiting 2D-structures (on singular substrates) and 3D-islands on surfaces with uniformly distributed defects of the same nature are only possible in the lattice gas model.

The adsorption of an inhibitor on a non-uniform metal surface can be accompanied by the formation of both two-dimensional films and three-dimensional structures. The former case is less probable than the latter, but exact solutions are possible for it within the scope of the models considered. In the 2D-case, for the adsorption of light particles (H, O, N, CO, etc.) on singular single-crystal planes, the discreteness of charges of single, strongly bonded substrate atoms in an ensemble is described relatively accurately. However, it is impossible to simulate the behaviour of a big particle on the surface within the Ising model. The situation is similar to that when one has to play chess using chesspieces larger not only than the board squares but also than the board itself. Models are required that take into account the direction (correlated with the surface structure) of particle movement along the crystal surface (along definite preferred trajectories) and the presence of periodic extended surface and subsurface defects. When complex particles (large inorganic and/or organic molecules) are adsorbed, the field of extended surface and subsurface defects creates conditions for the formation of 3D-phase islets.^{21, 22} The three-dimensional adsorbed formations of inhibiting particles interact with each other both through the substrate and directly, creating their own hierarchic structure.

The study of the phase transition upon metal dissolution in the presence of surface 2D-films is an example of the classical approach to the consideration of the corrosion problem. Inhibiting layers on a non-uniform metal surface are formed more commonly as a superposition of 2D-films and 3D-structures. Two-dimensional films are formed on surfaces of crystallite (grain) terraces, which are, as a rule, non-singular stepped high-index planes. The expanse (surface area) of terraces on such stepped surfaces is sufficiently large to be treated as main structural elements (as regards surface area). The lattice gas model is quite applicable for the description of the adsorption of a metal dissolution inhibitor on densely packed ideal terraces. The corresponding Hamiltonian contains terms describing not only the surfaces of the metal and adsorbed particles of a surfactant but also exchange energies of their interactions, i.e., the usual Ising Hamiltonian (1) becomes more complex

$$H = -E_{NN} \sum_{NN} \sigma_i \sigma_j - E_{NNN} \sum_{NNN} \sigma_i \sigma_j, \quad \sigma_i = \pm 1. \quad (9)$$

It contains exchange energies of interaction not only between the closest neighbours NN , but also between the next to the closest neighbours NNN . If one limits the consideration to $NN = 1$ and $NNN = 2$ and designates the NN - and NNN -interactions as E_1 and $E_2 = RE_1$, $R < 0$, then the parameter for the critical temperature (T_c) for the formation of a new phase on the surface is

$$\sinh \frac{2E_1}{kT_c} \sinh \frac{2E_2}{kT} = 1 \quad \text{or} \quad -\frac{2kT}{E_1} \ln \left(\tanh \frac{E_1}{4kT_c} \right) = \frac{E_2}{E_1}.$$

'Loose' steps and kinks on the steps have different adsorption characteristics from the terraces. Only in rare situations can adsorption be regarded as physical adsorption. The strength of bonds of adsorbed particles with kinks is high. The behaviour

(kinetics of movement and inhibition) of steps is described in terms of dislocation dynamics.

The formation of inhibiting covering 2D-films can be considered both from the viewpoint of the classical nucleation theory and taking account of the quantum-chemical nature of interaction in the adsorbate – adsorbent system.²³ In the classical variant, the surfactant particles that are adsorbed and form a uniform film are treated in the mean field approximation. The ratio of the density of this film (ρ) to the activity of spherically symmetrical particles in it (a_{surf}) is described by the equation:

$$\frac{\rho}{a_{\text{surf}}} = A \left\langle \exp \left(- \frac{E_{\text{attr}}(T, \theta_{\text{surf}})}{kT} \right) \right\rangle,$$

where $A = v_i(\theta_{\text{surf}}) \exp(\Delta S/k)$ is the Einstein configurational term, ΔS is the entropy change in the adsorption ensemble, and $E_{\text{attr}}(T, \theta_{\text{surf}})$ is the attraction potential. When a uniform temperature-independent field of the inhibiting film is created, $E_{\text{attr}}(T, \theta_{\text{surf}})$ can be approximated by the mean field potential $E_{\text{mf}}(\theta_{\text{surf}})$, or $E_{\text{attr}}(T, \theta_{\text{surf}}) \simeq E_{\text{mf}}(\theta_{\text{surf}})$.

The classical models of new phase growth on a crystal surface (they can be divided in three groups, Fig. 3) are based on the formation of 2D-films and insular 3D-structures. According to the FVdM model, the growth of inhibiting films occurs by a mechanism involving a ‘carpet’ of a 2D inhibitor layer ‘unrolling’ over the crystal surface; the VW model assumes that flat disks arise and then coalesce; the SK theory involves a combination of 2D-films and 3D-islets. There is also a variant of the VW model in which the new phase grows as a column composed of adsorbed particles (see Fig. 3). This is the ‘solid on solid’ model, whose distinguishing feature is a high process rate (in a particular case, high cathodic current density, i_c), low supersaturation of reacting particles in the near-electrode layer $\Delta\gamma^\neq$, and high force field of the surface (subsurface) active centre where the new phase appears.

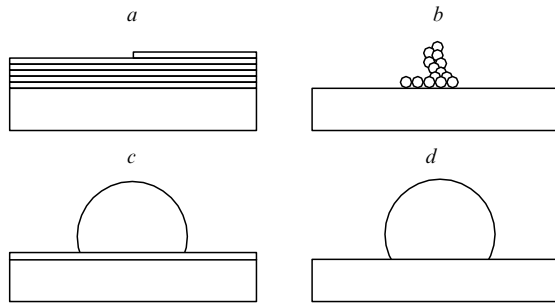


Figure 3. Scheme of growth of 2D and 3D structures on a crystal surface; (a) the Frank – Van der Merve model (FVdM); (b) ‘column’; (c) the Stransky – Krastanov (SK) model; (d) the Volmer – Weber (VW) model.

The estimated specific surface energy change, $\Delta\sigma$, is the criterion of applicability of these models. Under conditions of heteroepitaxial growth of covering films (where the pseudomorphism mechanism operates), if the structure of the covering film is analogous to that of the structure of the substrate or maintains its symmetry upon minimisation of $\Delta\sigma$, the FVdM mechanism operates. Thus, at $\Delta\sigma = 0$ the FVdM mechanism, at $\Delta\sigma > 0$ the VW mechanism, and at $\Delta\sigma < 0$ the SK mechanism operates. The latter model (SK) is used in computer simulations more commonly than the two others. The growth models considered above (see Fig. 3) provide a reasonably good description of the structures observed in experiments.^{24,25} The phase transition considered in classical models is initiated by changes in surface tension, which appear because of disagreement between the lattice spacing of the substrate and the adsorbate.

Presently, the main difficulty in making a complete quantitative description of metal – electrolyte systems is the adequate

representation of periodic 2D-structures at the level of regularly spaced particles (atoms, surfactant molecules) and accounting for the quantum-chemical nature of the interaction between the 2D-film and the substrate. The interaction mentioned above is described by model Anderson – Ising – Hubbard Hamiltonians²⁶ for each particular system ‘M – inhibiting surfactant – electrolyte’. It should be noted that calculations using model Hamiltonian methods are often rather complicated, and Hamiltonians for electrochemical systems contain many uncertain parameters.

Let us analyse the 2D-nucleation process. We shall take the topological principle as the base and consider a series of main models, gradually complicating the dimensionality. It is reasonable at the beginning to give a description of a lattice gas model for singular defect-free surface crystals. Nucleation can also be considered in a classical approximation in which joining and formation of films occurs from fragments larger than separate atoms and molecules, surface clusters. In the lattice gas model, the degree of coverage of a crystal surface by inhibiting surfactant particles is expressed by the formula²⁷

$$\theta_{\text{surf}} = \frac{1}{N_s} \sum_{i=1}^{N_a} \langle C_i \rangle_T, \quad (10)$$

where N_s and N_a are the number of lattice points of substrate atoms and the number of occupied points, respectively; C_i is the variable of coverage ($C_i = 1$ if the surface points N_s are occupied and $C_i = 0$ if these points are not occupied). In formula (10), θ_{surf} is the molar fraction of occupied active centres on the crystal surface, and angle brackets henceforth denote statistical averaging over the main system state at a certain temperature T .

The variable of coverage $C_i \equiv \sigma_i$ determines the Boltzmann factor

$$B = \exp \left(- \beta \sum_{i,j} \sigma_i \sigma_j \right),$$

where $\sigma_i = \pm 1$, $i \neq j$, $\beta = T^{-1}$. Equation (10) follows from the main relationship for the variable of coverage (S) in the Ising model

$$S = \frac{1}{N_s^d} \sum_{i=1}^{N_s^d} \sigma_i,$$

where $d \geq 2$ is the fractal dimensionality ($d = 2$ in the two-dimensional model).

Summation in equation (10) is performed over all lattice points whose size is close to that of the adsorbing surfactant particles. When the sizes of adsorption cells are close to those of adsorbate particles, the Ising 2D-model employs a diagram technique.²⁸ At a certain average temperature T , the surfactant forms a monolayer, whose particles are bonded to the substrate particles with an energy E_b . This energy is determined by the sum of correlation functions of the spin on the crystal surface and the spins of the adequately conjugated surfactant monolayer with the surface layer of the substrate. The loss of mechanical stability of the flat frontier of growth (dissolution) of crystal surfaces results in the formation of a surface with a cellular structure. In this process, the growth of cells during self-organising is accompanied by avalanche-like changes in the overall distribution of spins.²⁹

The energies of pair additive interactions of the neighbouring (E_{NN}), next-to-neighbouring (E_{NNN}) and third-to-neighbouring (E_3) adsorbed particles occupying highly coordinated s -states can be defined as shown in Fig. 4. In the case of unpaired interactions, the energy is $-2E_{NN} - E_{NNN} - E_t$ (E_t is the energy of interaction of the neighbouring, NN , and closest-to-neighbouring, NNN , points). The total (configurational) energy of the three-particle (i, j, k) system (potential as in the 2D lattice gas model) is:

$$U_0 = -E_b \sum_{i=1}^{N_a} C_i - \sum_{i \neq j} E_{ij} C_i C_j - \sum_{i \neq j \neq k} E_t C_i C_j C_k, \quad (11)$$

where $E_{ij} = E_{NN}$, E_{NNN} , or E_3 , if i and j are the neighbouring, the next-to-neighbouring, and third-to-neighbouring sites, respectively; C_i , C_j and C_k are variables of occupation. The second

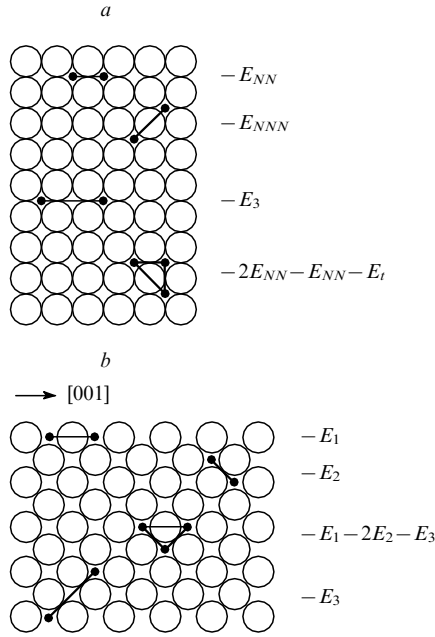


Figure 4. Energies of interaction of an adsorbed particle with a tetragonal (a) and centred rectangular lattice (b).

term in equation (11) describes all pair interactions, and the third term, all triple interactions. The prenucleation situation in the case of a centred rectangular lattice is analogous to that in the case of a square lattice (Fig. 5).

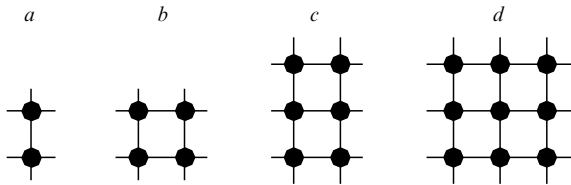


Figure 5. Completed ordered 2D-phases at $T = 0$ K; (a) $c(2 \times 2)$, $R < 0.5$; (b) L , $R > 0.5$; (c) $D_{0.25}$, $R > 0$; (d) $D_{0.25}$, $R > 0.5$.

The formation of condensed 2D-layers in the lattice gas model is described by statistical mechanics methods. Phases with low density (see Fig. 4) randomly distributed on a crystal surface are transformed into condensed phases due to the action of chemical and van der Waals forces. For example, on the (100) plane of a body-centred cubic (BCC) crystal (c) completed 2D-phases of various dimensionality are formed (see Fig. 5): $c(2 \times 2)$, L - and D -phases ($0 < R < 1$ is a dimensionless factor of confidence showing the divergence between experimental and calculated data). It should be noted that the Ising model for electrochemical contacts with charge transfer provides a good description of the results of *in situ* experiments performed by scanning tunneling electron microscopy in an electrolyte to study the initial steps of electrodeposition³⁰ and adsorption of solution particles on densely packed cubic crystal planes.³¹

Due to diversity of types of adsorption cells (Fig. 6) on the surface of the (100) plane, a type of unlimited percolation cluster can be formed in a 2D-structure.³² The kinetics of its formation is determined by the probability of sticking of the surfactant particles to the crystal surface (S), which is described by the equation:

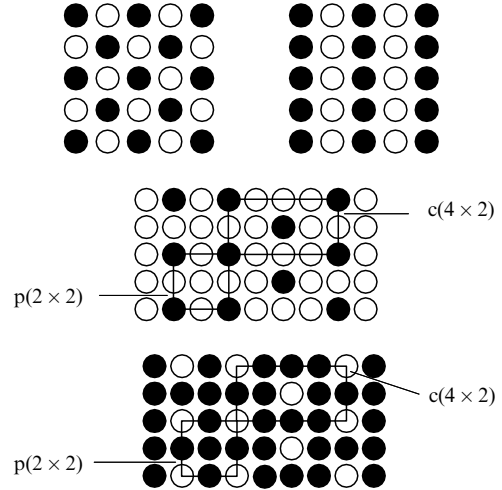


Figure 6. Types of adsorption cells on the (100) face of a body-centred cubic crystal. Here c and p are centred and primitive surface elementary cells, respectively; the black circle indicates a cell covered by an adsorbed particle.

$$S = S_0 K(E_{ij}, c_s) c_s^n,$$

where S_0 is the initial sticking coefficient (at the degree of coverage $\theta_{\text{surf}} = 0$), K is the configurational factor determining the form of the adsorption ensemble (e.g., $K = \pi$ for a dome-shaped ensemble and $K = 16\pi/3$ for a spherical ensemble), E_{ij} is the energy of interatomic (inter-particle) interaction, $c_s = f(N_s)$ is the surface concentration of vacant cells (unoccupied positions), which depends on the number of surface atoms of the substrate (total number of cells) N_s , and $n \simeq 0.3$ is a constant (degree) of nucleation of particles involved in the cluster.³³

Computations of the probability of sticking usually employ relationships of the Arrhenius type

$$S = S_0 (1 - \theta_{\text{surf}}) \exp\left(-\frac{E_{\text{ads}}}{RT}\right), \quad (12)$$

where E_{ads} is the activation energy of adsorption of the surfactant particles on the metal surface. A particular dynamic three-dimensional percolation cluster with a high specific surface area is formed on the electrode surface. A percolation cluster can appear upon deposition of particles on the surface in the mode of underpotential deposition,³⁴ in the formation of composite electrochemical coatings^{35,36} and oxide structures.^{37,38} In these cases, the subsurface layer behaves as a dynamic 3D-electrode.

If a model takes into account only the flux of surfactant particles hitting the crystal surface and sticking to it and ignores the possibility of their diffusive movement (when the magnitudes E_b are high) along the surface, the coalescence of islets of condensed phases according to the VW model results in the formation of condensed layers. The particles in adsorbed layers interact through repulsive and attractive forces, which differently depend on the distance. As the distance decreases, the repulsive forces grow more quickly than the attractive forces.

Within the lattice gas model with account of the U_0 energy [from equation (11)], the adsorption energy E_{ads} can be determined as follows:

$$E_{\text{ads}} = \frac{\langle U_0 \rangle_T}{N_s} = -E_b \theta_{\text{surf}} - \frac{1}{N_s} \sum_{i \neq j} E_{ij} \langle C_i C_j \rangle_T - \frac{1}{N_s} \sum_{i \neq j \neq k} E_{ijk} \langle C_i C_j C_k \rangle_T, \quad (13)$$

where N_s is the number of active lattice points to be occupied.

Equation (13) is written for a canonical ensemble at fixed independent T and θ_{surf} . If interaction of adsorbed particles occurs in a covering 2D-film, a term describing this should be added to equation (13), namely, $\mu_{\text{surf}}N_a$ (where μ_{surf} is the chemical potential of particles in the 2D-film, and N_a is the number of occupied points on the crystal surface). In the Ising model, the Hamiltonian for a crystal growing in an equilibrium mode has the form:³⁹

$$H = 2E_b \sum_{\langle i,j \rangle} [C_i(1 - C_j) + (1 - C_i)C_j] + \mu \sum_i C_i, \quad (14)$$

where E_b is the energy of cleavage of the interatomic bond between the closest NN -neighbours, summation $\langle i,j \rangle$ is carried out over pairs of NN -neighbours, and $\mu < 0$ is the energy of formation of a commensurate adsorbed 2D-phase 'not linked with the surface layer of the crystal'. The Hamiltonian for a system in which non-commensurate 'linked' films are formed from adsorbed layers, or the crystal lattice grows further, is more complex because it includes terms describing the interaction in 'linked' layers

$$H = U_0 - \mu_{\text{surf}}N_a = -(E_b + \mu_{\text{surf}}) \sum_{i=1}^N C_i - \sum_{i \neq j} E_{ij} C_i C_j - \sum_{i \neq j \neq k} E_i C_i C_j C_k. \quad (15)$$

At $T = \text{const}$, the dependence of μ_{surf} on θ_{surf} is described by the adsorption isotherm

$$\mu_{\text{surf}} = \frac{1}{N_a} \left(\frac{\partial F}{\partial \theta_{\text{surf}}} \right)_T, \quad (16)$$

where F is the Helmholtz free energy of the system

$$F = -kT \ln \text{Tr} \exp \left[-\frac{H\{C_i\}}{kT} \right], \text{Tr} = \sum_{i=1}^n a_{ii}, C_i = 0.1,$$

where the trace Tr means summation over all configurations (see Fig. 4). The condition $C_i = 0.1$ imposed on the Hamiltonian $H\{C_i\}$ means the absence of attraction–repulsion interactions in surface 2D-phases of adsorbed surfactant particles. In the Ising model taking account of the second limitation (see above), the variable of coverage C_i is given by the formula

$$C_i = \frac{1 - \sigma_i}{2}, \sigma_i = \pm 1,$$

where the spin is $\sigma_i = \pm 1$.

For particles of an adsorbing surfactant of the same type which do not interact, equation (13) is simplified when the temperature of the crystal increases to temperatures for desorption of the surfactant from the surface ($T \rightarrow \infty$):

$$E_{\text{ads}}(T \rightarrow \infty) = \quad (17)$$

$$= -E_b \theta_{\text{surf}} - 0.5 \theta_{\text{surf}}^2 \sum_{i \neq j} E_{ij} - 0.33 \theta_{\text{surf}}^3 \sum_{i \neq j \neq k} E_i,$$

where $\theta_{\text{surf}}^2 = \langle C_i C_j \rangle$, $\theta_{\text{surf}}^3 = \langle C_i C_j C_k \rangle$.

If the following designations are introduced: the Jackson–Temkin parameter

$$\beta_{\text{JT}} = 0.5 \frac{E_b}{kT},$$

$$m = \tanh \beta_{\text{JT}}, \quad \beta_{\text{JT}} = \ln \frac{1+m}{1-m} = \ln \frac{1-\theta_{\text{surf}}}{\theta_{\text{surf}}},$$

from equation (16) we obtain the Langmuir isotherm in the form

$$\frac{\mu_{\text{surf}} + E_{\text{ads}}}{kT} = \ln \frac{\theta_{\text{surf}}}{1 - \theta_{\text{surf}}}, \quad (18)$$

where the bond energy $E_b = 2(\mu_{\text{surf}} + E_{\text{ads}})$.

The anti-logarithm of isotherm (18) shows that the activation energy $\mu_{\text{surf}} + E_{\text{ads}}$ in the expression $\exp[(\mu_{\text{surf}} + E_{\text{ads}})/kT]$ is responsible for overcoming the potential difference in the double layer formed on the electrolyte side at the metal–electrolyte interface. This energy is related to variations in the Fermi energy of the metal, E_F , in the case of non-commensurate interaction in a film–substrate system and degree of solvation of surfactant particles in different phases that change the charge during the phase transition.

The Hamiltonian that describes the adsorption of surfactant particles within the Anderson–Newns model has the form:^{40, 41}

$$H = H_{\text{surf}} + H_M + H_{\text{surf-M}}, \quad (19)$$

where H_{surf} and H_M are Hamiltonians of the adsorbed particle and the pure substrate (metal), respectively; $H_{\text{surf-M}}$ is the Hamiltonian of the bond between them. The sum $H_{\text{surf}} + H_{\text{surf-M}}$ in operator (19) is usually replaced by a Hamiltonian taking the adsorption of the surfactant into account

$$H = H_M + H_{\text{ads}}, \quad (20)$$

where

$$H_{\text{ads}} = -kT \sum_{l,v} \ln \{ 1 + \exp[-\beta_{\text{JT}}(E_{l,v} - \mu_{\text{surf}})] \}.$$

Summation is done over all occupied adsorption cells N_s . Summation over l reflects the one-centre (on top) positions of the adsorbed surfactant particles, while summation over v corresponds to their bridging positions for a potential of the form

$$E_{l,v} = \sum_j \alpha_{lvj},$$

where α_{lvj} is the constant of attraction–repulsion interaction between the surfactant and the metal surface.

When estimating the degree of coverage within the Ising model, one performs summation over all adsorption cells $\{l,v\}$, and formula (10) is reduced to a more concrete expression

$$\theta_{\text{surf}} = \left\langle \sum_{l,v} \frac{1}{\exp[(E_{l,v} - \mu_{\text{surf}})/kT] + 1} \right\rangle.$$

In almost all cases, the surfactant particles adsorbed on a crystal surface induce reorganisation in first near-surface layers (phase transition of second order, without a heat effect or change in the specific volume). If the electronic subsystem of the crystal lattice is only slightly affected by surfactant adsorption, computer simulation can use the Hamiltonian (15) in the form:^{40, 41}

$$H = 0.5 \sum_{i \neq j} E_{ij} \langle C_i C_j \rangle_T + \sum_{i,j} C_i U(r_i^0 - r_i), \quad (21)$$

where E_{ij} is the energy of inter-particle interaction (adsorbate–adsorbent); U is the interaction potential, r_i^0 and r_i are the coordinates of a surface atom of the adsorbent before and after the reorganisation, respectively.

It should be noted that in electrolytes, the system 'metal surface–covering surfactant film' interacts with the solvent. The efficiency of interaction depends on the degree of coverage θ_{surf} . At $\theta_{\text{surf}} \ll 1$, it is necessary to take the predominating effect of interaction of particles in the film into account. Kornyshev and Schmickler⁴² introduce into Hamiltonian (19) an additional term of the type $E_{\text{sol}}(q_a) \langle C_i C_j \rangle_T$, where $E_{\text{sol}}(q_a)$ is the energy of interaction of an adsorbed particle with a mean charge q_a with the solvent.

In accordance with the classical concepts, the adsorbed particles have vibrational, translational and rotational degrees of freedom. The potential part of the total energy of these slow movements is determined by the electronic part of the Hamilto-

nian. As new physical aspects of interaction in the adsorbate–adsorbent system are discovered, the structure of the model Hamiltonian changes.

The van der Waals attraction or repulsion is caused by overlapping and orthogonalisation of wave functions of electronic states for the substrate and the adsorbed atom. The interaction between the adsorbed particles can be of at least four types:⁴³ electrostatic (Coulomb or dipole–dipole), due to overlapping of orbitals of adsorbed atoms or through phonons of the substrate by direct interaction ($\theta_{\text{surf}} \leq 1$) and by indirect interaction through electronic states of the metal. For covering layers of a surfactant with very low degrees of coverage ($\theta_{\text{surf}} \ll 1$), the Anderson's model Hamiltonian is constructed using Hubbard operators.⁴¹ The use of these operators makes it possible exactly to take into account the correlation of electrons on a doping (adsorbed) atom and to overcome the difficulties related to the need to combine the quantum character of an electronic subsystem with a classical representation (the Drude–Sommerfeld model⁹) of the crystal lattice.

A Hamiltonian for an adsorbate–adsorbent system in which reorganisation of the metal surface induced by adsorbed particles occurs has the form⁴⁴

$$H = U - \mu_{\text{surf}} \sum_{i=1}^{N_a} \langle C_i \rangle, \quad (22)$$

where the operator C_i equals unity if the act of adsorption has occurred, and $C_i = 0$ otherwise. The interaction potential in equation (22) can be presented as a sum of four terms

$$U = U_0 + U_M + U_{\text{surf}} + U_{M-\text{surf}}, \quad (23)$$

where U_0 is the potential from the 2D-lattice gas model for adsorbed surfactant particles with no account of reorganisation of the metal surface [see equation (11)], U_M is the potential reflecting pair interactions of atoms in the bulk and on the surface of a crystal M; U_{surf} and $U_{M-\text{surf}}$ are potentials composed taking account of the following effects of the substrate: lateral, dipole–dipole, those occurring due to overlapping of orbitals of adsorbed surfactant particles, electronic, and phononic.

In the case of 3D-nucleation at the interface, simulation requires ‘cutting’ of a definite volume including particles in the near-surface layer of the crystal, on the surface, and in the electrolyte. In this respect, lattice models have wider ‘possibilities’ in comparison with models based on the use of numerical methods. The cluster approach in the lattice gas model has been used for constructing equations that describe an equilibrium distribution of molecules in a multicomponent solution taking account of orientationally directed interactions.⁴⁵ To solve this problem, commensurate and non-commensurate layers of a surfactant are considered. The degree of commensurability depends on the sizes of surfactant particles and is primarily determined by the mean distance from adsorbing surfactant particles to the nearest adsorption points. Simulation of commensurability is performed by minimising the energy of additive interactions of atoms between each other $E(r_i - r_{i-1})$, which is very sensitive to the size of particles. If a commensurate phase of a protective inhibitor film has formed on a metal crystal surface ($\theta_{\text{surf}} \simeq 1$) that displays cooperative properties upon corrosive action of the medium, Hamiltonian (22) can describe the well-known Frenkel–Kontorova model⁴⁶

$$H = \sum_i [E(r_i - r_{i-1}) + U(r_i)], \quad (24)$$

where r_i is the coordinate of the i th atom and $U(r_i)$ is the periodic potential of substrate surface atoms in the form

$$U(r_i) \sim A \sin \frac{2\pi r_i}{\lambda},$$

where A and λ are the amplitude and length of the potential disturbance wave, respectively. The periodic potential of the lattice, which is the sum of local potentials $U(r_i - r_{i-1})$ of additive interactions of the particles, equals

$$U(r) = \sum_i U(r_i - r_{i-1}).$$

For simplification, one can accept

$$U(r) = U(r + 1)$$

and consider the action of this potential in a commensurate ‘cross-linked’ subsurface layer of the metal. Additive interactions $E(r_i - r_{i-1})$ occur in a commensurate M–surfactant ‘sandwich’. In the physical sense, Hamiltonians (24) are practically equivalent for 3D- and 2D-layers. In this model, a monolayer of a surfactant undergoes the action of the periodic potential of the substrate that is a plane of an ideal crystal, while particles of the adsorbate (surfactant) in the 3D-structure elastically interact with each other. Naturally, a Hamiltonian of the type (24) describes a very limited number of real cases, since rather strict limitations are imposed on it: the similarity of sizes of metal atoms and surfactant particles, of the electrical and vibrational characteristics of the metal and the surfactant. Perhaps, covering of the surface of a single crystal of a 3d-metal (Fe, Co, Ni) with atoms of noble 4d- or 5d-metals (Ru, Rh, Pd, Os, Ir, Pt) corresponds to this model.

When a real crystal surface is represented by a combination of steps and terraces (Fig. 7), Hamiltonian (24) becomes more complicated, as it includes terms corresponding to covering of both the steps and the terraces and can be expressed⁴⁷ by parameters for a partial coverage of the adsorption centres

$$n(i, j) = \left(\frac{N_a}{N_s} \right)^d,$$

where $2 < d < 3$ is the dimensionality.

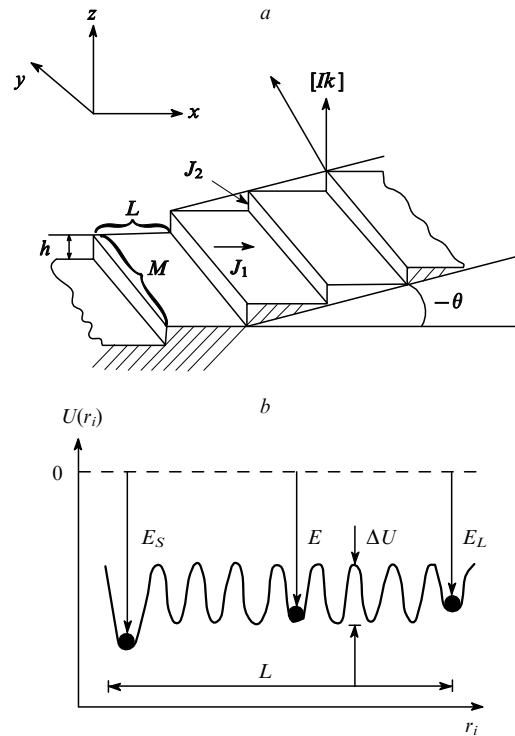


Figure 7. A model (a) and an energy diagram (b) for surfactant adsorption on a metal surface.

The complicated Hamiltonian has the form:

$$H = E_1 \sum_{j=1}^M n(1, j) - E_L \sum_{j=1}^M n(L, j) - E \sum_{i=2}^{L-1} \sum_{j=1}^M n(i, j) - \quad (25)$$

$$- 0.5 E_{\text{surf-surf}} \sum_{j=1}^M \{ n(1, j) [n(1, j-1) + n(1, j+1) + n(2, j)] +$$

$$+ n(L, j) [n(L, j-1) + n(L, j+1) + n(L-1, j)] +$$

$$+ \sum_{i=2}^{L-1} n(i, j) [n(i, j-1) + n(i, j+1) + n(i+1, j) + n(i-1, j)] \},$$

where E_1 , E_L , and E are energies of M-surfactant bonds at the end, at the beginning of a step, and on a terrace, respectively; $E_{\text{surf-surf}} = \mu_{\text{surf}} N_a$ is the energy of mutual repulsion in the adsorbate-adsorbent system. In relationship (25), the length of terraces is L , the length of steps is M , and the following condition is fulfilled: $M \gg L$. The step height is h , and the negative slope of the step face to the singular surface is $-\theta$ (see Fig. 7). A change in the sign of θ changes the dynamics of movement of the steps:⁴⁷ in one case, the adsorbed surfactant particles are forced back by the moving step, and in the other, they are absorbed in the crystal. The equidistant steps of finite length M take up the adsorbed surfactant particles, and the degree of coverage in a certain row l is determined by the relationship

$$\theta_{\text{surf}} = \langle n(l) \rangle_T = \frac{1}{M} \sum_{j=1}^M \langle n(l, j) \rangle_T. \quad (26)$$

As regards the retention of translational invariance in a bulk near-surface surfactant layer, since high-index planes of a single crystal with surface defects in the form of rectangular steps (without kinks) are considered, summation can be done over the index j of the coordinate y . Full coverage ($\theta_{\text{surf}} = 1$) of the terrace by the adsorbate is calculated using the formula

$$\theta_{\text{surf}} = \frac{1}{LM} \sum_{l=1}^L \sum_{j=1}^M \langle n(l, j) \rangle_T = \frac{1}{L} \sum_{l=1}^L \theta_{\text{surf}}. \quad (27)$$

The magnitude of θ_{surf} is considered to be a constant in this case.

The results of computer simulation using equations (25)–(27) agree satisfactorily with experimental data for well-characterised stepped planes of noble metal single crystals.⁴⁸ The growing steps maintain their faces in solutions where $\theta_{\text{surf}} \ll 1$. In the model of single step growth, the flux of surfactant from the terrace (J) that has higher kinetic coefficient or higher partial rate of direct reduction i_c [see relationships (29)] predominates. The flux of surfactant from the front terrace predominates,⁴⁹ i.e. $J_2 > J_1$ (see Fig. 7a).

Simulation of non-equilibrium single atomic steps showed⁵⁰ that the critical supersaturation

$$\Delta \gamma_c^\# = \ln \frac{c_{\text{surf},c}}{c_{\text{surf},0}}$$

[where $c_{\text{surf},0}$ and $c_{\text{surf},\text{crit}}$ are the equilibrium and critical (causing a phase transition) surfactant solution concentrations, respectively, at which the step starts growing linearly] depends on its inverse length M^{-1} for lattice spacing $k < 300$. Figure 7a shows a tetrahedral lattice with $\{Ik\}$ surface, where I is the number of steps and k is the lattice spacing (number of lattice sites along axis x on a densely packed terrace). As k grows, the surface ever more approximates a singular plane. At $k > 500$, critical supersaturation in the vicinity of the interface is not observed. However, actual steps in solutions containing surfactants have no distinct crystallographic faceting and non-uniformly move over the surface.

A particle that is adsorbed disturbs the electron density at the metal surface when it approaches the substrate. This disturbance propagates according to the law

$$\bar{n} = \bar{n}_0 + K_a \exp(-K_p z),$$

where $\bar{n}_0$ is the mean bulk concentration of electrons, K_a and K_p are coefficients of intensity and decay of electron density, and z is the coordinate on an axis normal to the metal surface. The magnitudes of K_a and K_p are determined by the nature of the metal, primarily by the work function of an electron and the Fermi level.

The interaction energy of the particles adsorbed on the substrate [$E_{ij} = E_{ij}(T, \theta_{\text{surf}}) = E_{\text{surf-surf}}(r)$] is determined by Friedel oscillations of electron density and depends on the shape of the Fermi surface⁵¹

$$E_{\text{surf-surf}}(x) \sim \frac{\sin(2\vec{k}_F r + m)}{r^n}, \quad (28)$$

where $\vec{k}_F$ is the Fermi wave vector, r is the distance between interacting surfactant particles, and the constants m and n depend on the nature of the metal. The Fermi surface, i.e., the surface of constant energy in a multidimensional space, is described by the $\vec{k}_F$ vectors, local Fermi levels (energies) E_F . At 0 K, all states 0.07 eV lower than E_F will be occupied, while the states higher than E_F by the same value will be vacant. The function $\phi = m/r^n$ is introduced in equation (28) to take into account the additional indirect (exchange of electrons in the surfactant-metal system through the conduction band of the substrate) contribution into the energy of the surfactant-surfactant interaction. The values of m and n depend on the shape of the Fermi surface. In terms of graphical 3D-models, the Fermi surface characterises a definite metal with fixed topology and constant energy in inverse space (in a particular three-dimensional case, in an inverse lattice; for example, see Ref. 52) with wave vector $\vec{k}_F$ of the electron angular momentum. A classical surface of a solid is a direct analogue of the quantum-mechanical Fermi surface for conductivity electrons in inverse space.⁵³ The Fermi surface is transformed to a usual classical surface as the relativistic mass of electron increases. Transition to a state of Fermi surface instability is accompanied by a second-order phase transition and, eventually, desorption of the surfactant from the crystal surface.⁵⁴ For an amorphous material, the Fermi surface is spherical, i.e. analysis of the Fermi surface topology affords the possibility of predicting the high chemical resistance (low corrosion rate) of solids in an amorphous state.

The Fermi surfaces of compounds that exist in the crystalline state contain cylindrical regions. In this case, the energy of interaction in the direction perpendicular to the cylinder axis (when $m = 0, n = 2$) is inversely proportional to the square of the distance r between the interacting particles

$$E_{\text{surf-surf}}(r) \sim \frac{\sin(2\vec{k}_F r)}{r^2},$$

while for planar regions of the Fermi surface, in the direction perpendicular to them (when $m = 0, n = 1$),

$$E_{\text{surf-surf}}(r) \sim \frac{\cos(2\vec{k}_F r)}{r}.$$

In Hubbard's model,^{41, 55} the penetration depth of the electric field of an adsorbed particle into a metal substrate depends on the Thomas-Fermi length of shielding⁹

$$l_{\text{TF}} = \left(\frac{E_F}{6\pi\bar{n}_0|e^-|^2} \right)^{1/2},$$

where n_0 is the bulk concentration of electrons in the conduction band. Such adsorbents as Fe, Ru and Os, which have considerably higher Fermi energies than Cu, Ag and Au, have better chemisorption characteristics with respect to particles that are adsorbed with charge transfer. In the series of transition d -metals, elements occupying the middle of a series have higher E_F than the elements with d -shells filled (Cu, Ag, Au).

The chemisorption activity of transition metals is considerably affected by light particles implanted in the near-surface layer; either these particles are local harmonic oscillators, or they create their own sublattice as a result of self-organisation (provided that they have high diffusion mobility). Absorption of hydrogen by the near-surface layer of the metal or 'poisoning' of the metal by other light chalcophilic elements change both the E_F and $\bar{n}_0$. Programmes are available for modelling the ionic implantation into crystals, which provide the possibility of building concentration profiles⁵⁶ and subsequently of assessing changes in the corrosion resistance of the crystals subjected to a treatment.

On translation-invariant substrates, the adsorption of solution particles (the primary act in metal dissolution) can be rather strictly described (in analytical form) within the Ising model. The formation of ordered adsorption structures determines the kinetics of the corrosion dissolution of a metal whose surface is homogeneous (and/or the structural defects of the near-surface layer of the metal are blocked). For computer simulation purposes, the rates of partial cathodic and anodic reactions (cathodic and anodic current densities, i_c and i_a) occurring in non-saturated solutions can be expressed by equations that follow from formula (4),

$$i_c = v_i \exp \frac{\mu_e}{kT}, \quad (29)$$

$$i_a = v_i \exp \frac{-n_{\text{ads}} E_b}{kT}, \quad (30)$$

where v_i is a frequency factor (of the order of the Debye frequency, 10^{13} s^{-1}), μ_e is the equilibrium chemical potential in solution, n_{ads} is the number of bonds of an adsorbed atom with other lattice atoms and E_b is the energy required for the cleavage of one M–M bond. In the absence of charge transfer, the equilibrium chemical potential μ_e and the chemical potential of surfactant particles on the interface, μ_{surf} , are related to the solution concentration c_{surf} and activity a_{surf} by the equation

$$\mu_{\text{surf}} - \mu_e = kT \ln \frac{c_{\text{surf}}}{c_e} = kT \ln \frac{a_{\text{surf}}}{a_e},$$

where c_e and a_e are the equilibrium concentration and activity of the surfactant in solution, respectively.

When a quasi-equilibrium stationary state accompanied by inter-phase transfer of charged particles has been established in a system, the well-known Nernst equation, which describes the inter-phase distribution of particles, is applicable in the thermodynamic description:

$$\mu_e = 0.5WE_b + \frac{RT}{nF} \ln \frac{c_{\text{surf}}}{c_e}.$$

Here W is the number of the closest neighbours of an atom (in bulk metal, $W = 12$ for a face-centred lattice and $W = 8$ for a body-centred lattice), n is the number of electrons transferred in an elementary discharge act, and F is the Faraday constant. The factor of 0.5 is introduced in the first term of the right-side expression (the two-particle potential $\mu_0 = 0.5WE_b$) in order to avoid counting the interaction of each pair of particles twice.

The coordination number W is determined by the topology of an adsorbed particle on the crystal surface. The magnitude of W on the crystal surface is considerably smaller (by a factor of two in a semi-crystalline position) than in the crystal bulk. The adsorption energies expressed according to Kaishev–Stransky⁵⁷ for different crystal faces (ΔE_{ads}) and the energies of semi-crystalline positions ($E_{1/2}$) depend strongly on the reticular density of the surface (the packing density of surface atoms) of the crystal, S_{hkl} . The magnitude of ΔE_{ads} for atomic-planar F -faces is 0.3 to 0.5 of the heat of sublimation ΔH ; the $E_{1/2}$ values increase along the series: body-centred, face-centred, hexagonal close packed crystal.

Analysis of equations (29) and (30) shows that the frequency factor

$$v_i = k_0 a_a^0 \equiv k_0 a_k^0,$$

[here $k_0 = (kT/2\pi h)(z^\# / z)$, where h is the Planck constant, $z^\#$ and z are the partition functions per unit volumes of the active complex and the reagents in the electrolyte, respectively] most strongly depends on the activities of the cathodic and anodic surface complexes a_c^0 and a_a^0 , which change in parallel with the concentration of Ox- and Red-particles in solution. The smaller W the easier it is to block the crystal surface element (cell) by an inhibiting surfactant. Conversely, adsorbed (mostly, semi-crystalline) particles have higher tendency to ionisation (dissolution). The excited state of an atom undergoing ionisation exists for a sufficiently long time ($\leq 10^{-8} \text{ s}$), that rapid transition of the surface atom to an unstable state is necessary. The characteristic times of electrochemical reactions ($\sim 10^{-11} \text{ s}$) are considerably longer⁵⁸ than the characteristic times of redistribution of bound charges of the solvent at the interface ($10^{-14} - 10^{-15} \text{ s}$). Hence, metal dissolution becomes possible. Increasing the electrochemical dissolution rate (decreasing the time t to $10^{-12} - 10^{-13} \text{ s}$) by application of anodic current to an activated surface considerably decreases the contribution of surface defects to the overall balance of mass loss by the crystal due to dissolution. This provides the opportunity to use the classical formal kinetics approach based on the Langmuir isotherm (18) in the computer simulation. It is assumed in equations (29) and (30) that the dependence of the equilibrium concentration c_e on the surface coverage by adsorbed particles obeys the Langmuir isotherm.

According to the classical concepts, an act of dissolution is preceded by the transition of a surface atom to a metastable state, which occurs with a frequency differing from the Debye frequency ν_D (which is characteristic of the bulk of the crystal), $\nu_i = 10^{13} - 10^{14} \text{ s}^{-1}$. This frequency ν_i [the pre-exponential factor in kinetic equations (4) and (29)] depends on the Debye frequency ν_D according to the formula

$$\nu_i = \nu_D \exp \left(\frac{-\Delta G}{RT} \right) = \nu_D \exp \left(\frac{\Delta S}{k} \right) \exp \left(\frac{-\Delta H}{RT} \right), \quad (31)$$

where the product $\nu_D \exp(S/k)^\ddagger$ is an insignificant deviation of a local volume of the system from the equilibrium state; ΔG , ΔS , and ΔH are the Gibbs free energy, the entropy and the enthalpy, respectively, required for the transfer of the atoms under consideration to the peak of the potential barrier between two equilibrium states of the structure.

Thus, in covering layers (commensurate or non-commensurate) on the surface and in the crystal bulk, a certain phonon mismatch (mechanical resonance) appears, which is, strictly speaking, the origin of phase transitions in these layers.

III. Models using the Monte Carlo method

In its canonical distribution variant, the MC method, which is based on statistical sampling of configuration mean values, calculates the mean values ($\bar{M}$) according to the formula

$$\bar{M} = \frac{\sum_i M_i \exp(-E_i/kT)}{\sum_j \exp(-E_j/kT)} = \sum_i M_i P_i,$$

where M_i is one of physical characteristics of the i th configuration, E_i is its energy, and P_i is the probability that the i th configuration would appear.

$$P_i = \frac{\exp(-E_i/kT)}{\sum_j \exp(-E_j/kT)}.$$

[‡] The Einstein formula describing the fluctuation probability in the first near-surface metal layer.

The MC method is a method of numerical experiment; it is versatile and provides highly reliable results.⁵⁹ The MC technique can be used for the 2D Ising model for which exact solutions can be obtained,⁶⁰ in particular, for the formation of fluctuations of material density (drops) at the interface.^{61,62} The stability of mesoscopic water clusters (small drops) and thin films is being studied intensively.⁶³ Ultra-thin water films on solid surfaces form crystal-like structures. The nucleation of small water clusters in the electrolyte bulk far from the interface occurs on ions of dissolved salts. The instability range of small water clusters results from the relative weakness of long-range electrostatic interactions. Large clusters form mesoscopic bubbles in polar liquids. Their shape is calculated using the MC method.⁶⁴ Calculations in independent sets (several hundred MC steps per adsorption cell) make it possible to access continuous thermodynamic functions of continuous thermodynamic variables. A stable state of a multi-particle system containing N particles corresponds to a minimum of the functional of inter-particle effective (resulting in the formation of chemical bonds) potentials $U_{\text{ef}}(r_i, r_j)$ of the type (2)

$$U_{\text{ef}}(r_i, r_j) = \int \dots \int [\exp(\beta_{\text{JT}, E_b}) - \exp(\beta_{\text{JT}, U_{\text{ef}}})]^2 dr_1 \dots dr_N.$$

Here the Jackson–Temkin parameter is

$$\beta_{\text{JT}, E_b} = \frac{-0.5E_b(r_1, \dots, r_N)}{kT} \text{ and } \beta_{\text{JT}, U_{\text{ef}}} = \frac{-0.5 \sum_{i < j}^N U_{\text{ef}}(r_i, r_j)}{kT}.$$

Naturally, the order in which problems are solved by MC simulation depends on the level of development of mathematical methods and computational means. Using the simplest pair potentials, electrochemical problems on the adsorption of chalcophilic particles on various faces of single crystals of noble transition metals were solved. Complication of the pair potentials is required if the act of adsorption involves more complex particles, such as water molecules.^{65,66} In this case, the effective potential $U_{\text{ef}}(r_i, r_j)$ also becomes more complex. For example, the Raman–Stillinger potential⁶⁷ contains a spherically symmetric term [Lennard-Jones potential (2a), $U_{\text{LJ}}(r_{ij})$] and an electrostatic potential [$U_{\text{el}}(r_i, r_j)$] of point charges displaced from the geometric centre of the molecule

$$U_{\text{ef}}(r_i, r_j) = U_{\text{LJ}}(r_{ij}) + \sigma(r_{ij})U_{\text{el}}(r_i, r_j). \quad (32)$$

Here $\sigma(r_{ij})$ is a smoothing function for correction of the interactions at small interatomic distances.

Lattice gas models can be realised in the 3D variant for the estimation of phase transformations at interfaces: these are Brunauer–Emmett–Teller generalised kinetic models, both in discrete and diffusion forms.⁶⁵ For example, problems on the absorption of electrolytic hydrogen by crystals are solved by numerical MC methods in three-dimensional systems⁶⁶ using 3D lattices with $> 10^6$ positions for occluded hydrogen and with variable parameters of the Gaussian distribution of equilibrium states and middle points between them. Subsequently, more complex systems were studied, such as M–chalcophilic particles, adsorption of CO, H₂O and halides, co-adsorption of CO and hydrogen on noble metal surfaces.^{67,68}

In early studies on the simulation of water adsorption on metal electrodes by the MC method,^{69,70} the crystal surface was simulated as a hard wall of a ‘jelly’-metal. The surface charge was distributed uniformly, and the interface was simulated as a ‘flat condenser’, d being the distance between the plates; the ions located in the water layer were approximated by spherically symmetrical particles.⁷¹ The inter-ionic interaction was described within the Poisson–Boltzmann model

$$U(r_{ij}) = \frac{n_i n_j |e^-|^2}{4\pi\epsilon_0\epsilon_r r_{ij}} \text{ for } r_{ij} > d,$$

$$U(r_{ij}) = \infty \text{ for } r_{ij} < d,$$

where r_{ij} is the distance between ions i and j ; n_i and n_j are the concentrations of ions (of the kind i and j , respectively); ϵ_0 and ϵ_r are the dielectric constants of the solvent and the solution, respectively; and the interaction between the solvent layer and the ‘jelly’-metal surface was described as

$$U(r_{ij}) = \frac{q_i n_i |e^-| \Delta z_i}{2\epsilon_0\epsilon_r}.$$

Here q_i is the surface charge density; Δz_i is the normal distance (along the z axis) between the charged surface of the ‘jelly’-metal and an ion with a radius of r_i . It should be noted that Δz_i is the major factor determining the formation of commensurate and non-commensurate covering adsorbed layers.

When an interface is simulated, a cylinder, which contains a certain number of chalcophilic particles, is ‘cut out’ of the electrolyte so that some of the particles are located at the interface. For example, various models of hydrogen bond networks in 3D water have been constructed using the MC method. Three variants of the model were considered in Ref. 72: with 125 and 343 particles in the unit cell and with two different starting conditions. The differences between the variants are almost not discernible in the pair correlation functions, *i.e.* atom–atom radial distribution functions, which reveal the specifics of orientation order at sufficiently long distances (> 10 nm). The use of radial distribution functions is caused by the impossibility of obtaining exact solutions from equations, which operate in terms of particle coordinates and atom–atom interaction potentials. When one starts calculations, it is important to make a correct selection of the pair potential $U(r_{ij})$, which is different in adsorption 2D layers and in the bulk of the liquid phase. A model Hamiltonian of the system should certainly involve the mapping effects (for transition metals, the distance from the mapping plane to the crystal surface, which correlates with reticular density variation and decreases on changing from a ‘loose’ face to a densely packed one), the reconstruction of the near-surface metal layer due to adsorption and the evolution of non-equilibrium defects in this layer under the action of an electrolyte.

In the Kossel–Stransky model (TLK model), equations resembling (29) are used at moderate solution oversaturations for computer MC calculations of growth and dissolution of crystals under the above assumptions.^{73–75} During the growth of an ideally smooth surface of a cubic crystal, the sticking probability of the particles that are deposited, P_a , is determined by the product of the probability of existence of n closest neighbours at one cell [$P_g(n)$] and the probability that the electrode potential E assumes a certain value, $P_\eta(E)$

$$P_a(n, E) = P_g(n)P_\eta(E).$$

In metal corrosion, the probability of detachment of an atom from the first (n_1) and second (n_2) closest neighbours $P(n_1, n_2)$ for the {001} faces of a cubic crystal depends on the energy of cleavage of M–M bonds due to corrosion according to an Arrhenius-type equation:⁷⁶

$$P(n_1, n_2) = v_i(n_1, n_2) \exp \frac{-E_b(n_1, n_2)}{RT}.$$

The bond energy, $E_b(n_1, n_2) \equiv n_{\text{ads}} E_b$, depends on solution under-saturation, as well as on the charge, ion size and concentration of an inhibitor if present. The physical meaning and structure of the equation presented above are similar to those of equation (30): the activation energy (energy of cleavage of one M–M bond) is $E_b(n_1, n_2) = n_2 E_2 - n_1 E_1 = -n_{\text{ads}} E_b$, and the frequency factor $v_i(n_1, n_2)$ is determined by equation (31). The values of E_1 and E_2 (bond energies for the first and second closest neighbours, respectively) can be calculated using pair potentials.

The MC method can be used for the computer description of both the development of local forms of corrosion (formation and

growth of a single pit) and the evolution of non-singular (diffusion) surfaces of crystals with surface defects in the form of steps and kinks. The growth of an ideally smooth (singular) single crystal surface is simulated by the MC method within the cellular automata model,⁷⁷ which takes the adsorption of discharging particles, their movement on the surface, incorporation, chemical reactions and desorption into account.^{78,79} The discrete growth of a new monolayer in a unit cell (Fig. 8) starts from the centre (single cell). A single cell is filled by an adsorbing particle in the case if two neighbouring sites are also vacant. The process is controlled⁸⁰ by a pair correlation function $\sigma(r, t)$, which changes with time (provided that the adsorption acts occur randomly)

$$\sigma(r, t) = \frac{-0.5 \exp(-2A) \sum_{n=0}^{\infty} (-2A)^{2n+r+1}}{(2n+r+1)!},$$

where $A = 1 - \exp(-t)$.

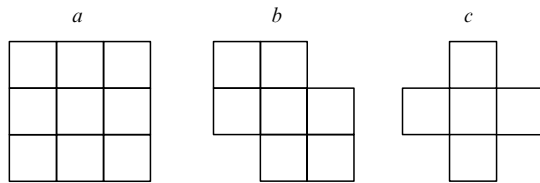
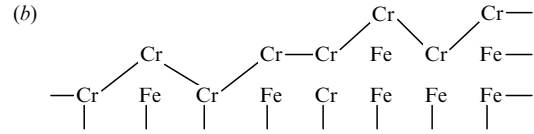
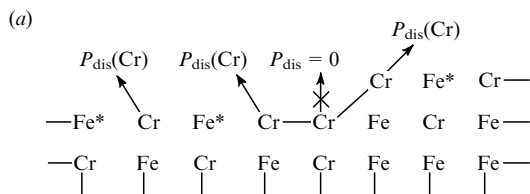


Figure 8. Types of elementary cells; (a) square (Neumann vicinity); (b) hexagon; (c) rhombus (Moore vicinity).

The distribution of adsorbed particles in a lattice that consists of cells with N_{ac} active centres on the surface has the dispersion $N_{ac}A \exp(-4A)$ at high N_{ac} . The cellular automata model is applicable to the description of selective dissolution of crystals occurring by generation of dissolution steps.⁸¹

The computer simulation of changes in the morphology of a pit growing at a dislocation exit on an 'atomically-smooth' surface is based on the concept that atoms with higher energies are preferentially removed from the crystal. In the first step, a 2D nucleus of the pit is formed. In the model suggested in Ref. 82, the authors considered the bonding of the atom being removed with the neighbouring metal atoms located in four types of positions at the closest distances. Computer calculations determine the energy of each atom along the perimeter of the 2D nucleus and select the atom with the weakest bonding to the substrate. After removal of this atom, the calculation of energies of perimeter atoms is repeated.

It has to be noted that this approach ('removal' of the most weakly bound atoms from the near-surface layer of a crystal) is also quite acceptable for the computer simulation of alloy corrosion or dissolution of high-index surfaces of pure metals.⁸³ Numerous experiments on the study of alloy corrosion⁸⁴ show that the most electronegative component is the first to be removed from the surface during alloy dissolution. For example, in modelling of the dissolution of an Fe–Cr alloy,⁸⁵ the percolation process is taken into account; this process can be visualised as follows in the 2D variant:



Here P_{dis} is the dissolution probability. At step *a*, the surface contains oxidised atoms of both iron and chromium. Removal of an iron atom from the surface (step *b*) results in the formation of a continuous surface coating by chromium, *i.e.*, a percolation 2D cluster is formed. The percolation leading to enrichment of the surface by chromium atoms results in surface passivation, structural stabilisation of the alloy and a decrease in the dissolution rate. A similar procedure of 'removal' of the most weakly bound atom in the 3D model of metal corrosion makes it possible to simulate the movement of dissolution steps on high-index crystal planes.

Eventually, corrosion stabilises the surface layers of crystals. The stabilisation occurs not only by percolation but also by forming a near-surface layer with particular grain composition. Problems of grain growth in near-surface metal layers were successfully solved using recrystallisation MC models.⁸⁶

In the scheme of layered growth (dissolution) by the FVdM mechanism, the computer simulation of the TLK model (Fig. 9) uses a MC principle in the random formation of the growth (dissolution) centres.⁸⁷ This eventually results in the formation of a quasi-stationary surface topography characterised by the Gaussian distribution of layer coverage. The mean rate of tangentially moving atom chains ($\bar{V}$) is proportional to the degree of surface coverage by adsorbed atoms (θ_{ads})

$$\bar{V} = \frac{L}{t} \theta_{ads},$$

where L is the distance between atom chains (steps) and t is the time of incorporation of an adsorbed particle into a step. Of course, the rate $\bar{V}$ also depends on the density of active centres on the step, N_{ac}

$$\bar{V} = \frac{L}{N_{ac} \Delta t},$$

where $\Delta t = t/N_s \theta_{ads}$ is the time (the Monte Carlo time) till a successful attempt to incorporate an adsorbed particle at a functioning active centre and N_s is the number of substrate surface atoms. It is important that the Monte Carlo time Δt matches the increment of real time (or time step in numerical simulation).⁸⁸ Of major importance are the transition probabilities $P_a(n, E)$ describing a system in the MC model. The sums

$$\sum_1^n P_a(n, E)$$

determine the trajectories of the system transition into the equilibrium state. The main mechanism of the growth of adsorbed layers in the MC model is diffusion of an adsorbed particle until it incorporates itself in an active centre. The role of active centres is usually played by kinks.

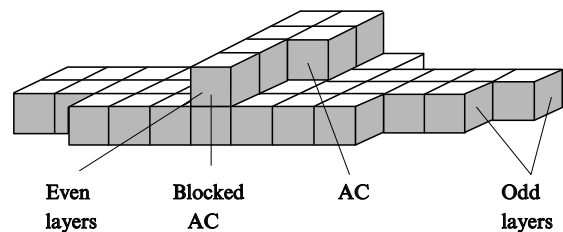


Figure 9. Scheme of increase in the crystal surface in the TLK model by the mechanism of anisotropic growth of 'orthogonal strings' (atomic chains); AC is the active centre.

The model of consecutive coverage by monolayers (see Fig. 9) is not the only one or the simplest one of TLK models. The following models have also been considered:^{75,89} the random deposition model in which an adsorbing particle striking the crystal surface is instantly attached to a stable position of a tetragonal lattice (substrate); the model of locally-perfect layer-by-layer growth on a tetragonal lattice in whose each cell 'perfect' (not correlated with other cells) layer-by-layer growth of a non-commensurate phase occurs; the local islets model in which the diffusing adsorbed particles are attached in highly-coordinated positions on a crystal surface.

For the stepped surface in the TLK model (see Fig. 7), the flux of adsorbing particles striking the crystal surface should consist of, at least, three components:⁹⁰

$$J = J_S + J_i + J_r,$$

where J_S is the flux of surfactant particles attaching themselves to a step; J_i is the flux of surfactant particles directed to active centres (2D-islets); and J_r is the flux of desorbing surfactant particles.

The MC method was used for the surface of a simple cubic crystal in a study of surface covering with an epitaxially growing film.^{90,91} It was shown that concentration oscillations appearing in the simulation of layer-by-layer film growth mechanism do not correspond to the exact filling of monolayers. As the length of surface migration of adsorbed atoms, λ ($\lambda < L$), increases, the oscillation region shifts from the region of high degree of coverage, $\theta_{\text{surf}} > 1$, to the region of small degree of coverage, $\theta_{\text{surf}} < 1$. It should be noted that concentration oscillations near the electrode surface in homogeneous nucleation have been reported as early as in Refs 92 and 93, which dealt with an MC simulation of polynuclear crystal growth. Concentration oscillations in solution give rise to non-uniformity of layer growth in galvanic coatings.

The electrodeposition of metals was studied using computer simulation methods.^{94,95} It was assumed that the new phase growth occurred under the conditions of simultaneous coverage of adsorption cells with various particles and that depolarisation on both components occurred due to changes in the free energies of the components.⁹⁶ In a model predicting the alloy composition, the shift of the equilibrium potential for each component of a two-component alloy was used as the main characteristics for computer simulation^{94,95}

$$E_i = \frac{RT}{nF} \ln c_i - (1 - c_i)^2 E,$$

where c_i is the molar fraction of the i th component in the alloy, $E = \Delta H/nF$, and ΔH is the integral enthalpy of mixing. In computer simulation of the formation of binary alloys AB in an electrochemical process by the VW mechanism, the work of formation of 2D-nuclei is determined taking account of the energy of elastic deformation of the crystal lattice

$$W_{hkl} = 6\pi \left(\frac{r_A - r_B}{r} \right)^2 r^3 \frac{c_B(1 - c_B)}{k_1 + k_2 C_B},$$

where r_A and r_B are the atomic radii of metals A and B, $r = (r_A + r_B)/2$ is the mean atomic radius, k_1 and k_2 are coefficients:

$$k_1 = \frac{3}{4} G_A + K_B,$$

$$k_2 = \frac{3}{4} K_B + G_A - \frac{3}{4} K_A - G_B,$$

G_A and G_B are the shear moduli of metals A and B, K_A and K_B are the deformability (compressibility) coefficients of metals A and B, respectively.

MC computer simulation was used in studies of the electrochemical growth of crystals, both in the form of islets⁹⁷⁻⁹⁹ and in vicinal form (pack of monoatomic steps).^{83,100,101} It was shown that surface evolution is in good accord with morphological

patterns of the growth of continuous galvanic deposits and with the structural features of insular coatings. For example, computer simulation using Lennard-Jones potentials (2a) showed⁹⁸ that on the surface of a crystal with a simple cubic lattice, subcritical size nuclei of the new phase have body-centred cubic structure, while after reaching the critical size, they have face-centred cubic (FCC) structure. This result totally agrees with experimental estimates of actual heteroepitaxial systems 'crystal surface – galvanic deposit'.

The use of the vicinal growth model on a crystal surface¹⁰² assumes correlated movement of not only monoatomic steps but also [taking account of equation (4)] electrochemically active adsorbed particles. The energy of the diffusion barrier $E(\theta_{\text{surf}})$ is expressed as the sum

$$E(\theta_{\text{surf}}) = E_s(\theta_{\text{surf}}) + nE_N(\theta_{\text{surf}}),$$

where $E_s(\theta_{\text{surf}})$ and $E_N(\theta_{\text{surf}})$ are contributions of interaction with the surface and with the closest neighbours, respectively; $n = 1-4$. The rate of movement of vicinals during crystal dissolution primarily depends on their height.¹⁰³⁻¹⁰⁶ Splitting of vicinals from a chain of atoms, which belong to a step and are transferred into solution, occurs in a correlated way. Consideration of corrosion of a crystal face having linearly-stretched defects is possible either in the classical variant or with account of wave cooperative features of the interaction of adsorbed particles and surface atoms on the interface.¹⁶

In the classical Kossel-Stransky's theory of attachment (separation) of particles to a monoatomic step of a crystal, the rates (currents) of the direct and reverse processes ($\vec{i}$ and $\vec{i}'$, respectively) obey equations of the type (31)

$$\vec{i}(\vec{i}') = v_D \exp\left(\frac{\Delta S}{k}\right) \exp\left[\frac{-(E_a + \Delta E_{\text{lat}}(T))}{kT}\right], \quad (33)$$

in which $E_a + \Delta E_{\text{lat}}(T) = \Delta H$, $\Delta E_{\text{lat}}(T)$ is the energy of lateral interaction of particles in a step (the Frumkin correction factor). An equation has been suggested for the estimation of the rate of movement of a single monoatomic step (V_L) containing kinks:

$$V_L = 0.5 \exp \frac{\Delta G^\ddagger}{RT} a_0 \left(\frac{2\text{ch}(3\sigma_L)}{RT} - 1 \right) \left(\exp \frac{\Delta \mu}{RT} - 1 \right), \quad (34)$$

where $\Delta G^\ddagger$ is the free activation energy of dissolution in a kink on the step; a_0 is the activity of the substance in a saturated solution; σ_L is the specific free surface energy per atom located in the step; $\Delta \mu$ is the difference between the chemical potentials of the material of the crystal that is dissolved in supersaturated and saturated solutions.

Estimates using equation (34) show that an increase in σ_L should increase the rate of step movement, V_L . If a step and/or kinks on crystal steps in a Kossel-Stransky crystal are blocked by a corrosion inhibitor, σ_L and probabilities of detachment of an atom from the surface, $P(n_1, n_2)$, change. The reasons for this are as follows: first, a decrease in the number of 'free bonds' of an atom in a certain position; second, a decrease in the number of bonds between the inhibitor atoms and the crystal lattice; third, attenuation of electronic vibrational modes (changes in the electronic and phonon spectra of the surface atomic layer of the crystal) due to the adsorption of solution particles. The attenuation of vibrations due to the inhibiting adsorption of small chalcophilic particles is stronger in the direction tangential to the surface than in the perpendicular direction.¹⁰⁷ The decrease in the probability of exit of an atom from a kink due to dissolution inhibition can be determined from the equation

$$\frac{\Delta P(n_1, n_2)}{P(n_1, n_2)} = 1 - K \exp(n_{M-M} + n_{\text{surf-M}} + n'_{M-M}), \quad (35)$$

where K is the metal deformability constant; $n_{\text{surf-M}}$ is the number of bonds between the inhibitor particles and the lattice atoms; n_{M-M} and n'_{M-M} are the numbers of free bonds of an atom in a

typical lattice position with and without an inhibitor, respectively. According to equations (2) and (34), each bond has distinct energetic characteristics, and the maximum contribution to its realisation in inhibiting adsorption is made by the electronic interaction in the adsorbate–adsorbent system [the third term $H_{\text{surf-M}}$ in Hamiltonian (19)]. In an adsorbed dipole, the attenuation of stretching vibrations of the M–surfactant bond is primarily caused by changes in the density of states at the Fermi level of the transition metal, E_F , due to the adsorption of an inhibiting particle.

Simulation of adsorption by MC methods showed⁴⁷ that mutual attraction of particles on a stepped surface strongly affects the adsorption isotherm, which leads to the separation of the system into phases with low and high degree of coverage. For example, the authors¹⁰⁸ who made a calculation of the effective interaction potential of the simplest adsorbing particle (hydrogen) also noted that the Hamiltonian for the full energy of an adsorbed hydrogen atom similar to Hamiltonian (20) consists of the energy of hybridisation of one-electron states with d -electrons of the adsorbent, the adsorption energy of hydrogen on a uniform surface, and the short-range attraction forces between the adsorbed atoms and the ion framework of the metal. The Hamiltonian for a hydrogen molecule desorbing from a metal surface and not bound to it by chemical forces is expressed by the sum (in atomic units)

$$\hat{H}_{H_a H_b} = \underbrace{-0.5\nabla_1^2 - r_{1a}^{-1}}_{\text{Hamiltonian of the atom } H_a} + \underbrace{-0.5\nabla_2^2 - r_{2b}^{-1} - r_{1b}^{-1} - r_{2a}^{-1} - r_{12}^{-1}}_{\text{Hamiltonian of the atom } H_b} - \underbrace{R_{ab}^{-1}}_{\text{Hamiltonian of the molecule } H_a H_b}. \quad (36)$$

Here the subscripts 1 and 2 signify the arbitrary numbers of 1s electrons of the H_a and H_b atoms; r_{1a} , r_{2a} and r_{1b} , r_{2b} ; r_{12} and R_{ab} are the electron–nucleus, nucleus–nucleus distances and the distance to the adsorption point, respectively.

When atoms H_a and H_b are remote from each other, they can be considered non-interacting, and the electronic state of each of them can be described by wave functions $G_a(1)$ and $G_b(2)$ of isolated atoms H_a and H_b

$$\begin{aligned} G_a(1) &\equiv 1S_a(1) = \frac{1}{\sqrt{\pi}} \exp(-r_{1a}), \\ G_b(2) &\equiv 1S_b(2) = \frac{1}{\sqrt{\pi}} \exp(-r_{2b}). \end{aligned} \quad (37)$$

The spins in the H_2 molecule are anti-parallel; hydrogen atoms adsorbed on a metal (with parallel spins) interact through van der Waals forces (repulsion).

A thermodynamic estimation of surface states shows that the lowest equilibrium chemical potential μ_e for surface states is realised for the most loosely packed {110} FCC and {111} BCC faces. This ensures their preferential filling with adsorbed particles within the model of hard spheres with uniform charge ('jelly'-spheres).

Results of computer simulation by methods of statistical selection of configurations (MC method) based on the concepts described above, with the assumption that E_b in a crystal does not depend on the direction $\langle hkl \rangle$, lead to certain conclusions on new phase formation on singular and low-index single crystal faces. This approach is quite satisfactory for the problem of corrosion inhibition, since films formed on the surface are two-dimensional and comply to the pre-phase formation condition. For example, on a face-centred crystal under monoepitaxy conditions (direct continuation of the solid phase lattice into solution) and with the Jackson–Temkin parameter $\beta_{JT} = 0.5E_b/kT = 0.3$ ($\Delta\mu \simeq 0.01kT$ for crystal growth from solution), the rate of new phase formation depends considerably on the reticular density of the face.^{92,93} It is lower on the most densely packed (111) FCC face than on the 'loose' (110) FCC face. According to Gilmer,^{5,6} this follows even from simple geometric considerations: an atom adsorbed on the (111) face of an FCC crystal is bound to three substrate atoms, as

compared to four on the (001) FCC face and five on the (011) FCC face, *i.e.* the reverse process (dissolution) on an FCC crystal will not occur as easily on the densely packed (111) face as on the 'loose' (110) face.

IV. Molecular dynamics models

The molecular dynamics (MD) method is less widespread than the MC method. Both methods provide information on the structures of phases interacting in electrolytes; it is impossible to obtain such data by statistical methods. The MD method is based on calculations of trajectories for separate adsorbed particles on a crystal surface and for groups of interacting atoms. The calculation of new positions occupied by the particles moving on the surface is made using classical equations of motion. Pair potentials (2b) are used; for densely packed structures, the Lennard-Jones potential summed over all atom pairs

$$U_{LJ}(r_{ij}) = \sum_{i < j} U(r_{ij}) = \sum_{i < j} 4E_L \left[\left(\frac{B_a}{r_{ij}} \right)^{12} - \left(\frac{C_{lat}}{r_{ij}} \right)^6 \right], \quad (38)$$

where $r_{ij} > 2.5(C_{lat}, B_a)$, is used most commonly. If $r_{ij} \leq 2.5(C_{lat}, B_a)$, potential (38) is complicated by introducing a Coulombic correction when solving electrochemical problems^{109,110}

$$\sum_{i < j} U(r_{ij}) = \sum_{i < j} 4E_L \left[\left(\frac{B_a}{r_{ij}} \right)^{12} - \left(\frac{C_{lat}}{r_{ij}} \right)^6 \right] + \frac{n_i n_j |e^-|^2}{4\pi\epsilon_0 \epsilon_r r_{ij}}.$$

For loose structures, the Stillinger–Weber (SW) potential,¹¹¹ which takes three-particle interactions into account, is used. The SW potential for a triplet of atoms (i, j, k) has the form¹¹² (if $B_a = C_{lat}$)

$$U_{CB}(r_{ijk}) = f\left(\frac{r_{ij}}{\sigma}\right) f\left(\frac{r_{ik}}{\sigma}\right) \left(\cos \theta_{ijk} + \frac{1}{3} \right)^2.$$

In this expression, the smoothing nonparametric function $f(r/\sigma)$, which is common at small interatomic distances r , approaches zero at $r \rightarrow 1.8\sigma$, and θ_{ijk} is the internal angle of the triplet.

The diffusion coefficient of adsorbed particles on the crystal surface is calculated using the Einstein's equation

$$D_{\text{surf}} = \frac{\{ \langle [\vec{R}_i''(t_2) - \vec{R}_i''(t_1)]^2 \rangle_i \}_c}{4(t_2 - t_1)},$$

where $\vec{R}_i''(t_1)$ and $\vec{R}_i''(t_2)$ are radius-vectors of the i th surface-adsorbed surfactant particle at instants t_1 and t_2 after the equilibrium state has been reached; $\vec{R}_i'' = (x_i, y_i)$ are vector projections on the 2D crystal surface; the angle brackets $\langle \dots \rangle_i$ and braces $\{ \dots \}_i$ mean statistical averaging over all i particles (on the surface and in the bulk of the 3D layer at the metal–electrolyte interface). A diffusing surfactant particle comes to an equilibrium position on the crystal surface by crossing the quasi-stable bridging positions. This crossing occurs through thermal activation. The minimum path, $l_{\min}$, that has to be overcome along a crystal surface with a surface concentration of active lattice sites N_s (10^{18} – 10^{19} m⁻² for cubic crystals) is controlled by the well-known 'directed movement of a salesman' relationship

$$l_{\min} = \frac{1}{N_s} + \frac{1}{L_l} \frac{2[2P_a(n, E) - 1]}{N_s^2},$$

where L_l is the characteristic size of the substrate tetragonal lattice and $P_a(n, E)$ is the probability of occupying a point by the i th surfactant particle to be adsorbed.

The equations for D_{surf} and $l_{\min}$ presented above are also valid under conditions of self-diffusion of particles, adsorbed on a metal crystal, along its surface. Adsorbed surfactant particles (including large organic molecules) can form structures 'cross-linked' with the near-surface metal layer. Calculation by the MD method of the height of surface barriers upon intrusion of surfactant particles into thin channels (pores) of a metallic adsorbent makes it possible

to assess the steric factor.¹¹³ The surface layer itself is considered within the MD method as a non-commensurate ‘cross-linked’ adsorption layer of particles of the same type as the crystal atoms.

Finally, the MD method determines the position of a surface-adsorbed particle with a local minimum of potential energy. Along one of the pathways for the formation of adsorption layers, minimisation of energy as a function of position of the adsorbed particle occurs through thermal activation. An increase in temperature accelerates the attainment of low-entropy surfactant state (self-organisation) on the crystal surface. Computer simulation by the MD method showed¹¹⁴ that in the temperature range close to the melting point, non-commensurate and adsorbed surfactant layers are transformed to a particular state that precedes melting. In this case, a correction for the attraction of particles, $\Delta E_{\text{attr}}(T, \theta_{\text{surf}})$, similar to the Frumkin’s correction factor²⁰ for the description of adsorption in the double electric layer, should be introduced to the Arrhenius equation for the diffusion coefficient

$$D_{\text{surf}}(T) = D_0 \exp \left\{ \frac{-[E_a + \Delta E_{\text{attr}}(T, \theta_{\text{surf}})]}{kT} \right\},$$

The value of $\Delta E_{\text{attr}}(T, \theta_{\text{surf}})$ depends on the degree of coverage of the crystal surface by surfactant particles and on the force of interaction of these particles between each other.

Combining the MD and MC methods provides a possibility of separating the first-kind phase transition as such¹¹⁵ from processes of rapid but continuous changes in the physical parameters measured. This possibility is particularly important in the simulation of non-commensurate surfactant particles on crystal surfaces in the electrochemical contact with an electrolyte. Computer simulation by the MC method (using the Lennard-Jones potential) of the near-surface layer of the (100) face of a FCC crystal showed¹¹⁶ that the temperature of non-commensurate first surface atomic layer is lower than that in the bulk of the crystal. Thus, non-commensurate adsorption layers stabilise or ‘slow down’ the near-surface crystal layers thus increasing its dynamic stability in a corrosive medium.

The MD method is widely used in the description of the movement of light particles (particularly, hydrogen¹¹⁷) on the surface and in the bulk of metal crystals.¹¹⁸ The diffusion of hydrogen is simulated by the MD method taking account of the reticular density of near-surface metal layers.¹¹⁹ It was found that light surfactant particles quickly form commensurate and non-commensurate phases on the crystal surface. As MD simulation shows,¹²⁰ non-commensurate islets are formed from particles in the first stage, in agreement with the VW model (see Fig. 3). In the crystal bulk, the hydrogen atoms which get into the metal due to an electrochemical process occupy tetra- or octahedral interstices. Comparison of results obtained using lattice gas models with MD results^{121, 122} makes it possible to identify reliably the topology of hydrogen absorbed by the crystal.

The vast majority (95%) of atom jumps from one interstice to another in the crystal bulk occur in a non-correlated Brownian way. For example, the movement of adsorbed hydrogen on the surface of a metal saturated with hydrogen occurs in a directed (correlated with the potential energy surface) way, along valley bottoms of the potential pattern. Computer simulations of this process virtually always use the lattice gas model, and calculations using this model are carried out by the MC method.¹²³

Hydrogen absorbed by a metal crystal changes the hierarchy of internal defects of various dimensionality, particularly near interfaces.^{123–125} 2D-Models of external and internal interfaces of polycrystals that form a lattice of coinciding points or densely-packed hexagons are used for the description of changes in macroscopic deformation characteristics, as well as the evolution of dislocation ensembles in terms of the monoatomic steps model by Frenkel–Kontorova.^{126–128} Computer simulation of dislocation rearrangements on a metal surface in the 3D-variant and assessment of the topology of the electric pattern of the process¹²⁹

make it possible to predict the adsorption coverage of not only singular but also diffuse surfaces.

The pair potentials used in MD computer simulations are relatively simple. For example, the following potentials are used in the description of hydrogen behaviour in palladium:¹²¹

$$U_{\text{Pd-Pd}}(r) = \begin{cases} \sum_{S=0}^6 K_S r^S, & r < r_0 \\ 0 & r \geq r_0 \end{cases}, \quad (39)$$

$$U_{\text{Pd-H}}(r) = \begin{cases} K_S \exp\left(-\frac{r}{\rho}\right), & r < r_1 \\ 0, & r > r_1 \end{cases},$$

$$U_{\text{H-H}}(r) = U_{\text{Pd-H}}(r),$$

where K_S is the volume factor characterising the height of the energy barrier (when a hydrogen atom passes through it) of a surface Pd-cluster (up to six Pd atoms); r is the interstice (pore) radius; r_0 is the radius of pore ‘cutting’ in the formation of a 2D lattice of surface Pd atoms; r_1 is the radius of an adsorbed hydrogen atom (it is smaller than that of a hydrogen atom, $r_{\text{H}} = 0.46$ nm, and depends on the nature of the transition metal adsorbent); the constants for palladium are as follows: $\rho = 0.05$ nm, $r_1 = 0.38$ nm, $K_S = 15.3$ eV.

The MD method is successfully used for the simulation of the co-adsorption of chalcophilic particles on surfaces of transition metal single crystals;^{128–130} it is also convenient for the simulation of water/metal interfaces.¹³¹ In early studies, lattice 3D-models of H₂O adsorption on a homogeneous metal surface (Hg) were calculated by the MC method using asymmetric multi-particle pair potentials.^{132–134} All calculation models are based on the Gouy–Chapman theory of the double layer structure. In analytical form, the pair potentials for the system water–platinum are represented as follows:

$$U_{\text{H}_2\text{O-Pt}} = U_{\text{O-Pt}}(r_{\text{O-Pt}}, \vec{R}_{\text{O-Pt}}) + U_{\text{H-Pt}}(r_{\text{H-Pt}}) + \quad (40)$$

$$+ U_{\text{H-Pt}}(r_{\text{Hb-Pt}}),$$

$$\text{where } U_{\text{O-Pt}} = [1894 \exp(-1.1004r) - 1886.3 \exp(-1.0966r)] f(\vec{R}) + 10^6 \exp(-5.3568r) [1 - f(\vec{R})],$$

$$U_{\text{H-Pt}} = 1.7142 \exp(-1.2777r),$$

where $f(\vec{R}) = \exp(-0.5208 \vec{R}^2)$, r is the distance between adsorption cells on the metal surface (pore radius), $\vec{R}$ is the projection of the vector of displacement of an adsorbed H₂O molecule on the metal surface; $\vec{R}$ and r are expressed in nm, and the potentials are in eV. In adsorbed water layers on single crystal faces, a periodic structure with a definite oscillation period was observed. The interaction energy $E_b \equiv U_{\text{H}_2\text{O-M}}$ for water–metal contacts is 51.1 (Al), 33.7 (Ni), and 36.6 kJ mol^{−1} (Cu). Based on results of MD simulations,¹³¹ four main configurations can be suggested for the geometry of a water molecule on an ideal metal ‘jelly-surface’ (Fig. 10); they do not differ much from the well-known Okamoto’s model¹³⁵ in which water molecules, whose ‘oxygen ends’ form an angle of 10–35° with the crystal surface.

Consideration of this process within the Ising model suggests the formation of periodic surface low-entropy water structures¹³⁶

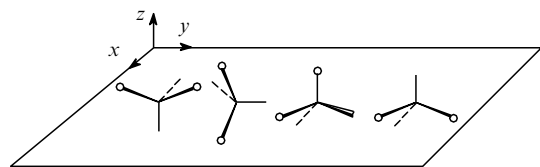


Figure 10. Variants of location of adsorbed water molecules on an ideal metal surface (according to results of the MD method).

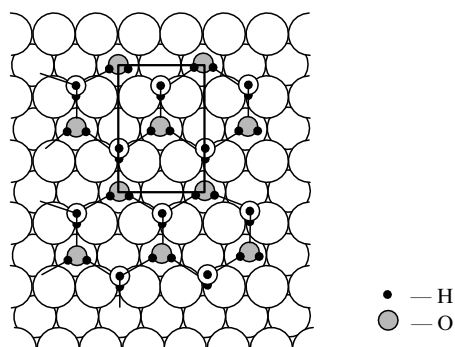


Figure 11. Schematic crystallographic model of adsorbed water on the (110) surface of a face-centred crystal.

(Fig. 11). On stepped crystal surfaces, water structures with a certain fractal dimensionality are formed.¹²⁴

It has been shown³¹ that water molecules are displaced from 'loose' steps to densely packed terraces by HSO_4^- or SO_4^{2-} ions, which have larger surface areas; a portion of water molecules are moved into the second adsorption layer.

V. Conclusions

Physicochemical patterns obtained by computer simulation of corrosion-electrochemical processes on metal–electrolyte interfaces satisfactorily describe many features of these complex phenomena. The computer models used now have good predicting ability. Although model Hamiltonians for the systems in question have many drawbacks, consideration of the main physical features of crystallisation – decrystallisation mechanisms provides the possibility to determine the types of materials that would be most stable in corrosive environments, to obtain information on the kinetics of corrosion-electrochemical processes, to predict the character of anticipated metal degradation and the structure of a galvanic coating to be formed.

Irrespective of the simulation method, the main direction of studies on computer simulation of electrochemical processes is related to the description of collective phase transitions. The speed and amount of memory available in modern computers make it possible to take into account not only the behaviour of separate particles in an ensemble (nearest environment) and the evolution of ensembles (clusters) in translation-invariant structures on the surface, but also mass and charge transfer of a material in a continuous medium. Therefore, the computer description of the behaviour of commensurate (floating) and non-commensurate (cross-linked) adsorption layers is based on non-linear relationships, which take into consideration the wave character of processes in these layers. One of the features of computer simulations is that they take into account correlated movements of adsorbed particles on the crystal surface involved in the formation of certain structures of adsorbed layers with fractal dimensionality and in adsorption-induced rearrangements (second-order phase transitions) in the crystal near-surface layer. It is believed that the development of mathematical methods and the coming of new-generation computers will make it possible to simulate the cooperative behaviour of resonance-linked double electric layers on the sides of the crystal and the electrolyte (the Frumkin double plane-parallel capacitor).

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Chemistry of semiconductor nanoparticles

R F Khairutdinov

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Abstract. Basic advances and prospects of further research in the field of the chemistry of nanoparticles are considered. The principal factors determining the unusual physicochemical properties of semiconductor nanoparticles are discussed. It is pointed out that the kinetics of chemical transformations on the surface and in the bulk of nanoparticles differs from that in infinite space. The classical equations of chemical kinetics can be used for the description of the processes on the surface of nanoparticles down to a size that exceeds the size of the reacting molecules by an order of magnitude. The large relative fraction of surface atoms in nanoparticles determines the size dependences of the melting temperature and pressure at which the crystal lattice of a semiconductor rearranges (*i.e.*, a phase transition occurs in the semiconductor crystal). Because of the comparable size of nanoparticles and the delocalisation radii of charge carriers non-linear optical effects arise and the redox properties and optical characteristics of nanoparticles become dependent on their size. The bibliography includes 219 references.

I. Introduction

It is usually assumed that the properties of solid semiconductors are independent of their size. However, this assumption is only valid for the solids containing a macroscopic number of atoms. Recent studies have shown that if the characteristic size of semiconductor particles is less than 10 nm, then many of their physicochemical properties appear to be essentially different from analogous properties of macroscopic objects. This is related to the fact that semiconductors are characterised by high energies of intermolecular interactions and a macroscopic crystal can be considered as one large molecule when its electronic properties are described. The electronic excitation of semiconductor crystals results in the formation of a loosely coupled electron–hole pair. In semiconductors, the size of the delocalisation area of such a pair can be many times larger than the lattice constant. The decrease in the size of a semiconductor crystal down to a size comparable with the delocalisation area of the electron–hole pair affects its electronic characteristics. The blue shift of the excitonic absorp-

tion band of a semiconductor crystal with decreasing its size is a remarkable manifestation of this effect.^{1–3} For CdS, which is the best studied semiconductor material, the blue shift of the excitonic absorption band is observed beginning from a crystal size of 5–6 nm. Ultrasmall semiconductor crystals are known in the literature as nanocrystals, particles with quantum size effect, or nanoparticles. The intensive studies of physicochemical properties of nanocrystals that have been carried out during the last decade have revealed a large number of other their unusual characteristics, such as the size dependence of the radiative lifetime of the electronic excitation, melting temperature, pressure needed for the rearrangement of the crystal structure (*i.e.*, for a phase transition to occur in the crystal), and character of the kinetics of chemical processes on the surface of nanoparticles.

Unusual physicochemical properties of nanoparticles are due to three main reasons. First, as has been noted above, the size of nanoparticles is comparable to the Bohr radius of the excitons in semiconductors. This determines the optical, luminescent, and redox properties of nanoparticles. Second, the surface atoms constitute a considerable fraction of the total number of the atoms of the nanoparticle. For example, a 5-nm CdS nanocrystal has about 15% of the atoms on the surface. The surface atoms contribute largely to the thermodynamic characteristics of solids and determine to a considerable extent the melting temperature and structural transitions for nanoparticles. Third, the natural size of the nanoparticles is comparable with the size of molecules. This determines the peculiarities of the kinetics of chemical processes on the surface of nanoparticles.

Most of the studies of semiconductor nanoparticles are of interdisciplinary character and are devoted to investigation of their colloidal solutions. To date, nanoparticles of ZnO, Fe₂O₃, SiO₂, MoS₂, CdS, HgS, GaP, Cd₃P₂, BiI₃, PbI₂, and a number of other semiconductors have been synthesised and investigated. For several semiconductor nanoparticles, the structure of the electronic bands and electrochemical characteristics, optical properties and photochemical reactions, processes of charge separation and recombination, mechanical and thermal properties, regularities of reactions of the molecules adsorbed on the surface have been investigated.

In this review, the major achievements in the chemistry of semiconductor nanoparticles are considered. Methods for the synthesis of nanoparticles, quantum size effects characteristic of semiconductor nanoparticles, photocatalytic processes with participation of semiconductor nanoparticles and films prepared on their base are considered. The primary attention is given to the prospects of the use of the nanostructures to implement practically important processes of photomineralisation of environmentally

R F Khairutdinov N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117977 Moscow, Russian Federation. Fax (7-095) 938 21 56. Tel. (7-095) 939 74 85. E-mail: rafail@center.chph.ras.ru

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hazardous organic compounds. In the concluding section of this review, a brief outline of feasible lines for further development of nanochemistry is given.

II. Methods for the synthesis of nanoparticles

Methods for the synthesis of nanoparticles can be divided into three main groups.

1. Synthesis of semiconductor nanoparticles in solutions of the corresponding salts by controlled addition of anions (or cations) or by hydrolysis.^{4–19}

2. Preparation of nanoparticles as a result of phase transformations.^{20–22}

3. The synthesis of nanoparticles in aerosols.^{23–25}

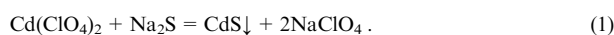
The radiation-chemical method for the synthesis of nanoparticles is also known.³ Methods for the synthesis of complex multicomponent nanoparticles have been developed. Most of the semiconductor colloidal systems studied to date have been obtained by synthesising the semiconductor nanoparticles in homogeneous solution.

Commercial colloidal solutions containing the SnO₂ nanoparticles (with an average diameter of 3 nm) are available from Johnson Matthey (USA). A Degussa P25 TiO₂ powder containing 80% of anatase and 20% of rutile is often used in photocatalysis.²⁶

1. Synthesis of semiconductor nanoparticles in colloidal solutions

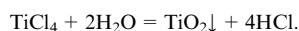
The semiconductor nanoparticles are prepared by chemical synthesis in homogeneous solutions,^{4–7} in micelles, vesicles, and Langmuir–Blodgett films,^{8–11, 27, 28} in polymers,^{12–14} in glasses,^{15, 16} in zeolites,^{17–19} and in β -cyclodextrin.²⁹

The easiest and most common method for the preparation of semiconductor nanoparticles is the synthesis from the starting reagents in solution by arresting the reaction at a definite moment.^{4–7} Nanoparticles of metal sulfides are synthesised by a reaction of a water-soluble metal salt and H₂S (or Na₂S) in the presence of an appropriate stabiliser such as sodium metaphosphate. For example, the CdS nanoparticles can be synthesised by mixing Cd(ClO₄)₂ and Na₂S solutions:



The growth of the CdS nanoparticles in the course of reaction is arrested by an abrupt increase in pH of the solution.

Colloidal particles of metal oxides can be obtained by hydrolysis of the corresponding salts. For example, the TiO₂ nanoparticles are readily formed in the hydrolysis of titanium tetrachloride

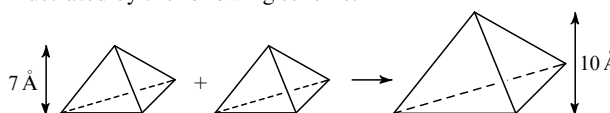


Unfortunately, most of the colloidal solutions of nanoparticles have low stability towards coagulation and possess a large size dispersion. Coagulation can be prevented by passivation³⁰ of the surface of nanoparticles by hydroxyl ions,³¹ amines,³² or ammonia.¹³ Yet another procedure for the stabilisation of colloidal solutions of nanoparticles is the coating of their surfaces with polyphosphates³³ or thiols.^{34–38} As a result, one can obtain a stable colloidal solution of nanoparticles, isolate the nanoparticles as a powder, and then prepare a colloidal solution again by dispersing the powder in a solvent.

Usually, the methods for the synthesis of nanoparticles discussed above result in a nonuniform size distribution. It is possible to decrease the width of this distribution by monitoring the synthetic procedures and using high-pressure liquid chromatography and capillary electrophoresis.^{39, 40} In the latter case, the separation of nanoparticles is achieved due to the different charge/size ratios for nanoparticles of different sizes.

Small monodisperse semiconductor clusters can be obtained by performing the synthesis inside zeolite cages.^{17–19, 41, 42} Thus Cd₄S₄ clusters were synthesised inside zeolite Y.^{17–19}

It is possible to synthesise larger semiconductor nanoparticles of fixed size by introducing additional molecules to a small initial cluster stabilised by organic ligands in a colloidal solution.^{7, 43–47} For instance, it was found that the size of CdS clusters coated with thiophenolate ions can be increased if a metal sulfide is added to the solution.⁴⁵ Such a polymerisation of inorganic compounds appeared to be applicable to the synthesis of large semiconductor clusters of strictly fixed size from small particles. Wang and Herron⁴⁸ succeeded in obtaining the [Cd₂₀S₁₃(SC₆H₅)₂₂]^{8–} clusters containing 55 cadmium and sulfur atoms from the pyramidal [Cd₁₀S₄(SC₆H₅)₁₆]^{4–} clusters containing 30 cadmium and sulfur atoms.³⁴ The introduction of additional five sulfide ions leads to the fusion of two small clusters into one larger cluster. The process of the formation of a large cluster from two small ones can be illustrated by the following scheme:



The pyramidal structure of the [Cd₂₀S₁₃(SPh)₂₂]^{8–} clusters was confirmed by X-ray analysis. Further addition of sulfide ions made it possible to obtain the Cd₃₂S₁₄(SC₆H₅)₃₆ tetrahedral clusters containing 82 cadmium and sulfur atoms.⁴⁶

Usually, it is assumed that the nanoparticles containing several hundreds of atoms have a spherical or ellipsoidal shape. However, recent investigations have shown that the nanoparticles often have clearly defined facets and their shape is analogous to that of macroscopic crystals.^{49, 50}

The shape and size of nanoparticles is determined by electron microscopy. For a rough estimation of the size of nanoparticles, it is also possible to use the optical spectra of colloidal solutions. These estimates are based on the dependence of the position of the excitonic band of nanoparticles on their size. However, overestimated values are obtained for small nanoparticles⁴⁸ (this problem is discussed in more detail below).

2. Dispersion of macroscopic particles in solutions

It is possible to obtain semiconductor nanoparticles by sonication of colloidal solutions of large particles. Nanoparticles of layered semiconductors are also formed upon mere dissolution of large particles in an appropriate solvent, which was observed for MoS₂ and WS₂.²⁰ Layered MoS₂-type semiconductors are characterised by a weak van der Waals interaction between separate S–Mo–S layers. In the course of dissolution, the solvent molecules penetrate between the layers of the semiconductor and destroy large particles. In the case of MoS₂, the process of destruction can proceed until the formation of a two-layer particle. No further stratification of the semiconductor occurs, since the formation of single-layer particles is accompanied by a considerable increase in the free energy of the system.^{20, 21, 30}

Sonication of a disperse system of large semiconductor particles can also result in the formation of nanoparticles. The nanoparticles of MoS₂, WS₂,^{20, 21} PbI₂,⁵¹ and α -Fe₂O₃^{52, 53} were obtained by this procedure.

Nanocrystals of layered PbI₂-type semiconductors have a disk-like shape and discrete ‘magic’ sizes of the disks.⁵¹ For these semiconductors, a stable nanoparticle of a minimum size is assumed to be the smallest crystallite conserving the hexagonal symmetry of the macroscopic crystal. Such a crystallite is composed of two seven-atom iodine layers and two lead layers. Large stable nanoparticles are obtained from this ‘seed’ by the layer-by-layer addition of extra iodide ‘caps’ symmetrically around the perimeter. An analogous structure is also assumed for MoS₂ nanoparticles.^{30, 54}

3. Gas-phase synthesis of nanoparticles

The gas-phase synthesis of TiO₂ and Si nanoparticles was carried out by Visca and Matijevic⁵⁵ and Fojtik *et al.*⁵⁶ Thus the Si nanoparticles are formed in 67% yield in the combustion of SiH₄

under oxygen-deficient conditions as a result of thermolysis of SiH_4 .

An interesting method for the gas-phase synthesis of nanoparticles of various materials has been suggested:^{23–25} the nanoparticles were obtained by pulsed laser vapourisation of metals in a chamber filled with a known amount of a reagent gas and by controlled condensation of nanoparticles onto the support. A schematic view of the installation for the synthesis of nanoparticles is given in Fig. 1. As the metal atoms diffuse from the target to the support, they interact with the gas to form the desired compound (for instance, oxide in the case of oxygen, nitride for nitrogen or ammonia, carbide for methane, *etc.*).

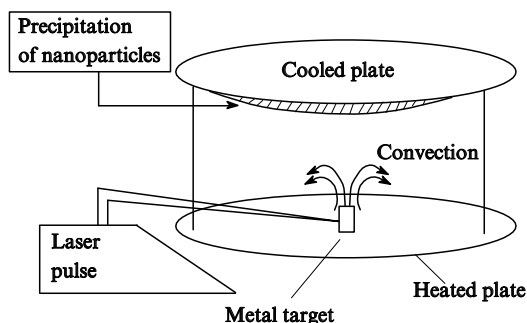


Figure 1. Schematic view of the installation for the synthesis of nanoparticles by laser vapourisation of metals.

The pulsed laser vapourisation of metals in the chamber is a modification of the known method for the synthesis of metal compounds in a diffusion cloud chamber and makes it possible to prepare nanoparticles of mixed molecular composition, such as mixed oxides/nitrides and carbides/nitrides or mixtures of oxides of different metals. Along with the reagent gas, the chamber contains an inert gas, such as He or Ar, at a pressure of 10^{-2} –1 Torr, which favours the establishment of steady convection between the heated bottom plate and cooled top plate. In an experiment with a single pulse of a Nd:YAG laser (532 nm, 15–30 mJ pulse⁻¹, 10^{-8} s), over 10^{14} metal atoms are vapourised. A new compound is formed due to the reaction between the ‘hot’ metal atoms and the gas molecules, which is accompanied by the energy loss of the molecules formed by collisions with the inert gas atoms. The metal atoms that did not enter into reaction and the molecules of the new compound are carried by convection to the nucleation zone on the cooled top plate. By changing the composition of the inert gas and the reagent gas in the chamber and varying the temperature gradient and laser pulse power, it is possible to control the elemental composition and size of nanoparticles that are obtained.

4. Synthesis of nanoparticles of mixed composition

The high efficiency of recombination of the light-generated electrons and holes presents obstacles to the practical application of the semiconductor nanoparticles in photocatalysis. In this connection, the semiconductor nanocrystal hetero-structures composed of semiconductors with different structures of the electronic levels are of considerable interest. With these structures, it is possible to attain high quantum yields of charge separation. The nanoparticles schematically shown in Fig. 2 belong to this class of hetero-structures. The structures analogous to that shown in Fig. 2a are known for CdS/TiO₂,^{57–60} CdS/ZnO,^{57,61} CdS/AgI and CdS/HgS,^{62,63} Cd₃P₂/TiO₂ and Cd₃P₂/ZnO,⁶⁴ and AgI/Ag₂S.⁶⁵ For CdS/TiO₂, photoexcitation into the absorption band of CdS results in the electron transfer from CdS to TiO₂, while the hole remains in CdS. These structures are also of interest as nanoscale rectifier units for molecular electronics.⁶⁶

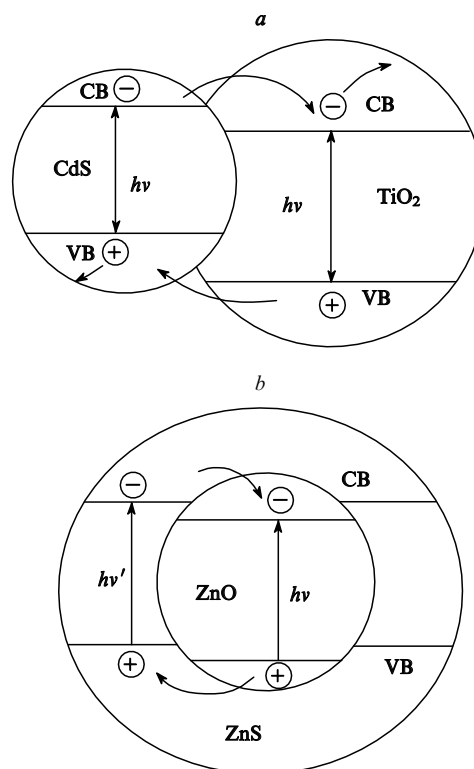


Figure 2. Schematic view of hetero-nanoparticles of different structure. (a) and (b), see text; CB stands for conduction band; VB stands for valence band.

The formation of hetero-structures of the ‘core–shell’ type (see Fig. 2b) has been demonstrated using the CdSe/ZnS and ZnS/CdSe nanoparticles as an example.⁶⁷ These nanoparticles are obtained by controlled precipitation of semiconductor molecules of one type (‘shell’) on the pre-synthesised nanoparticles of another type (‘core’). The synthesis of the shell is carried out in colloidal solution by methods analogous to those for the synthesis of one-component nanoparticles considered above. The crystalline shells grow on the nanocrystal core despite the fact that the lattice constants in CdSe and in ZnS differ by 13%.

The following ‘core-shell’ type nanoparticles have also been synthesised: HgS/CdS,⁶³ ZnS/ZnO and ZnO/ZnSe,^{68,69} TiO₂/SiO₂ and TiO₂/SnO₂,⁷⁰ and TiO₂/ZnO.⁷¹ These hetero-nanoparticles can, in turn, be coated with a layer of one more semiconductor. Below we shall consider the use of nanocrystal hetero-structures in photocatalysis.

5. Preparation of nanostructured semiconductor films

Thin films of semiconductor nanoparticles are of considerable practical interest. Synthesis of these films is carried out by precipitation of pre-formed nanoparticles from colloidal solutions onto the supports, by direct precipitation of semiconductor molecules onto the support, and by oxidative hydrolysis of the corresponding metal salts at the anode. Usually, the films are 0.1–1 μm thick. The following films of semiconductor nanoparticles are known: SnO₂,⁷² ZnO,^{61,73} TiO₂,⁷⁴ WO₃,^{75,76} and Fe₂O₃.⁷⁷ The SnO₂, ZnO, TiO₂, and WO₃ films were obtained by precipitation of nanoparticles. Direct precipitation of semiconductor molecules onto the support is used to prepare films of nanoparticles of semiconductors on the basis of Group II–VI elements.

Oxidative hydrolysis of TiCl₃ at pH 2.3 and a platinum anode potential of 0 V vs. saturated calomel electrode (SCE) results in the formation of nanoparticles with an average diameter of 1–2 nm on the anode surface.⁷⁸

Nanostructured films containing nanoparticles of different semiconductors can be prepared by coprecipitation. A schematic view of such a film supported by the optically transparent electrode is given in Fig. 3. Yet another method for the preparation of such films consists in wetting of a plate coated with a film of a certain type of nanoparticles with a solution containing metal ions followed by wetting of the plate with a solution containing sulfide ions. This procedure was used for the synthesis of films containing ZnO and CdS nanoparticles.^{61,79}

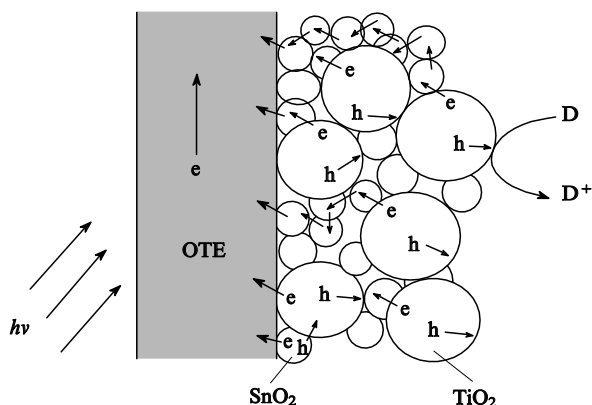


Figure 3. Schematic view of the process of photostimulated charge separation in the nanostructured film composed of TiO₂ and SnO₂ nanoparticles adsorbed on an optically transparent electrode (OTE).

III. The quantum size effects

1. Specific features of the kinetics of chemical processes on the surface of nanoparticles

Surface reactions determine the behaviour of nanoparticles in colloidal solutions and the possibility of using the semiconductor nanoparticles in photocatalysis. For reagents adsorbed on the surface of nanoparticles, a chemical reaction cannot be considered as a process occurring in an infinite volume with a constant average density of the molecules. This is associated with the fact that the surface area of nanoparticles is rather small and comparable with the size of the reagents. In such a system, the kinetics of a bimolecular chemical reaction differs from the classical kinetics.

The mathematical approach to the classical, or deterministic, chemical kinetics ignores fluctuations in the concentration of reacting molecules. However, the nanoparticles composed of a small number of reacting molecules are characterised by relatively large fluctuations in the number of reagents. This results in different changes in the concentration of reagents on the surface of different nanoparticles with time; the general kinetic law for a macroscopic sample can be obtained by averaging the kinetics over all nanoparticles. A mathematical description of the processes occurring in such systems is based on the use of a stochastic approach, which takes into account the statistical fluctuations in the number of reacting molecules.⁸⁰

General regularities in the kinetics of diffusion-controlled reactions for a small number of reacting molecules have been analysed.^{81,82} The kinetics of a bimolecular reaction was analysed assuming that the reaction can be characterised by the rate constant k , which is the same for all the reagent pairs. The results of these studies can be used for the analysis of the kinetics of reactions occurring on the surface of nanoparticles.

For a reaction



the kinetics of the loss of the reagents is described by the following equation:⁸³

$$\frac{\bar{N}(t)}{\bar{N}(0)} = \sum_{n=1}^{\infty} B_n \exp\left[-\frac{1}{2}n(n-1)kt\right] \quad (3)$$

where $\bar{N}(t)$ and $\bar{N}(0)$ are the current and initial concentrations of the reagents on the surface of nanoparticles averaged over the sample containing a macroscopic number of nanoparticles,

$$B_n = \frac{(2n-1)}{2^n} \frac{\exp[-\bar{N}(0)]}{\bar{N}(0)} \sum_{j=n}^{\infty} \frac{\bar{N}(0)^j}{(j-n)!} \frac{\Gamma[(j-n+1)/2]}{\Gamma[(j+n+1)/2]},$$

$$j = n, n+2, n+4, \dots$$

and $\Gamma(x)$ is the gamma function.

The assumption in Eqn (3) that the rate constant k is the same for all the reagent pairs may appear to be invalid for small nanoparticles. Actually, it was shown⁸⁴ that Eqn (3) is only valid for nanoparticles the size of which exceeds that of the reagents by at least an order of magnitude. In Fig. 4, the results of the analysis of the kinetic curves of the reaction occurring on the surface within a circle of radius R are presented as an example. The analysis was performed using Eqn (3) and the curves were calculated by the Monte Carlo method for various size of the reagent particles and the circle. The triplet-triplet annihilation of molecules recombining at a distance of R_{ef} was considered as a model reaction. It can be seen that for $R < 10R_{ef}$ the k value becomes dependent on the radius of the circle and, hence, Eqn (3) is no longer valid for small radii R .

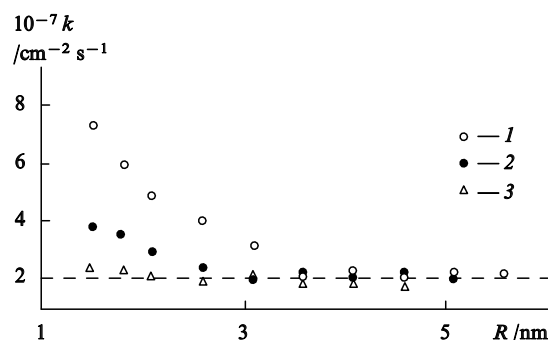


Figure 4. The dependence of the rate constant for the triplet-triplet annihilation on the circle radius for different effective radii of the triplet-triplet annihilation.

R_{ef} / Å: (1) 4.3; (2) 2.9; (3) 2.3.

The Monte Carlo method can also be used for the description of the kinetics of processes on the surface of nanoparticles. The number of reagent molecules on the surface of each nanoparticle is small, and calculations of the reaction kinetics by the Monte Carlo method do not require much effort. The parameters of the process used in the calculations are chosen so as to achieve the best agreement between the calculated and experimental kinetic dependences.^{84,85}

Only a few processes occurring on the surface of nanoparticles have been studied to date. The triplet-triplet annihilation of the zinc tetraphenylporphyrin (ZnTPP) molecules adsorbed on the surface of disk-like MoS₂ nanoparticles, whose size did not exceed 2 nm, has been studied.⁸⁶ The annihilation of the triplet molecules occurs by an exchange mechanism and its efficiency (w) is determined by the distance between the reagents (r)^{87,88}

$$w(r) = v \exp\left(\frac{-2r}{a}\right), \quad (4)$$

where v and a are the parameters of the process.

Typical curves of the decay of triplet-excited molecules on the surface of MoS₂ nanoparticles and the results of their analysis by the Monte Carlo method are shown in Fig. 5. This analysis appeared to be very 'sensitive' to the parameters of the interaction

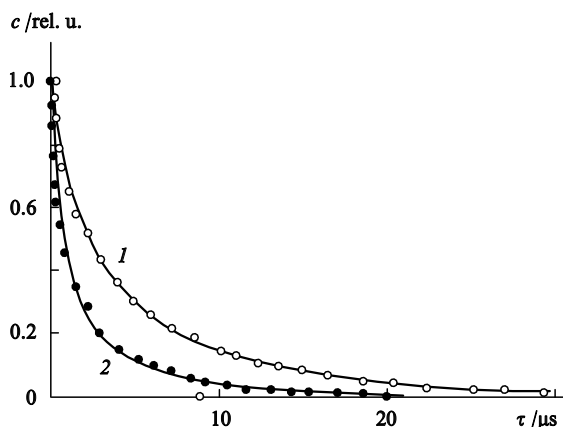
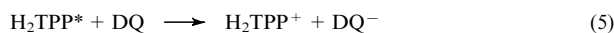


Figure 5. The decay curves of triplet-excited ZnTPP molecules on the surface of the MoS₂ nanoparticles. The average number of the triplet-excited ZnTPP molecules on the surface of the MoS₂ nanoparticles is equal to 6.4 (1) and 22 (2); the lines correspond to the experimental data, the dots correspond to the results of the Monte Carlo calculations.

between the triplet molecules and their diffusion over the surface of MoS₂ nanoparticles. The following values of the parameters were obtained: $\nu = 10^6 \text{ s}^{-1}$ and $a = 3 \text{ \AA}$, and the diffusion coefficient of the zinc porphyrin molecules over the surface (D) was found to be equal to $10^{-8} \text{ cm}^2 \text{ s}^{-1}$.

Quenching of the singly excited molecules of ZnTPP and its metal-free analogue (H₂TPP) by various quinones (Q) on the surface of the MoS₂ nanoparticles has been studied.⁸⁴ The kinetics of the processes was analysed by both the Monte Carlo method and kinetic equations⁸⁵ derived for the reactions occurring on the surface of the disk-like nanoparticles. The decay curves of the singlet-excited H₂TPP molecules in the reaction with duroquinone (DQ)



are shown as an example in Fig. 6.

The theoretical decay curves (dots in Fig. 6) calculated by the Monte Carlo method are in good agreement with the experimental ones.

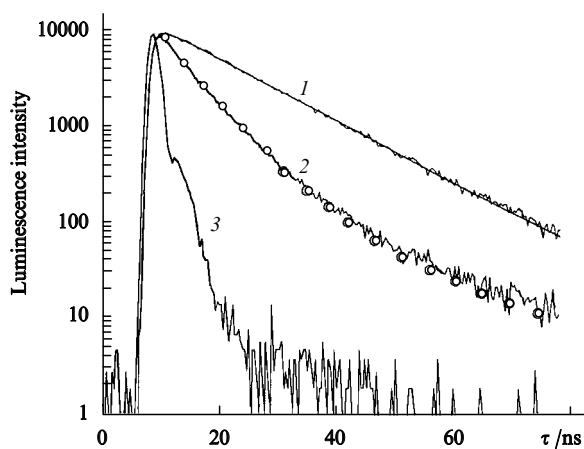


Figure 6. The kinetics of the luminescence decay of the singlet-excited H₂TPP molecules on the surface of the MoS₂ nanoparticles; (1) in the absence of the quencher; (2) each nanoparticle is capped, on the average, with five duroquinone molecules; (3) the shape of the excitation light pulse. The dots on curve 2 correspond to the results of the Monte Carlo calculations.⁸⁴

The detailed kinetic analysis of bimolecular processes of electron and energy transfer on the surface of nanoparticles of various shapes has been carried out.^{84, 89} It has been possible to obtain an analytical solution of the kinetic problem only for the reactions occurring on the surface of planar disk-like nanoparticles. It has been shown that the corresponding equations derived for the disk-like nanoparticles can be applied to nanoparticles of different (*viz.*, cubic, spherical, and tetrahedral) shape.

The kinetic equations for the processes of electron and energy transfer on the surface of nanoparticles are rather complicated. For example, the kinetics of electron transfer from a donor to acceptors on the surface of disk-like nanoparticles is described by the following equation:⁸⁵

$$\frac{N(t)}{N(0)} = \quad (6)$$

$$= \frac{2}{R^2} \int_0^R r_0 \exp \left\{ -\bar{n} \left[1 - \exp \left\{ -\frac{1}{\pi(R^2 - d^2)} f(r_0, t) \right\} \right] \right\} dr_0,$$

where $\bar{n}$ is the average number of the acceptor molecules on each surface of a disk-like nanoparticle, d is the sum of the donor and acceptor radii,

$$f(r_0, t) = \int_d^{R+r_0} \left\{ 1 - \exp[-w(r)t] \right\} 2r \varphi_{\max} dr, \quad (6a)$$

$w(r)$ is the function describing the dependence of the probability of the electron transfer from the donor to the acceptor on the distance between them, and the meaning of other parameters is evident from Fig. 7.

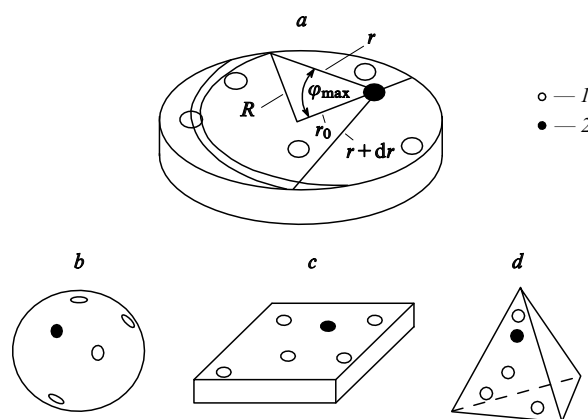


Figure 7. Disk-like (a), spherical (b), square (c), and pyramidal (d) nanoparticles. The acceptor (1) and donor (2) species.

The use of the kinetic equations similar to Eqn (6) for the description of the processes on the surface of nanoparticles requires time-consuming calculations. In this connection, the problem of applicability of simpler kinetic equations derived for the processes occurring on the unbounded surface to nanoparticles appears to be important.⁸⁹

To solve this problem, an analysis according to the following scheme was performed in considering specific equations used for the description of the processes occurring with participation of nanoparticles. First, the decay curves of the reagents on the surface of nanoparticles were calculated by the Monte Carlo method. Then, these curves were considered as 'experimental' kinetic curves and were used to find the characteristics of the process using the corresponding kinetic equations. The coincidence between the calculated characteristics and the

corresponding parameters used in the calculations of the kinetic curves by the Monte Carlo method served as the criterion of the applicability of the kinetic equations for the description of the processes occurring on the surface of nanoparticles.

It was shown^{84,89} that the classical equations of chemical kinetics can be used to determine the parameters of the processes occurring on the surface of nanoparticles down to their characteristic linear size that is 2–7 times larger than the size of reacting molecules or effective radii of the interaction between them. The application of the classical equations of chemical kinetics to nanoparticles of smaller size results in considerable errors in the calculations of characteristics of the processes. For small nanoparticles, the parameters of chemical reactions can be calculated using the corresponding equations for the nanoparticles or by the Monte Carlo method.

The following equation is an analogue of Eqn (6) for an unbounded surface and the $w(r)$ function defined by Eqn (4):

$$\frac{N(t)}{N(0)} = \exp \left[-c \left(\frac{\pi a^2}{4} \ln^2 vt - \pi d^2 \right) \right], \quad (7)$$

where c is the surface concentration of an acceptor. The possibility of using Eqn (7) to analyse the kinetic curves on the surface of disk-like nanoparticles of various size has been considered.⁸⁹ It was shown that Eqn (7) can be used for calculating the parameters of interaction between the reagents (a and v) down to the disk size 7 times greater than the sum of the donor and acceptor radii.

2. The effect of the nanoparticle size on their optical and luminescent characteristics

a. Dependence of the optical and luminescent characteristics of nanoparticles on their size

It seems evident that the excitation energy of small semiconductor crystals must differ from that of a large semiconductor. In fact, the energy of the electronic excitation of an isolated molecule is usually considerably higher than the energy of the interband transition in the corresponding macroscopic semiconductor. Hence, a size range must exist in which the low energy of the electronic excitation of a crystal changes smoothly to the high value characterising the individual molecule on going from the crystal to the molecule. For semiconductor crystals, such a transition occurs in the nanometric range. So far, the effect of the nanoparticle size on their optical spectra has been found for many types of semiconductors.^{3,38,90–108} The optical spectra of CdSe nanoparticles of various size are shown in Fig. 8a as an example.¹⁰⁸ It can be seen that the absorption band of nanoparticles does shift to the shorter wavelength (blue) region as their size decreases.

The quantitative dependence of the minimum electronic excitation energy of a nanoparticle on its size can be approximately calculated taking into account the relation between the uncertainty in the position (Δx) and the uncertainty in the momentum (Δp) of the exciton in a macroscopic crystal and in a nanoparticle:

$$\Delta p \Delta x \geq \frac{\hbar}{2}. \quad (8)$$

The delocalised exciton has no fixed position in the periodic potential of the macroscopic crystal, whereas its energy (E) and momentum ($p = \hbar k$) are strictly fixed, and at small k

$$E = \frac{\hbar^2 k^2}{2\mu}, \quad (9)$$

where μ is the effective mass of the exciton.¹⁰⁹ For a nanoparticle, the uncertainty in the position of the exciton depends on the characteristic size of the nanoparticle

$$\Delta x = d.$$

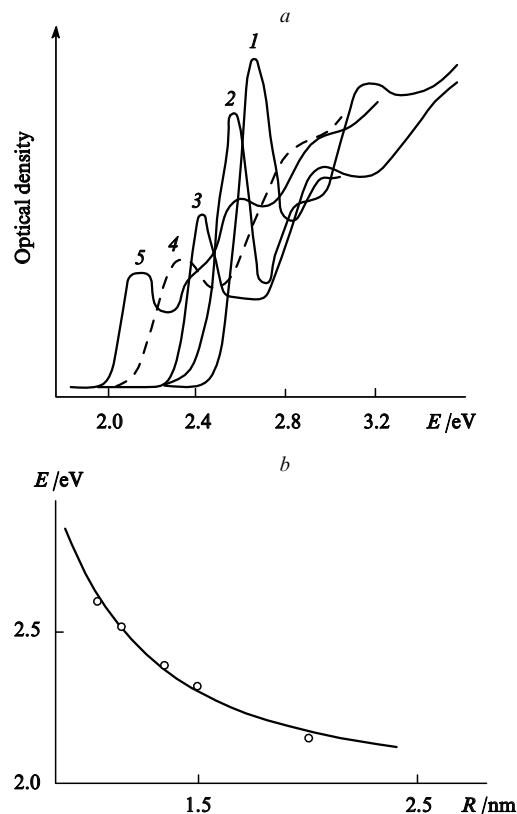


Figure 8. The absorption spectra of the CdSe nanoparticles of various size (a) and the dependence of the energy at the maximum of the absorption band of the CdSe nanoparticles on their radius (b).

(a): R /nm: (1) 2.1; (2) 2.3; (3) 2.7; (4) 3; (5) 4; (b) the line corresponds to the $1/R^2$ dependence.

Assuming that the relation between the energy and momentum is independent of the particle size, the exciton energy will change in inverse proportion to the square of the characteristic size of the nanoparticle.

A more rigorous analysis of the effect of the size on the energy of excitonic excitation of spherical nanoparticles (E_n) gives the following relationship:

$$E_n = E_m + E_l, \quad (10)$$

where E_m is the energy of the interband transition in a macroscopic semiconductor, E_l is the energy of exciton localisation in the nanoparticle:

$$E_l = \frac{\hbar^2 n^2}{8R^2\mu} - \frac{1.78e^2}{\epsilon R} - 0.248E_R^*, \quad (11)$$

where n is an integer, R is the radius of the nanoparticle, $\mu = (m_e^{-1} + m_h^{-1})^{-1}$ (m_e and m_h are the electron and hole effective mass, respectively), ϵ is the dielectric constant of the semiconductor, and E_R^* is the effective Rydberg energy.^{1,2,110} The first term on the right of the equation is predominant, and its nature was considered above, the second term takes into account the Coulomb interaction between the electron and hole inside the nanoparticle, and the third term is responsible for the spatial correlation. The n values larger than 1 in Eqn (11) correspond to the exciton transitions to higher excited states (see Fig. 8a).

In the case of anisotropic semiconductors, the electron and hole effective masses depend on the direction of motion and Eqn (11) becomes more complex with allowance for this anisotropy⁵¹

$$E_{n_x, n_y, n_z} = \frac{\hbar^2}{8} \left(\frac{n_x^2}{\mu_x L_x^2} + \frac{n_y^2}{\mu_y L_y^2} + \frac{n_z^2}{\mu_z L_z^2} \right) - \frac{1.78e^2}{\epsilon R} - 0.243E_R^*, \quad (12)$$

where n_x , n_y , and n_z are integers; μ_x , μ_y , and μ_z are the effective masses of the exciton along the corresponding directions, and L_x , L_y , and L_z are the dimensions of the nanoparticle.

The dependence of the energy at the maximum of the absorption band of CdSe nanoparticles on their radii calculated from the data in Fig. 8a is shown in Fig. 8b. It can be seen that the exciton energy of nanoparticles is well described by the $1/R^2$ dependence.

The effective mass approximation and, hence, Eqn (11) become inapplicable for small nanoparticles. The observed values of the exciton energies of nanoparticles appear to be lower than those predicted from Eqn (11). A more exact expression for the exciton energy can be found by quantum-chemical methods.^{111, 112} However, quantum-chemical calculations cannot also be applied to very small nanoparticles. The lower confidence level of the exciton energy calculations varies for different semiconductors. In the case of the effective mass approximation, it is determined by the value of the Bohr radius of the exciton. The dependence of the energy of the first excitonic CdS band on the nanoparticle size and the results of the corresponding calculations performed in the effective mass approximation⁴⁸ and by quantum-chemical methods¹¹³ are shown in Fig. 9 as an example.

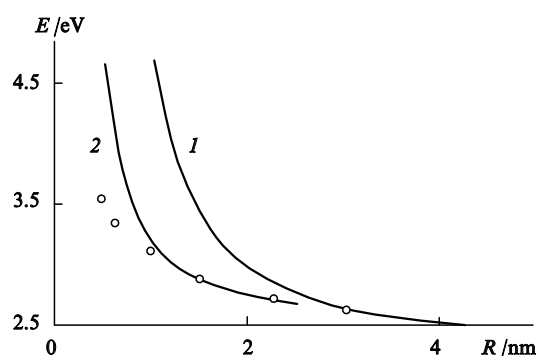


Figure 9. Dependence of the energy of the first excitonic band of CdS on the nanoparticle size and the results of the corresponding calculations performed in the effective mass approximation (1)⁴⁸ and by quantum-chemical methods (2).¹¹³

Equation (11) is often used for the estimation of the size of nanoparticles. Usually, the last two terms on the right side of this equation are neglected. For the first excitonic transition we have

$$R = \frac{\hbar}{\sqrt{8\mu E_1}}. \quad (13)$$

As was mentioned above, the effective mass approximation and, hence, Eqn (13) is inapplicable for very small nanoparticles. The use of Eqn (13) results in overestimation of the size of nanoparticles; the smaller the true size of nanoparticles the larger the overestimation.

Another manifestation of the size effect in the optical characteristics of nanoparticles is the blue shift of their optical spectrum, which occurs when an excess electron is injected into the nanoparticle.^{114–121} Three different reasons may account for the shift: first, the increase in the exciton energy due to the influence of the electric field of the excess electron;^{119, 121} second, the effect of filling the lowest vacant state with the excess electron whose excitation to a higher vacant state requires higher energy;^{122, 123} and third, a decrease in the oscillator strength of the excitonic transition due to the effect of trapped electrons and holes.^{13, 124}

Recombination of light-generated charges results in luminescence of nanoparticles. In this case, the blue shift is also observed

as the nanoparticle size decreases. The luminescence of ZnO,^{61, 68, 68, 117} ZnS,^{125–127} CdS,^{128–136} and CdSe^{137, 138} has been studied in detail.

The luminescence spectra of colloidal CdS solutions are shown in Fig. 10. It can be seen that the decrease in the nanoparticle size results in a shift of the luminescence spectra towards the short-wavelength region. The kinetics of the luminescence decay of nanoparticles is nonexponential and the characteristic time of decay for nanoparticles of the same size depends on the luminescence wavelength. The shorter-lived luminescence corresponds to a higher energy of the emitted light quantum. The dependence of the lifetime of the excited state on the wavelength is explained by the contribution of the Coulomb interaction between the electron and hole to the energy of the emitted light quantum.¹³⁹

$$\hbar\nu = E - (D_+ - D_-) + \frac{e^2}{\epsilon R_h}, \quad (14)$$

where E is the minimum excitation energy of nanoparticles, D_- and D_+ are the depths of the electron and hole traps, respectively, and R_h is the distance between the electron and hole. If the electron–hole recombination follows the tunnel mechanism, then the pairs with small R_h emit light faster and at higher energies than the pairs with larger R_h .

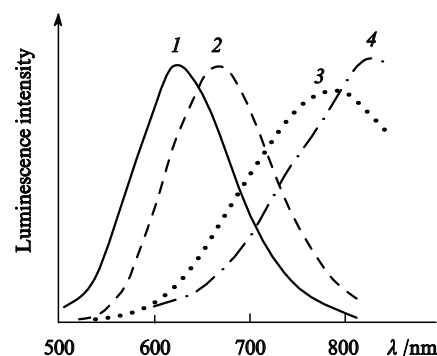


Figure 10. The luminescence spectra of colloidal solutions of CdS nanoparticles in acetonitrile.¹³¹

Average size of nanoparticles /nm: (1) 2.5; (2) 3; (3) 3.7; (4) > 4.2.

b. Dependence of the intensity of electronic transitions and radiative lifetimes on the nanoparticle size.

The increase in the volume-normalised oscillator strength of the excitonic absorption with the decrease in the size of nanoparticles^{110, 140–143} is one more manifestation of the quantum size effect. This is associated with the increase in the overlap integral of the electron and hole wave functions with the decrease in the size of nanoparticles.

For large spherical semiconductor particles ($R \gg a_B$, where a_B is the Bohr radius), the overlap integral of the wave functions is independent of the particle size and the oscillator strength of excitonic absorption (f) is determined by the macroscopic dipole moment of the transition. Assuming that the exciton moves coherently throughout the particle, the number of energy levels in the excitonic band is equal to $(R/a_B)^3$ (see Ref. 110). In the low-temperature limit, the integrated oscillator strength of all $(R/a_B)^3$ levels is concentrated in the lowest excitonic transition. The oscillator strength of the particle increases linearly as the volume increases

$$f \propto \left(\frac{R}{a_B} \right)^3,$$

whereas the volume-normalised oscillator strength (f/V) remains unchanged.

For nanoparticles ($R \leq a_B$), the overlap integral of the electron and hole wave functions increases as the nanoparticle size decreases. As a result, the oscillator strength of nanoparticles depends only slightly on their size, while the volume-normalised oscillator strength increases with decrease in the nanoparticle size

$$\frac{f}{V} \propto \left(\frac{a_B}{R}\right)^3.$$

As is known, the oscillator strength determines the radiative lifetime of excited state at low temperatures, while the volume-normalised oscillator strength determines the light absorption coefficient. It follows from the analysis performed above that the radiative lifetime of the exciton decreases while the absorption coefficient increases linearly as the nanoparticle volume increases. For typical semiconductor crystals, the excitonic band width is of the order of 0.15–0.3 eV. The possibility for the integrated oscillator strength to be concentrated on the transitions whose widths are of the order of 10^{-3} – 10^{-4} eV with the decrease in the nanoparticle size results in a giant increase in the excitonic absorption of nanocrystals. These effects have been observed experimentally.^{2, 13, 108, 143} However, complete quantitative agreement between the experimental data and the theoretical concepts of the light absorption by nanoparticles cannot be achieved because of the difficulties in obtaining nanoparticles of fixed size and the effect of surface defects on the processes of light absorption and emission by nanoparticles.

3. Redox properties of semiconductor nanoparticles

Evidently, changes in the nanoparticle size resulting in the change in the energy of formation of electron–hole centres affect the redox properties of light-irradiated semiconductor nanocrystals. It seems most likely that the conduction and valence bands may be shifted towards more negative and more positive potentials, respectively, by decreasing the size of semiconductor nanoparticles. The energy diagram for CdTe nanocrystals¹⁴⁴ is shown in Fig. 11 as an example. It can be seen that the decrease in the size of nanoparticles affects more strongly the position of the energy level of the electron centre than that of the hole centre.

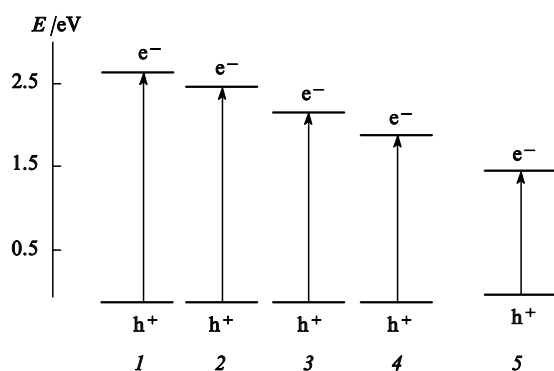


Figure 11. The energy diagram of the CdTe nanoparticles. Average size of the nanoparticles /nm: (1) 1; (2) 1.25; (3) 1.75; (4) 2; (5) ∞ (the last corresponds to the macroscopic crystal).

According to the modern theoretical concepts of the electron transfer,^{87, 145, 146} an appreciable change in the position of the energy level of the electron centre may result in a considerable change in the rate of redox processes occurring with the participation of nanoparticles. The dependence of the rate constant for the luminescence quenching of light-irradiated MoS₂ nanoparticles by oxygen molecules on the particle size^{30, 54} is shown in Fig. 12. The processes occurring in the MoS₂ nanoparticles upon their irradiation by light are described by the following scheme:

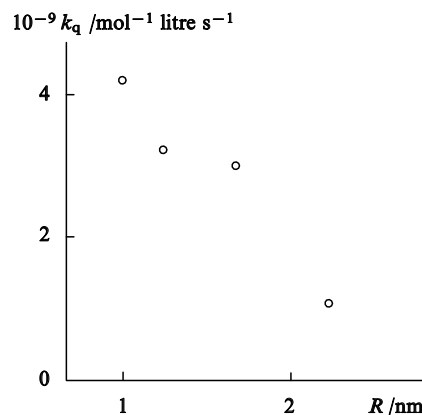
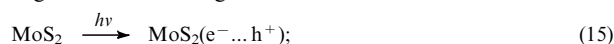


Figure 12. Dependence of the rate constant for the oxygen quenching of the luminescence of light-irradiated MoS₂ nanoparticles on their size.

Photogeneration of charge carriers:



stabilisation of charge carriers in shallow traps:



recombination luminescence:



luminescence quenching:



The luminescence of MoS₂ nanoparticles is due to the recombination of electrons trapped into shallow traps (e_t^-) and holes (h_t^+). In the presence of oxygen, luminescence quenching is observed due to the electron transfer from the trap to O₂. A decrease in the size of MoS₂ nanoparticles results in an increase in the energy of the trapped electrons and, hence, in an increase in thermal effect of the process. According to the modern concepts of electron transfer in the condensed phase,^{87, 145–147} the reaction rate of the electron transfer from the trap to the oxygen molecule must also increase in this case.

It is of note that the potential of the bottom of the conduction band of the macroscopic MoS₂ semiconductor is equal to 0.2 V vs. SCE, while the reduction potential of the oxygen molecule is equal to 0.82 V vs. SCE.¹⁴⁸ Comparison of these values shows that the photoreduction of oxygen using a macroscopic MoS₂ crystal is thermodynamically impossible.

The dependences analogous to that shown in Fig. 12 were found for the luminescence quenching of MoS₂ nanoparticles by methyl viologen and nitrobenzene.^{30, 54}

A dependence of the quenching efficiency of singlet-excited ZnTPP molecules by CdS nanoparticles on the nanoparticle size was found by Chrysochoos.¹⁴⁹ Analysis of experimental data¹⁴⁹ has shown⁸⁴ that the rate constant for quenching (k_q) changes from 0 to 10^{12} mol litre⁻¹ s⁻¹ as the localisation energy of the exciton in the CdS nanoparticles changes from 0.7 to 0.5 eV. From the results shown in Fig. 9 one can easily estimate that the change in the nanoparticle size from ~ 0.8 to ~ 1.2 nm corresponds to this range of the change in the localisation energy of the exciton. Large values of the quenching rate constant ($\sim 10^{12}$ mol litre⁻¹ s⁻¹) indicate that it was quenching of the porphyrin molecules adsorbed on the surface of CdS nanoparticles that has been observed by Chrysochoos.¹⁴⁹

4. Dependence of thermodynamic parameters of nanocrystals on their size

As has been mentioned above, a considerable portion of the atoms of nanoparticles is on the surface and it increases as the nanoparticle size decreases. Correspondingly, the surface atoms make a large contribution to the nanocrystal energy. In this connection, the dependence of the melting temperature of nanoparticles on their size shown in Fig. 13 for CdS¹⁵⁰ becomes understandable. In fact, the surface energy of a liquid is always lower than the surface energy of the corresponding crystal. A decrease in the size of nanoparticles leads to an increase in the proportion of the surface energy and, hence, to a decrease in the melting temperature of nanocrystals. As can be seen from Fig. 13, this decrease can be considerable.

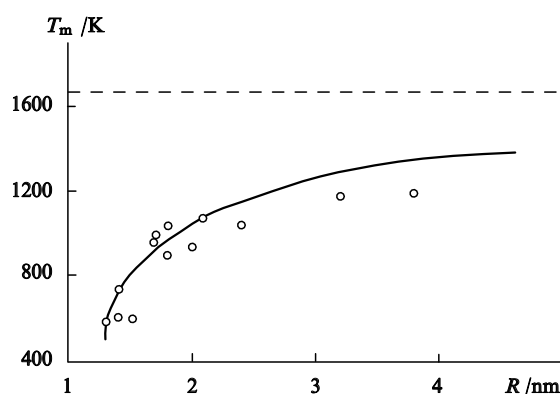


Figure 13. Dependence of the melting temperature (T_m) of CdS nanoparticles on their size.¹⁵⁰

The geometry of the crystal lattice of a macroscopic crystal can be changed by applying hydrostatic pressure to the crystal, which results in closer crystal packing. An analogous transformation can also be performed for nanocrystals. Thus, the application of hydrostatic pressure to the CdSe nanocrystal with the wurtzite type structure (hexagonal crystal lattice) results in the change to the sphalerite type structure (face-centred cubic crystal lattice). As a result, a less ordered surface with high surface energy is formed. Therefore, one should expect that increased pressure (P) is necessary for changing the crystal lattice geometry as the nanocrystal size decreases because of the large fraction of surface centres characteristic of nanocrystals. These are just the dependences of P on the nanoparticle size that were found for CdSe,¹⁵¹ CdS,¹⁵² InP, and Si.¹⁵³ However, in the case of colloidal solutions of nanoparticles it could be expected that both the magnitude and

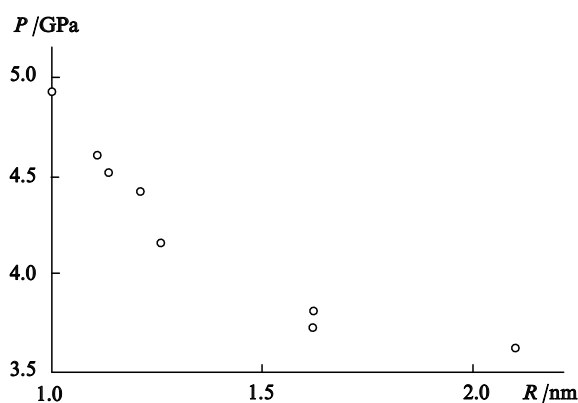


Figure 14. Dependence of hydrostatic pressure necessary for the phase transition to occur on the size of the CdSe nanoparticles.¹⁵⁰

sign of the effect must be strongly dependent on the nature of the solvent molecules coordinated on the surface of nanoparticles and thus affecting the surface energetics in both structural modifications of nanocrystals. The dependence of P on the size of CdSe nanoparticles¹⁵¹ is shown in Fig. 14 as an example.

IV. Photocatalytic processes with the participation of semiconductor nanostructures

Unusual physicochemical properties of semiconductor nanoparticles gave rise to various speculations concerning their practical implementations. Sensors and systems of light energy storage, electronics and photodetoxication of waste waters, non-linear optics and catalysis, and lithography and lasers (see, for example, Refs 154 and 155) are considered as possible fields of uses of semiconductor nanoparticles. However, in most cases it is premature to discuss practical application of semiconductor nanoparticles. Only investigations in the field of photocatalysis carried out so far make it possible to consider the possibilities of practical use of nanoparticles.

1. The use of semiconductor nanoparticles in photocatalytic processes

As has been mentioned above, a decrease in the size of semiconductor nanoparticles results in a shift of the conduction and valence bands towards more negative and more positive potentials, respectively. It seems to be tempting to use the possibility of controlling the redox properties of nanoparticles by changing their size in photocatalytic systems of water decomposition and the synthesis and destruction of organic compounds. Additionally, the fact that nanoparticles have a large specific surface area is of importance for carrying out photocatalytic processes on the surface of semiconductors. And finally, the small size of semiconductor nanoparticles can provide high efficiency of detrapping of light-generated electrons and holes, thus increasing the probability of a photocatalytic process on the surface of the semiconductor.

However, it should be noted that the semiconductor nanoparticles used in photocatalytic studies are, as a rule, rather large ($\sim 10^2$ nm) and no pronounced quantum size effects are observed for them. A correlation between the photocatalytic activity of TiO₂ nanoparticles and their size was found only in one study.¹⁵⁶ High quantum efficiencies of photocatalytic processes with the participation of nanoparticles are achieved by designing specifically ordered structures based on these particles.

The idea of using nanoparticles for photocatalytic water decomposition was first proposed by Henglein¹⁵⁷ and Duong-hong *et al.*,¹⁵⁸ who have demonstrated the possibility of photoreduction of methyl viologen in colloidal solutions of semiconductors. The photoreduction of methyl viologen on the surface of nanoparticles was studied by laser flash photolysis in colloidal solutions of TiO₂^{158–166} and metal chalcogenides.^{65, 167–170} Photoreduction of various dyes by nanoparticles has also been studied.^{171–175} Photoexcitation of nanoparticles results in one-electron reduction of dye molecules followed by the formation of a leuco-product.

The possibility of using nanoparticles in photocatalytic synthesis of organic compounds was demonstrated for the first time by Kraeutler *et al.*^{176–178} Photocatalytic synthesis of an amino acid and the Kolbe reaction were carried out by the interband excitation of TiO₂ nanoparticles coated with platinum. Later, *cis-trans* isomerisation of styrene derivatives upon photoexcitation of CdS nanoparticles was reported.^{179, 180} The process of isomerisation includes the formation of alkene radical cation on the surface of nanoparticles. Photocatalytic processes of oxidation of a number of alkanes, arenes, amines, and alcohols on the surface of nanoparticles are also known.^{181, 182}

Light-generated holes can be used in photooxidation of various substrates on the surface of nanoparticles until their complete destruction.^{131, 160, 168, 172, 183–188} The use of semicon-

ductor nanoparticles for photochemical purification of water from various contaminants seems to be rather tempting and attracts particular interest of researchers in recent years. Systems based on TiO₂ seem to be the most promising for photocatalytic mineralisation of organic compounds in waste waters.

Of the three major structural modifications of TiO₂ (rutile, anatase, and brookite), anatase is the most photocatalytically active. The difference in the photocatalytic activity of different TiO₂ modifications is most likely due to their different crystal structures. Anatase has a bandgap of 3.2 eV and UV radiation needs to be applied for the electronic excitation of this compound; hence, only a small portion of the sun light can be used for the photocatalytic processes involving anatase to occur. Nevertheless, among a wide variety of semiconductor materials, TiO₂ is most often used as a photocatalyst due to the high oxidation ability of its photogenerated holes ($E = 2.9$ V vs. NHE at pH 0), its stability in aqueous solutions, safety for living organisms, and low price.

Titanium dioxide has long been used in paint industry as the photocatalyst in the oxidation of organic substances. This property of TiO₂ has determined its wide use as the white pigment.¹⁸⁹ Later, attempts were made aimed at using TiO₂ for photodecomposition of water.^{190, 191} However, its efficiency appeared to be low because of a low quantum yield of charge photoseparation. Recently, the problems of the environment protection forced many researchers to direct their attention again to the systems based on TiO₂ and to make efforts to use TiO₂ for photocatalytic mineralisation of ecologically hazardous organic compounds both in aqueous media and gases.

The scheme of the photocatalytic process involving semiconductor nanoparticles is shown in Fig. 15. The absorption of a light quantum with an energy of $h\nu$, that exceeds the bandgap of the semiconductor, results in the primary charge separation. In this case, the nanoparticle can be considered as a short-circuit electrode initiating the processes of oxidation and reduction of the substrate molecules adsorbed on the surface. The oxidation and reduction of non-adsorbed substrate molecules is possible if the primary electrons and holes are transformed into stable intermediates on the surface of nanoparticles.

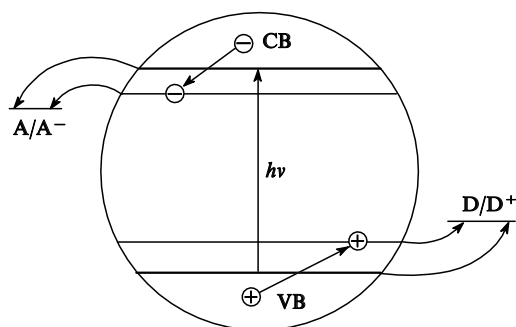
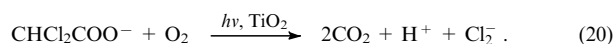


Figure 15. Schematic view of charge separation processes in a semiconductor nanoparticle.

Good results have been obtained for the detoxication of waste waters containing hydrocarbons, phenols, chloroaromatic compounds, surfactants, and nitro compounds (see, for example, reviews^{192–196} and references cited therein). A typical example of photocatalytic mineralisation is the oxidation of the dichloroacetate ion by oxygen in water:



The detailed mechanism of the processes of the photoreduction of acceptors and photooxidation of donors with the participation of TiO₂ nanoparticles includes a large number of events occurring both in the bulk and on the surface of nanoparticles; the basic events are outlined below (see also Fig. 16).¹⁹⁶

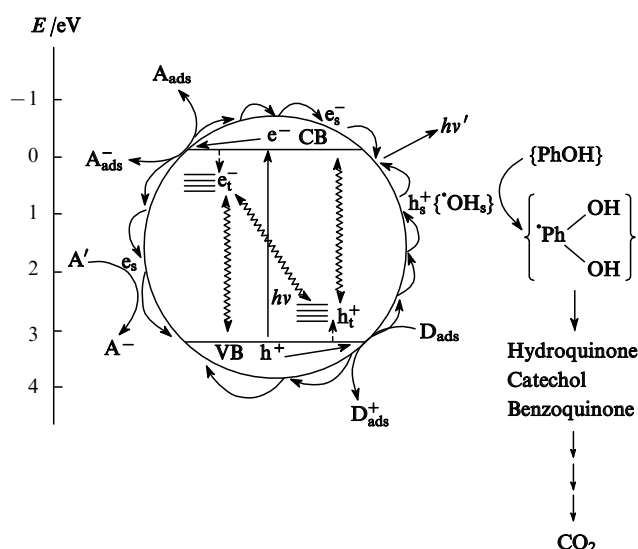
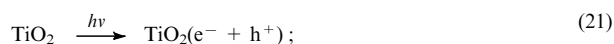
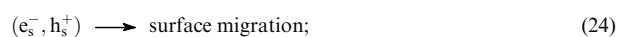


Figure 16. Schematic view of processes of photoreduction of acceptors and photooxidation of donors by TiO₂ nanoparticles.

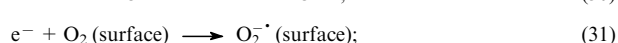
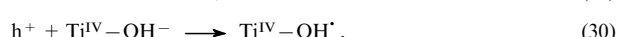
Photostimulated generation of electrons and holes in the conduction and valence band, respectively



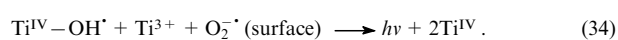
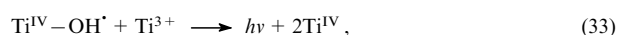
charge carrier migration to the surface of the nanoparticle



charge carrier trapping by acceptor centres and into shallow traps (ST)



charge carrier recombination (radiative and nonradiative)



It is usually assumed that the photooxidation of organic substrates in aqueous suspensions of TiO₂ can occur by both the direct interaction of the holes with the substrate molecules and the formation of the OH· radicals in the reaction of the holes with H₂O or OH⁻.

The prospects of the use of semiconductor nanoparticles in photocatalysis have stimulated studies of the possibility of spectral sensitisation of nanoparticles and modification of their surface by noble metals. In the photocatalytic systems of water decomposition, the metal deposited on the surface of nanoparticles acts as the catalyst of the photosplitting of water to produce hydrogen gas. The effect of coating the surface of TiO₂ nanoparticles with platinum^{197, 198} and other noble metals and metal oxides^{199–202} on the quantum yield of water photodegradation has been studied.

Sensitisation of semiconductors is widely used for expanding the spectral sensitivity region of these materials. Thus, TiO_2 has a bandgap of 3.1 eV and its use in a photocatalytic system is only expedient in the case of expanding the spectral sensitivity region of the system into the visible region. Sensitisation of TiO_2 nanoparticles is performed with the participation of both singlet^{203–206} and triplet^{207–209} excited dye molecules.

Semiconductor hetero-nanoparticles can be of considerable practical interest. The processes of charge separation in mixed CdS/TiO_2 semiconductor nanoparticles⁷⁹ and in the ZnO nanoparticle coated with a ZnS layer²¹⁰ are depicted schematically in Fig. 2. Production of large-bandgap hetero-nanoparticles can favour their spectral sensitisation. Additionally, as has been mentioned above, multicomponent nanoparticles are of interest, since it is possible to increase the efficiency of charge photo-separation because of the effective spatial separation of the electrons and holes in such structures. There are only a few experimental data^{211,212} on the photocatalytic activity of hetero-nanoparticles analogous to those shown in Fig. 2. The possibility of increasing the quantum yield of charge separation in such hetero-nanoparticles has been demonstrated experimentally. In Fig. 17, the short-lived optical spectra of colloidal solutions of CdS and TiO_2 nanoparticles in CH_3CN generated by a laser pulse upon the excitation of CdS by light⁵⁸ are shown as an example. The short-lived optical absorption in the 500–750 nm region is caused by the electrons trapped by the Ti^{4+} centres of titanium dioxide. As can be seen from this picture, the excitation of CdS in CdS/TiO_2 nanoparticles leads to the electron transfer from CdS to TiO_2 .

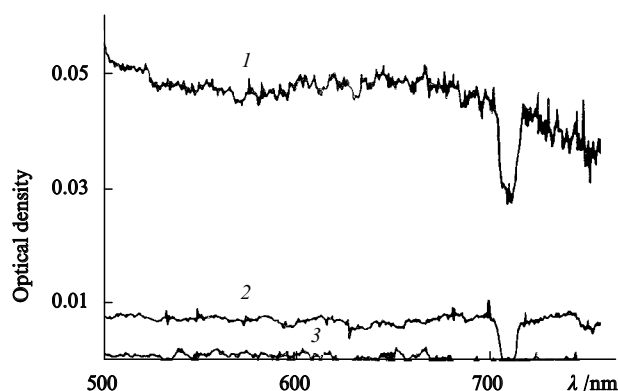


Figure 17. The absorption spectra of colloidal solutions of nanoparticles in CH_3CN after a laser pulse ($\lambda = 355 \text{ nm}$, $\Delta\tau = 0 \text{ ps}$). The concentration of nanoparticles in solution /mmol litre⁻¹: (1) 0.75(CdS) + 1.15(TiO_2); (2) 0.75(CdS); (3) 1.15(TiO_2).

The high photocatalytic activity of nanoparticles of the ‘core–shell’ type has been demonstrated in the example of the photo-oxidation of I^- and SCN^- anions by $\text{SnO}_2/\text{TiO}_2$ nanoparticles.⁷⁰ It was found that the quantum efficiency of the photooxidation of I^- anions by $\text{SnO}_2/\text{TiO}_2$ nanoparticles is 2–3 times higher than the quantum efficiency of the photooxidation by $\text{SiO}_2/\text{TiO}_2$ or TiO_2 nanoparticles. The use of systems of the ‘core–shell’ type is also promising in view of cutting the costs of hetero-nanoparticles if inexpensive materials are used for the synthesis of the cores for such structures.^{63, 67, 71, 210, 213, 214}

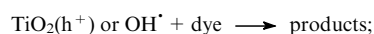
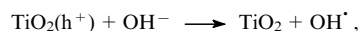
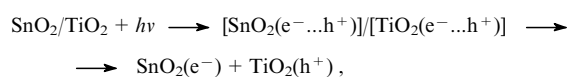
2. Photocatalysis based on nanostructured films of semiconductors

Colloidal solutions of nanoparticles are suitable objects for the demonstration of the possibility of their use in photocatalysis. However, the practical use of colloidal solutions is difficult because of the need to separate nanoparticles from the solution after the completion of the photocatalytic process. Thin layers of

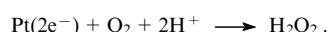
nanoparticles adsorbed on a carrier seem to be much more promising, especially the films composed of hetero-nanoparticles shown in Fig. 3. These films have many advantages over films composed of nanoparticles of the same nature, namely, the expanded spectral sensitivity region of the large-bandgap semiconductor nanoparticles, increased quantum efficiency of charge photoseparation,²¹⁵ and high efficiency of spectral sensitisation of films by dyes.²¹⁶

An idealised illustration of photocatalytic processes occurring on the surface of a conducting electrode with the participation of films composed of heteronanoparticles is exemplified in Fig. 3 with $\text{TiO}_2/\text{SnO}_2$ films. The position of the bottom of the SnO_2 conduction band is lower than that of the TiO_2 conduction band (0 and -0.5 V vs. NHE at pH 7, respectively). This causes the light-generated electrons to transfer from TiO_2 to SnO_2 . The holes move in the opposite direction and are accumulated on the TiO_2 nanoparticles. As a result, an increase in the quantum efficiency of charge photoseparation and, hence, in the efficiency of the oxidation of donor molecules in solution can be observed in the structure under consideration. High efficiency of the $\text{TiO}_2/\text{SnO}_2$ film was demonstrated experimentally in the example of photocatalytic degradation of dyes (Acid Orange 7 and Naphthol Blue Black).^{217,218} The overall processes occurring at the anode and cathode can be described by the following scheme:

at the photoanode



at the cathode



Porous nanostructured films possess high adsorption capacity to organic dyes and organometallic compounds. Large specific surface area of such films allows adsorption of a considerable amount of a dye. The use of these properties of the nanostructured films makes it possible to increase substantially their photocatalytic efficiency due to sensitisation into the visible region.^{72, 219}

V. Conclusion

Some interesting peculiarities in the solution behaviour of the ultrasmall semiconductor particles containing several hundreds of atoms have been revealed in the studies of their properties. Unusual physicochemical properties of semiconductor nanoparticles depend on three main factors. First, the size of nanoparticles is comparable with the molecular dimensions. This determines the difference between the kinetics of chemical transformations on the surface or in the bulk of nanoparticles and the kinetics of chemical transformations in infinite space. The classical equations of chemical kinetics can be used for the description of the processes on the surface of nanoparticles down to a size that exceeds the actual size of the reacting molecules by an order of magnitude. The processes occurring on the surface of smaller nanoparticles can be described by the Monte Carlo method or by the methods of stochastic kinetics.

Second, the surface atoms constitute a considerable proportion of the total number of atoms of a nanoparticle. This strongly affects the thermodynamic characteristics of nanoparticles and determines the size dependences of melting temperatures and pressures at which the crystal lattice of a semiconductor rearranges (*i.e.*, phase transition occurs).

And, finally, third, the non-linear optical effects arise and the energies of excitonic transitions in nanoparticles, oscillator strengths, and redox characteristics become dependent on the nanoparticle size as the latter becomes comparable with the delocalisation area of charge carriers.

Intensive investigations in the field of the chemistry of semiconductor nanoparticles have been carried out during the last decade. The major efforts of researchers are directed to the development of methods for the synthesis of nanostructures with controlled characteristics and investigation of their photocatalytic properties. Considerable progress has been achieved in the demonstration of the possibility of the use of semiconductor nanostructures for photocatalytic mineralisation of various environmentally hazardous compounds. In our opinion, the most promising lines in the study of semiconductor nanoparticles in the coming years will be associated with the development of methods for the synthesis of nanoparticles with predetermined geometric characteristics, studies of the mechanisms of chemical transformations at the liquid–solid interface in colloidal solutions of nanoparticles, practical implementation of nanoparticles and films produced on their basis in photocatalysis, and design of complex ordered systems for electronics.

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Excited state proton transfer dye lasers

B M Uzhinov, S I Druzhinin

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Abstract. Reactions of proton phototransfer in organic compounds and photochemical lasers based on these reactions are considered. A principle of operation of a photochemical laser is described. Selection criteria of acid-base systems to serve as active media in photochemical lasers are determined. A list of acid-base laser systems, conditions of their fabrication, and emission characteristics are collated. Specific losses in photochemical lasers are analysed. Methods of expanding the spectral range of tunable emission in the photochemical lasers are described. The bibliography includes 134 references.

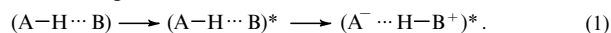
I. Introduction

Laser radiation is the emission of light upon transition of excited molecules to the ground electronic state. The emission of light is stimulated by an external electromagnetic field under the conditions of an optical resonator. The phenomenon of light amplification by the effect of stimulated radiation emission is called laser action, which stems from the abbreviation of the expression 'light amplification by stimulated emission of radiation'. Among numerous types of lasers used in the different fields of science and technology, those based on organic compounds (dyes) occupy a special place.¹ The advantages of the dye lasers over the others include the possibility of fine and continuous tuning of the laser radiation wavelength over a wide range (up to 100 nm), a high coefficient of emitted light amplification by the active medium, and the possibility of obtaining multiband radiation.² The latter is employed for the solution of a number of practically important problems (in particular, atmospheric probing, multipulse multi-colour spectroscopy, *etc.*). Dye lasers are the main source of pico- and femtosecond pulses.³ The possibility of achieving the femtosecond pulses is determined by the existence of highly effective amplification medium with a broad range of laser radiation tuning. A significant increase in the spectral range of tuning, up to 220 nm,⁴ can be attained in the dye lasers with adiabatic photochemical reactions.

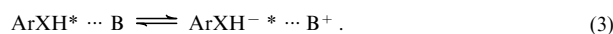
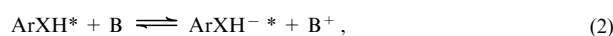
A dye produces stimulated light emission in the spectral range of its fluorescence. The excited dye molecules may be generated in two ways: (1) as a result of direct excitation from the ground state through absorption of a photon or under electron impact; (2) as a result of an adiabatic photochemical reaction (photochemical laser). The regularities of radiation for the first type of dye laser are considered in numerous reviews and original papers.^{5–11} The reactions of electron and proton phototransfer belong to the best studied adiabatic photochemical reactions of organic compounds.¹² The electron phototransfer reactions result in the formation of excited charge-transfer complexes (exciplexes).¹³ The radiative transition in exciplexes is partially forbidden, therefore, the generation of laser radiation by the products of electron phototransfer reactions and, consequently, photochemical lasers based on these reactions are hardly probable.¹⁴ The radiative transition in excited products of numerous proton phototransfer reactions is permitted.¹⁵ These excited products are the potential generators of the laser radiation.

II. An operation scheme for a photochemical laser based on proton phototransfer reactions

Proton phototransfer reactions in organic compounds occur according to static and dynamic mechanisms. In the former case the reaction occurs 'instantaneously' in the excitation of a hydrogen-bonded complex of a proton donor with acceptor, which is formed in the ground state.



In the latter case, the interaction between the excited molecule of an aromatic compound and a molecule of a base or acid is realised. Fluorophores that can participate in the acid-base interaction may be divided into two groups. Proton-donor fluorophores ArXH constitute the first group, their acidity being increased upon excitation. A reaction with a base B in the ground state occurs according to the scheme

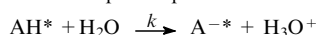


The majority of compounds of this group possess an aromatic radical Ar bound by a single bond to the proton-donor group XH (X = O, S, NR, and NR₂⁺).^{16–19} The kinetic and thermodynamic parameters of reaction (2) and spectral-kinetic characteristics of the forms ArXH and ArX[−] for the known laser acid-base systems are listed in Table 1.

B M Uzhinov, S I Druzhinin M V Lomonosov Moscow State University, Department of Chemistry, Leninskie gory, 119899 Moscow, Russian Federation. Fax (7-095) 932 88 46. Tel. (7-095) 939 26 85 (B M Uzhinov). E-mail: drush@comp.chem.msu.su

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Table 1. The spectral-luminescence characteristics of conjugated acid-base forms of dyes for photochemical lasers and the parameters of the intermolecular proton phototransfer reactions

Laser dye	AH, A [−]	λ_a /nm	ε /mol ^{−1} litre cm ^{−1}	λ_f /nm	φ_f (%)	τ /ns	k /mol ^{−1} litre ns ^{−1}	$\text{p}K_a^* - \text{p}K_a$	Ref.
2-Naphthol	AH	327 ^a	3.08 ^a	357 ^a	40 ^b	7.9	0.075 ^c	2.78 ^d	17
	A [−]	345 ^a	1.78 ^a	418 ^a	57 ^b	9.0	46	−6.79	17
Potassium 7-hydroxy-naphthalene-1,3-disulfonate	AH	337	1.69 ^c	385	—	10.5	> 5 ^c	0.76 ^d	23
	AH	—	—	388	—	14.5	3.8 ^c	0.60 ^d	24
	A [−]	359	3.38 ^c	470	—	15.5	< 200	−8.34	23
	A [−]	389	—	458	—	26.2	16	−7.29	24
Sodium 8-hydroxypyrene-1,3,6-trisulfonate	AH	402 ^f	19.2 ^f	441	—	5.2	8.0 ^c	1.28 ^d	26
	AH	—	—	—	70	4.8	6.1 ^c	0.95 ^d	27
	A [−]	453 ^f	18.2 ^f	510	85	5.3	115	—	26
	A [−]	—	—	—	85	6.0	55	−6.45	27
Sodium 8-acetylaminopyrene-1,3,6-trisulfonate ^g	AH	371	28	443	—	4.0	1.48	6.9 ^d	19
	A [−]	408	20	553	85	5.0	2.1 × 10 ^{−9} ^c	−7	19
1,3-Disulfo-7-naphthylammonium hydrogensulfate	AH	281	5.55	345	—	15	20 ^c	< −4.7 ^d	22
	A [−]	350	3.96	450	84	14.7	< 10 ^{−4}	< −7.6	22

Note. Here and in Tables 2 and 3, the following designations are used: λ_a is the absorption spectrum maximum, λ_f is the fluorescence spectrum maximum, ε is the extinction coefficient for the absorption spectrum maximum, φ_f is the fluorescence quantum yield, τ is the fluorescence lifetime.

^a From Ref. 20. ^b From Ref. 21. ^c Rate constant for a unimolecular tautomerisation reaction or a quasi-unimolecular reaction with the solvent (s^{−1}).

^d $\text{p}K_a^*$. ^e From Ref. 22. ^f From Ref. 25. ^g Reaction (2) with the OH[−] ion.

Table 2. Spectral-luminescence characteristics of conjugated acid-base forms of dyes for the photochemical lasers and the parameters of proton intermolecular phototransfer reactions (4) in ethanol.

Laser dye	AH, A [−]	λ_a /nm	ε /mol ^{−1} litre cm ^{−1}	λ_f /nm	φ_f (%)	τ /ns	Reagent	k /mol ^{−1} litre ns ^{−1}	$\text{p}K_a^* - \text{p}K_a$	Ref.
<i>N</i> -Phenylacridone	B	399	—	406	100	12	H ₃ O ⁺	7.4 ^a	2.05 ^b	33
	BH ⁺	427	—	450	—	—			2.92	33
3-Methoxybenzanthrone	B	445	24.3 ^c	547	57	7.8	H ₃ O ⁺	6.4 ^a	2.2 ^b	33
	BH ⁺	585	—	640	28	3.8			5.85	33
2,3,6,7-Tetrahydro-1 <i>H</i> ,5 <i>H</i> -benzopyrano[6,7,8- <i>ij</i>]quinolizin-11-one	B	389 ^d	21.5 ^d	470	95	4.52	EtOH ₂ ⁺	4.33		35
	BH ⁺	—	—	533	40	—			5.51 ^c	35
9-Methyl-2,3,6,7-tetrahydro-1 <i>H</i> ,5 <i>H</i> -benzopyrano[6,7,8- <i>ij</i>]quinolizin-11-one	B	396 ^d	25.0 ^d	470	83	4.36	EtOH ₂ ⁺	3.56		35
	BH ⁺	—	—	530	47	5.45 ^f			5.14 ^c	35
5 <i>H</i> -9-Diethylamino-5-imino-benzo[<i>a</i>]phenoxazine	B	510	—	605	—	1.85	EtOH	0.04 ^g	3	38
	BH ⁺	625	—	660 ^h	22 ⁱ	1.3 ^h			1.5 ^j	38
	BH ⁺	633	77.5	672	—	—				34
5-Phenyl-2-(4-pyridyl)-oxazole	B	322 ^k	24.5 ^k	400 ^k	46	2.12	AcOH	0.314	8.27 ^l	30
	BH ⁺	370 ^k	24.5 ^k	475 ^k	59				8.44 ^c	30
5-(4-Methoxyphenyl)-2-(4-pyridyl)oxazole	B	335 ^k	21.5 ^k	447 ^k	91	2.45	AcOH	0.501	8.78 ^l	30
	BH ⁺	399 ^k	21.0 ^k	550 ^k	64	3.08			10.04 ^c	30
5-Phenyl-2-(2-quinolyl)oxazole	B	350 ^k	21.5 ^k	423 ^k	61	1.89	AcOH	0.175	8.85 ^l	30
	BH ⁺	412 ^k	18.5 ^k	515 ^k	73	3.66			9.01 ^c	30
5-Phenyl-2-(4-quinolyl)-oxazole	B	350 ^k	18.5 ^k	437 ^k	63	1.87	AcOH	0.263	8.04 ^l	30
	BH ⁺	412 ^k	23.9 ^k	525 ^k	45	2.18			9.01 ^c	30
1,4-Bis(5-phenyloxazol-2-yl)benzene ⁿ	B	360	47.2 ^m	420	93 ^m	1.4 ^m	CF ₃ COOH	—		42
	BH ⁺	—	—	486	—	—			6.78 ^l	42
1,4-Bis[5-(4'-methylphenyl)-oxazol-2-yl]benzene ⁿ	B	362	51.1 ^m	430	93 ^m	1.5 ^m	CF ₃ COOH	—		42
	BH ⁺	—	—	500	—	—			6.83 ^l	42

^a $k_1/(1 + k_{-1}\tau_0)$ from Ref. 32. ^b $\text{p}K_a^*$. ^c From Ref. 32. ^d From Ref. 34. ^e According to the Förster cycle³⁶ using the absorption spectra. ^f From Ref. 37.

^g Rate constant for a unimolecular tautomerisation reaction or a quasi-unimolecular reaction with the solvent (ns^{−1}). ^h Ion pair. ⁱ From Ref. 39. ^j $\text{p}K^*$ for an equilibrium ion pair – complex with H-bond. ^k From Ref. 40. ^l According to the Förster cycle³⁶ using the fluorescence spectra. ^m In cyclohexane. ⁿ In dioxane, reaction (5).

Proton-acceptor fluorophores constitute the second group, their basicity is increased upon excitation



In this type of base, the π -system is linked by a double bond to the proton-acceptor centre. The proton-acceptor centre can be exocyclic or endocyclic.

Aromatic carbonyl compounds (aldehydes and ketones) and their imine derivatives belong to the organic bases with an exocyclic proton-acceptor centre. Organic carbonyl compounds are weak bases.²⁸ Their basicity is increased in the excited state.²⁹ The protonation rate constants for aminocoumarins in the excited state in solution are close to the diffusion rates.²⁹ The rate constants for the protonation of pyridine and oxazole derivatives in the excited state by carboxylic acids are one or two orders of magnitude smaller than the rate constants for the diffusion-limited reactions, respectively.^{30,31} The photoprotonation of pyridine and oxazole derivatives occurs either according to the

static [reaction (5)] or dynamic [reaction (4)] mechanism.^{30,31} The kinetic and thermodynamic parameters for the reactions (4) and (5) and spectral-kinetic characteristic of the forms B and BH^+ for the known laser acid-base systems are listed in Table 2.

Aromatic C-bases possess low basicity. These compounds are protonated in the ground state only in concentrated strong acids. The acid-base interaction in the excited state leads to quenching of the fluorescence. No excited products are generated in this reaction.^{43,44}

In numerous organic compounds, the proton-donor and proton-acceptor groups are linked by an intramolecular hydrogen bond.^{45–48} The proton-donor and proton-acceptor ability of these reaction centres of the molecule is increased upon excitation of these compounds, which results in the intramolecular proton phototransfer. This type of reaction can be assigned to the stationary proton phototransfer. The kinetic and thermodynamic parameters for the reactions of intramolecular proton phototransfer as well as spectral-kinetic characteristics for the known laser systems of this type are listed in Table 3.

Table 3. Parameters of reactions of intramolecular proton phototransfer in dye molecules for photochemical lasers and spectral-luminescence characteristics of the initial form (N) and its tautomer (T).

Laser dye	Form	Solvent	λ_a /nm	ϵ /mol ⁻¹ litre cm ⁻¹	λ_f /nm	ϕ_f (%)	τ /ns	pK _a [*] –pK _a	Ref.
Sodium salicylate	N	EtOH	298	4.2	–	–	–	–	41
	T				405	27	26 ^a	–	41
Salicylamide	N	DMF	305	–	–	–	–	–	49
	T				438	27	2.6	–	49
3-Hydroxyflavone	N ^b	MeOH	344	16.35	405	–	1.24	–9.61 ^c	51
					–	–	–	4.08 ^d	51
	T	Methyl- cyclohexane	–	25 ^h	531	–	2.34	–12.3 ^e	51
	N ^f				410	–	–	–	50
	T ^g				526	36	3	–	53
2,2'-Bipyridyl-3,3'-diol	N ⁱ	3-Methyl- pentane	360 ^j	17.5 ^j	–	<0.01	6.6 ^a	–	55
	T				513	31	3.2	–	54
2-(Benzimidazol-2-yl)phenol	N	Dioxane	333	28.0 ^k	350	–	–	–15.1 ^e	57
	T				468	65	4.2	–	57
	N	MeCN	331	22.1 ^k	354	–	–	–13.9 ^e	57
	T				463	55	3.7	–	57
	N	DMF	333	27.5 ^k	354	30	1.4	–13.9 ^e	57
	T				463	72	4.1	–	57
	N	MeOH	329	28.0 ^k	351	37	1.5	–8.0 ^e	57
	T				405	57	3.8	–	57
2-(Benzimidazol-2-yl)- 4-methylphenol	N	Dioxane	339	22.8 ^k	352	5	1.5	–16.7 ^e	57
	T				489	65	4.5	–	57
2-(Benzimidazol-2-yl)- 4-fluorophenol	N	MeCN	339	24.1 ^k	359	–	–	–14.5 ^e	57
	T				478	73	4.7	–	57
2-(Benzimidazol-2-yl)- 4-methoxyphenol	N	Dioxane	341	20.2 ^k	368	7	1.9	–17.4 ^e	57
	T				530	48	4.2	–	57
2,5-Bis(benzimidazol-2-yl)- hydroquinone	N	"	345	34.0 ^k	358	6	2.0	–18.6 ^e	57
	T				525	39	3.4 ^l	–	57
	N	MeCN	342	19.6 ^k	369	6	1.8	–16.3 ^e	57
	T				517	18	3.4	–	57
	N	DMF	347	22.0 ^k	381	8	1.8	–15.1 ^e	57
	T				525	21	2.6	–	57
3,6-Bis(benzoxazol-2-yl)- 4-methoxyphenol	N ^m	MeTHF	381	24.7	445 ⁿ	35	–	–8.9 ^e	59
	T				548	50	4.6	–	59
<i>N</i> -[2-(5-Phenyl-1,3,4-oxadiazol- 2-yl)phenyl]toluene- <i>p</i> -sulfamide	N	EtOH	312	12.5	330	–	–	–22.4 ^e	60
	T				510	3	0.90	–	60

^a Radiative lifetime of fluorescence. ^b Rate constant of proton phototransfer (k) > 8000 ns⁻¹ (Ref. 50). ^c Deprotonation. ^d Protonation. ^e According to the Förster cycle³⁶ using the fluorescence spectra. ^f k = 4200 ns⁻¹. ^g k = 30 ns⁻¹ in cyclohexane.⁵² ^h In cyclohexane.⁵² ⁱ k > 7000 ns⁻¹. ^j From Ref. 54. ^k From Ref. 56. ^l From Ref. 58. ^m k = 20 ns⁻¹. ⁿ For 1,4-dimethoxy-2,5-bis(benzoxazol-2-yl)benzene.

Intramolecular proton phototransfer reactions leading to species with effective fluorescence are wide-spread (see Tables 1 and 2). Compounds that give products with a high quantum yield of fluorescence of the intramolecular proton phototransfer product are scarce.^{59,61–64} The fluorescent reaction products of the proton phototransfer, as with usual fluorophores, under appropriate conditions can amplify the light passing through the solution.

In a number of studies that were performed over the period from 1960 to 1964, the possibility of the light amplification by the dye solutions has been demonstrated,⁶⁵ and the principles of generation of laser radiation (lasing) as a result of electron-vibrational singlet–singlet transitions in anthraquinone molecule have been discussed.⁶⁶ Certain theoretical calculations on lasing taking into account the vibrational structure of the electronic levels of dyes were carried out.^{67,68} The processes that occur in the excitation of complex molecules, including the processes of stimulated light emission, were analysed in detail.^{69,70} Slight amplification of light upon photoirradiation of a solution of perylene in benzene was detected in 1964.⁷¹

The lasing of organic compounds was first observed independently by two research groups.^{72,73} Chronologically, the first dye laser was created by Sorokin and Lankard⁷³ in 1966. Excitation of an ethanolic solution of phthalocyanine complex with aluminium chloride by the radiation of a ruby laser induced laser radiation resulting from electronic transitions in the organic ligand of the metal complex. Currently, dye lasing with a high conversion efficiency (71% for the Rhodamine 6G in EtOH⁷⁵ and 78% for the dye LKK-756 in MeCN⁷⁶) can be obtained in a spectral range from 322 nm⁷⁴ to 1800 nm.¹⁰ Arylazole, coumarin, xanthene, oxazine, and polymethine dyes are the most efficient laser dyes.⁷ Active media for the dye lasers are liquid solutions of dyes,^{1–5} solid solutions in polymers,⁷⁷ and gaseous mixtures of dye vapour with buffer gases.⁷⁸

A solution of an organic compound can generate laser radiation (lase) if its optical density $[-k_a(v)x]$ at some frequency v is less than zero (negative absorption).⁷⁹

$$\ln \left[\frac{I_0(v)}{I(v)} \right] = -k_a(v)x,$$

where $I_0(v)$ and $I(v)$ are the radiation flux intensities before and after the light has passed through the layer of a solution with a thickness x , $k_a(v)$ is an amplification coefficient of the medium.

In the simplest case of a two-level scheme, $k_a(v)$ is described by the equation

$$k_a(v) = \frac{h\nu}{v} [N_2 B_{21}(v) - N_1 B_{12}(v)],$$

where N_1 and N_2 are the population of the lower (1) and upper (2) levels, $B_{12}(v)$ and $B_{21}(v)$ are the probabilities of absorption and stimulated emission (Einstein's coefficients for induced transitions), respectively, v is the velocity of light in the medium. More often, a cross-section of stimulated transition is used instead of $B(v)$

$$\sigma(v) = \frac{h\nu}{v} B(v).$$

The Einstein coefficients, cross-sections of absorption and stimulated emission are the same, *i.e.*,

$$B_{12}(v) = B_{21}(v) \text{ and } \sigma_{21}(v) = \sigma_{12}(v).$$

The condition for lasing

$$k_a(v) = N_2 \sigma_{21}(v) - N_1 \sigma_{12}(v) = \sigma_{21}(v)(N_2 - N_1) > 0$$

is fulfilled when $N_2 > N_1$, *i.e.*, in the presence in the system with an inverted (relative to thermal population) level population. This cannot be achieved in the two-level system with optical pumping. The currently known laser systems lase according to three- (1–3)

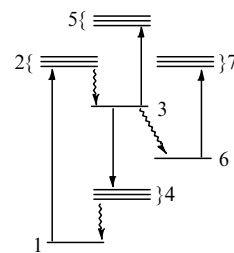


Figure 1. The energy level diagram of a laser dye molecule.

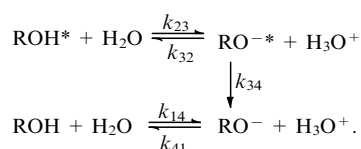
and four-level (1–4) schemes (Fig. 1). Optical transitions occur between the levels 1–2 and 3–4. The system is excited from the lower vibrational sublevel of the main electronic state (level 1) to higher vibrational sublevels of the first excited electronic state (level 2). The lower laser level (level 4) consists of higher vibrational sublevels of the ground electronic state of the dye, the upper laser level (level 3) is a zero vibrational sublevel of the first excited electronic state. The transitions between the levels 2–3 and 4–1 are radiationless (the rate constant of these processes is $\sim 10^3$ ns⁻¹). They represent vibrational relaxation in the excited and ground electronic states, respectively. As the higher vibrational sublevels of the ground state are virtually unoccupied at room temperature, the concentration of excited molecules at the level 3 (N_3) exceeds that of molecules at the level 4 (N_4) upon excitation of the system even by light of relatively low power. In this case, an inverted population of the levels 3 and 4 is observed in the system ($N_3 > N_4$). An inverted population of the zero vibrational sublevels of the ground and excited states cannot be achieved. In addition to these processes, optical transitions from the level 3 to the highest singlet states of the molecule (level 5), intersystem transitions to the triplet state (level 6) and optical transitions from the level 6 to the highest triplet level of the molecule (level 7) as well as photochemical decay of the dye occur in the dye lasers. For the system that is described by this scheme the amplification coefficient is determined by the equation

$$k_a(v) = N_2[\sigma_{34}(v) - \sigma_{35}(v)] - N_1\sigma_{12}(v) - N_6\sigma_{67}(v) - \sum_i N_{p_i}\sigma_{p_i}(v) - k_w(v), \quad (6)$$

where the number in subscript indicates the number of the level, N_{p_i} is the population of levels, $\sigma_{p_i}(v)$ is the cross-section of absorption of photoproduct p_i at a frequency v , $k_w(v)$ is the constant loss coefficient. Spectral criteria for the selection of a dye to produce efficient lasing have been formulated by Simonov⁸⁰ and Denisov and Uzhinov⁸¹.

The idea of creating an inverted electronic state population as a result of the adiabatic reaction of organic compounds in excited state was suggested practically simultaneously by Derkacheva⁸² and Kuz'min⁸³ (3 years before the appearance of the first dye laser⁷³). It was assumed that photochemical reactions of dissociation, isomerisation, complexation, dimerisation, and polymerisation and redox processes can be adiabatic.⁸³ In the four-level scheme suggested,^{82,83} the ground and excited states of the initial form of the dye involved in the reaction correspond to levels 1 and 2 (see Fig. 1). The excited and ground state of the proton phototransfer product correspond to levels 3 and 4. In this case, the direct reaction in the excited state and the reverse reaction in the ground state play the roles of radiationless relaxation processes (transitions between the levels 2–3 and 4–1), respectively. The change in the equilibrium constant in the excited state compared to the ground state is crucial for lasing.

Derkacheva⁸² has considered the mechanism of lasing of products of photoprolytic reactions of phenols in water, which occur according to the following scheme.



The value k_{34}^{-1} is the lifetime of the excited product of the photoreaction. It was considered^{82,83} that the attainment of an inverted population between the zero vibrational sublevels of the excited and the ground states of RO^- is a prerequisite for lasing. The difference in populations of these states under steady-state conditions is determined by the equation⁸²

$$\begin{aligned}
 [\text{RO}^{-*}] - [\text{RO}^-] = [\text{ROH}] & \left[\frac{\alpha k_{23}/k_{34}}{1 + k_{32}[\text{H}_3\text{O}^+]/k_{34}} \times \right. \\
 & \left. \times \left(1 - \frac{1}{k_{41}[\text{H}_3\text{O}^+]/k_{34}} \right) - \frac{k_{14}}{k_{41}[\text{H}_3\text{O}^+]} \right],
 \end{aligned}$$

where $\alpha = [\text{ROH}^*]/[\text{ROH}]$.

The following two conditions should be fulfilled to ensure an inverted population in the reaction product ($[\text{RO}^{-*}] > [\text{RO}^-]$): (1) $[\text{H}_3\text{O}^+] > k_{34}/k_{41}$; (2) sufficiently intense excitation, which determines the value of α , as well as large value of k_{23} , which provides for the high formation rate of the excited molecules of the deprotonated form. In the case of acid dissociation of the excited 2-naphthol, the first condition is fulfilled at $\text{pH} < 1.7$ ($[\text{H}_3\text{O}^+] > 0.02 \text{ mol litre}^{-1}$), and the second condition if sufficiently powerful excitation sources are employed.⁸²

More recent studies have shown that the mechanism of lasing suggested earlier^{82,83} is invalid. Currently, it is believed that an inverted population between the zero vibrational sublevels of the excited state and the vibrational sublevels (excluding zero sublevel) of the dye ground state is the prerequisite for lasing in organic compounds.⁷⁹ This is also a prerequisite for the radiation of a photochemical laser. However, in this case the inverted population can also occur between the zero vibrational sublevels of the excited and ground states of the lasing species.

Due to spectral overlap of the stimulated emission of the components, the initial form influences significantly the emission by the photochemical reaction product, and *vice versa* the product influences the emission by the initial form. Thus, the properties of both components of an acid-base system determine the radiation characteristics of the photochemical laser. The energy diagram of the photochemical laser is a combination of 7-level schemes for the initial compound and the photoreaction product. In a general case, the diagram contains 14 levels (Fig. 2). The amplification coefficient of the active medium in such a laser is determined by the equation²²

$$\begin{aligned}
 k_a(\nu) = N_3[\sigma_{31}(\nu) - \sigma_{35}(\nu)] - N_1\sigma_{12}(\nu) - N_6\sigma_{67}(\nu) + \\
 + N_{3'}[\sigma_{3'1'}(\nu) - \sigma_{3'5'}(\nu)] - N_{1'}\sigma_{1'2'}(\nu) - \\
 - N_{6'}\sigma_{6'7'}(\nu) - \sum_i N_{p_i}\sigma_{p_i}(\nu) - k_w(\nu),
 \end{aligned} \quad (7)$$

where the quantities corresponding to the photoreaction product are primed.

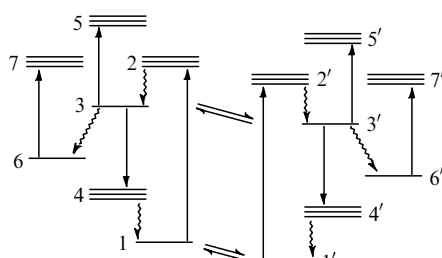


Figure 2. The energy level diagram of the components of a photochemical laser.

Analysis of the features of laser radiation of a system with an intermolecular proton transfer reaction at steady-state excitation⁸⁴ shows that the system is described by two pairs of electronic-vibrational levels for the initial form (1, 2) and the photoreaction product (1', 2'), respectively; the transitions to the triplet levels are absent and the concentration of the reaction product in the ground state $N_{1'}$ is taken to be equal to zero.⁸⁴ When the intensity of excitation (I_e) is higher than the threshold for the photoreaction product (I'_t) and lower than the threshold for the initial form (I_t) and the laser radiation is generated only by the photoreaction product at a frequency ν' , its radiation power is increased with the intensity of excitation up to the maximum value $I'_{\max}$ at $I_e = I_t$. On further increase in I_e , the passage of the system into a two-band generation mode occurs with frequencies ν' and ν :

$$I'(\nu') = I'_{\max}(\nu') - \frac{\sigma_{2'1'}(\nu')}{\sigma_{2'1'}(\nu')} I(\nu),$$

$$I(\nu) = C(I_e - I_t),$$

$$I'_{\max} = \frac{\sigma_{12}(\nu)(N - k_w(\nu)/\sigma_{2'1'}(\nu')) + k_w(\nu)}{k_w(\nu')\sigma_{21}(\nu)[1 + \exp(h(\nu' - \nu_{00})/kT)](k_{22'} - k_{22}^{\min})},$$

$$k_{22'}^{\min} = \frac{k_w(\nu')\sigma_{21}(\nu)k_{2'1'}}{\sigma_{2'1'}(\nu')},$$

where C is a coefficient, N is an analytical dye concentration, ν_{00} is the frequency of the 0–0-transition in the reaction product, $k_{22'}^{\min}$ is a minimum rate of the proton transfer reaction in the excited state, which provides the appearance of lasing of the product. The coefficient c is independent of pump power.

If fluorescence spectra of the initial form and the reaction product do not overlap at the frequencies of lasing ν and ν' [$\sigma_{21}(\nu') = \sigma_{2'1'}(\nu) = 0$], then the laser radiation power for the photoreaction product is independent of I_e if $I_e \geq I_t$. It was concluded⁸⁴ that $I'_{\max}$ is proportional to the rate constant for the proton transfer reaction in the excited state. If fluorescence spectra of the initial form and the product overlap at the frequency of lasing of the initial form [$\sigma_{21}(\nu') = 0$, $\sigma_{2'1'}(\nu) > 0$], then participation of the reaction product in the lasing of the initial form leads to an increase in amplification at the frequency of its lasing. For $I_e \geq I_t$, this leads to the situation, where the power of laser radiation at the frequency ν increases faster than in the previous case, but at the frequency ν' the power drops until the ceasing of generation at

$$I(\nu) = \frac{I'_{\max}(\nu')\sigma_{2'1'}(\nu')}{\sigma_{2'1'}(\nu)}.$$

In other words, two thresholds (upper and lower) in the lasing of the photoreaction product should be observed for such a system. The range of I_e , where two-band laser radiation exists, is the wider the smaller $\sigma_{2'1'}(\nu)$ and the larger $k_{22'}$. Analysis of changes in the generated power of laser radiation at frequencies ν and ν' provided $N_{1'} > 0$ has shown⁸⁴ that at $I_e > I_t$ and $\sigma_{21}(\nu') = \sigma_{2'1'}(\nu) = 0$ the generation threshold at the frequency ν depends on the acidity of the medium due to absorption of the excitation radiation by the photoreaction product $N_{1'}\sigma_{1'2'}(\nu_p)I_p$. A limiting value for the ratio of the rate constants for the direct reaction in the excited state and the reverse reaction in the ground state exists

$$\frac{k_{22'}}{k_{1'1}} = \frac{a}{\sigma_{1'2'}(\nu)},$$

where coefficient a is independent of I_e . If this ratio is greater than the limiting value, the generation threshold for laser radiation of initial form becomes infinitely large.

Neglecting the terms that correspond to the absorption of light by the products of irreversible reactions of photodecay and constant losses in the resonator, Kasha and co-workers^{53,85–87} derived an expression similar to (7) for the change in the

amplification coefficient of a photochemical laser based on the reaction of intramolecular proton phototransfer of 3-hydroxy-flavone in methylcyclohexane. In the approximation of a fast proton transfer reaction in the excited ($k_{3'3} < 8$ ps) and ground states and neglecting the induced absorption $S_n \leftarrow S_1$ [$\sigma_{35}(v) = 0$], $T_n \leftarrow T_1$ [$\sigma_{67}(v) = 0$], $S_n' \leftarrow S_1'$ [$\sigma_{3'5'}(v) = 0$], and $T_n' \leftarrow T_1'$ [$\sigma_{6'7'}(v) = 0$], they obtained an amplification coefficient of the active medium equal to 10 cm^{-1} at an excitation power of 500 kW ($\lambda = 337 \text{ nm}$) and dye concentration of $1.64 \text{ mmol litre}^{-1}$ (Ref. 53).

Radiation kinetics of a photochemical laser based on a binary mixture of dyes, 2-(biphenyl-4-yl)-6-phenylbenzoxazole and 2-(2-hydroxyphenyl)benzoxazole, was studied^{58,88} in the generation band of the first dye and a bifluorophore comprising these two dyes bound chemically. The solution of a direct kinetic problem to describe the radiation kinetics was attempted.⁸⁸ Using literature data on the optical properties of dyes, and experimental characteristics of the exciting radiation (308 nm) and optical resonator, and neglecting the light absorption by the singlet- and triplet-excited molecules, it was concluded⁸⁸ that the laser pulse duration of the first dye should be much smaller in the presence of the second dye. The results of calculation were in agreement with experiment. The laser pulse duration was 3.3 ns in the absence of the second dye and 80 ps in the presence of the second dye. It was assumed in the calculation⁸⁸ that the induced absorption in this system corresponds to absorption of a tautomer of the second dye in the ground state [$\sigma_{1'2'}(v) > 0$]. However, the induced absorption in 2-(2-hydroxyphenyl)benzoxazole was later assigned to $T_n \leftarrow T_1$ absorption of the dye [$\sigma_{67}(v)$].^{89,90}

The dynamics of lasing of the product of the intramolecular proton transfer in salicylamide and derivatives of 2-(2-hydroxyphenyl)benzoxazole in DMF⁴⁸ was described by the system of differential equations based on a previously employed model.^{53,85–88} It was assumed in the calculation that the rate constants for the direct proton transfer in singlet excited state of initial form ($k_{22'}$) and reverse proton transfer in triplet excited state ($k_{6'6}$) are equal to 10^{12} and 10^9 s^{-1} , respectively. Absorption by the excited singlet state [$\sigma_{35}(v) = \sigma_{3'5'}(v) = 0$] was neglected. The values calculated $\sigma_{1'2'}(v) = 8.0 \times 10^{-19} - 2.3 \times 10^{-17} \text{ cm}^2$ correlate linearly with a cross-section of stimulated emission of the tautomer at a frequency of the spectral maximum of lasing (this was estimated from the fluorescence spectrum). It was concluded⁵⁸ that the rate of reverse proton transfer in the ground state ($k_{1'1} = 1.50 \times 10^8 \text{ s}^{-1}$) and light absorption by the reaction product in the ground state are the main factors determining lasing of the product of intramolecular proton phototransfer of 2-(2-hydroxyphenyl)benzoxazoles and salicylamide.

III. Selection criteria of acid-base systems for active media in photochemical lasers

The cross-section of stimulated emission (σ_{34}) is the main criterion, which determines the possibility of lasing by an organic compound on a certain frequency. The cross-section should exceed the threshold value estimated according to the following formula¹¹

$$\sigma_{34}^{-1} = 8\pi n^2 c v_f^2 \Delta v_f \tau_f,$$

where n is the refractive index of the medium, c is the velocity of light, τ_f is the radiative lifetime of fluorescence, v_f and Δv_f are the frequency of maximum and the peak halfwidth of the fluorescence spectrum, respectively.⁸⁰ Analysis of cross-sections of stimulated emission for the known laser dyes allows one to determine the threshold value σ_{34} for the existence of lasing in organic compounds as $\sigma_{34} > 5 \times 10^{-17} \text{ cm}^2$ (Ref. 91). Spectral criteria for the occurrence of lasing in organic compounds were suggested⁸¹ taking account of the relation between the cross-section of stimulated emission and spectral characteristics of a laser dye. Quantum-chemical criteria for the occurrence of laser radiation in organic compounds were also formulated.^{92,93}

Along with cross-section σ_{34} the product of a photochemical reaction, thermodynamic and kinetic parameters of the reaction determine the efficiency of photochemical laser radiation. There are no rigorous quantitative criteria for the selection of lasing systems with proton phototransfer reactions. The following spectral-kinetic criteria for the selection of systems for the photochemical laser were suggested based on the analysis of the known laser systems with proton phototransfer reactions.^{9,15}

1. The initial compound (which absorbs light and in which the proton phototransfer reaction occurs) should absorb light strongly in excitation spectral range. The extinction coefficient should be greater than $10^4 \text{ litre mol}^{-1} \text{ cm}^{-1}$ at the excitation frequency.

2. The proton phototransfer reaction should be fast and efficient (*i.e.*, with low efficiency of competing radiationless deactivation processes). The rate constants for the intermolecular and intramolecular proton phototransfer should be greater than $10^8 \text{ litre mol}^{-1} \text{ s}^{-1}$ and 10^9 s^{-1} , respectively.

3. The product of the proton phototransfer reaction should possess intense fluorescence. The fluorescence quantum yield should be greater than 0.2.

4. The acid-base properties of the dye should be changed significantly ($\Delta pK_a > 1$) upon excitation to provide for the direct reaction of the proton transfer in the initial excited form of the dye and reverse reaction of the proton transfer in the product in the ground state.

5. The radiative transition in the product of the proton phototransfer reaction should possess a short radiative lifetime of fluorescence ($\tau_f < 10 \text{ ns}$).

6. The rate of the reverse proton transfer reaction in the ground state should be significantly higher than the overall rate of the direct reaction of proton phototransfer in the excited state and the formation of the product of proton transfer in the ground state resulting from deactivation of the excited state.

7. The absorption spectra $S_n \leftarrow S_0$, $S_n \leftarrow S_1$ and $T_n \leftarrow T_1$ of the initial form of the dye and reaction product of proton phototransfer should possess minimum overlap with the fluorescence spectrum of the proton phototransfer product. The absorption coefficient at the frequency of lasing should not be higher than 0.01 cm^{-1} .

8. The steady-state concentration of molecules in the triplet state of the initial form of the dye and the proton phototransfer product should be low, which is ensured by a low rate constant for intersystem crossing from the S_1 state and a large rate constant for intersystem crossing from the T_1 state.

9. The initial form of the dye and the product of the proton phototransfer reaction should be photochemically stable.

The majority of dyes listed in Tables 1–3 fulfil the above-mentioned requirements. 2-Naphthol, potassium 7-hydroxynaphthalene-1,3-disulfonate, 1,3-disulfo-7-naphthylammonium hydrogensulfate, and sodium salicylate are the exceptions. The extinction coefficients for these compounds at the excitation wavelength are smaller than $10^4 \text{ litre mol}^{-1} \text{ cm}^{-1}$. The radiative lifetime of fluorescence of the proton phototransfer products is greater than 10 ns. In spite of this, the reaction products of proton phototransfer of these compounds, except for the deprotonated form of 2-naphthol, lase. This is due to the fact that the numerical value of the criterion 5 permits selection of lasing dyes among all fluorophores. Aqueous 2-naphthol solution is also a useless laser system because the rate constant for the proton phototransfer for 2-naphthol in water is significantly smaller than $10^8 \text{ litre mol}^{-1} \text{ cm}^{-1}$. The overlap of the absorption and fluorescence spectra will be the smaller the higher Stokes' shift of fluorescence. In the formation of the lasing form as a result of reaction in the excited state, Stokes' shift is increased significantly (see Tables 1–3).

IV. Acid-base laser systems

Schaefer⁹⁴ was the first to report in 1968 on a photochemical laser based on a product of intermolecular acid photodissociation reaction of sodium 8-acetylaminopyrene-1,3,6-trisulfonate. In the ground state in basic solution the dye exists in the form of a trianion. In the excited state, the trianion dissociates to form a tetraanion. In the excitation by a lamp the laser radiation in a neutral solution is observed for the trication and in a basic solution for the tetraanion. The laser radiation spectrum in basic solution is shifted to longer wavelengths by 125 nm compared to the spectrum in neutral solution. The duration of the radiation pulse in basic solution (1400 ns) is greater than in neutral solution (250 ns).⁹⁵

Laser radiation was obtained in 1970 from an ethanolic solution of sodium salicylate upon laser-induced excitation.⁹⁶

The species that lased was not identified. However, the data then available and current data on fluorescence of sodium salicylate in ethanol allow assignment of this radiation to the product of intramolecular proton phototransfer to the oxygen of the carboxy group.⁹⁷ For the first time lasing of a product of intramolecular proton phototransfer and identification of a radiating species was reported⁹⁸ in a study of stimulated emission of 2-(2-tosylaminophenyl)-5-phenyl-1,3,4-oxadiazole and 2-(2-tosylaminophenyl)-benzoxazole in ethanol. The lasing species results from the intramolecular proton phototransfer from the nitrogen of the amino group of the phenyl ring to the nitrogen atoms of the oxadiazole and oxazole rings, respectively. The photochemical lasers known to date based on intermolecular and intramolecular reactions of proton phototransfer of organic compounds are listed in Tables 4 and 5.

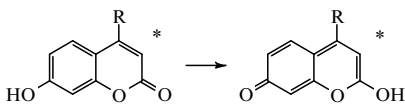
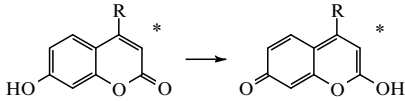
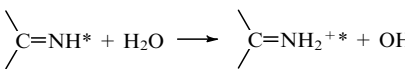
Table 4. Characteristics of photochemical lasers based on intermolecular proton phototransfer reactions of organic compounds.

Reagents	c_1 /mmol litre ⁻¹	c_2 /mol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
$\text{ArOH}^* + \text{H}_2\text{O} \longrightarrow \text{ArO}^{*-} + \text{H}_3\text{O}^+$						
Potassium 7-hydroxynaphthalene-1,3-disulfonate + H ₂ O	1	56	Water	475 ^a	—	99
	4.6	56	"	466–484 ^b	—	15
	4.6	56	Water, pH 5	460–490 ^b	—	22
Sodium 8-hydroxypyrene-1,3,6-trisulfonate + H ₂ O	0.2	56	Water	516–532 ^c	—	100
	0.02	56	Water, pH 5.6	520 ^d	—	101
				(2.9×10^{-16} , Ref. 2) ^e		
7-Hydroxycoumarin + H ₂ O	5	44	EtOH, water (1:4)	460 ^b	10	102
	1	56	Water	457 ^c	—	103
7-Hydroxy-4-methylcoumarin + H ₂ O	5	44	EtOH, water (1:4)	460 ^b	7	102
	1	56	Water	430–485 ^c	—	104
	5	22	MeOH, water (3:2)	425–545 ^a	—	105
7-Hydroxy-4-trifluoromethylcoumarin + H ₂ O	5	2.8	EtOH, water (19:1)	513 ^b	14.8	102
Ethyl 7-hydroxycoumarin-3-carboxylate + H ₂ O	—	56	Water	465 ^c	—	106
3-Cyano-7-hydroxy-4-methylcoumarin + H ₂ O	2	28	EtOH, water (1:1)	450–510 ^a	—	107
$\text{ArOH}^* \cdot \cdot \cdot \text{NAlk}_n\text{H}_{3-n} \longrightarrow \text{ArO}^{*-} + \text{H}_{4-n}\text{NAlk}_n$						
7-Hydroxy-4-methylcoumarin + Et ₃ N	—	—	Toluene	415 ^d	—	108
7-Hydroxy-4-methylcoumarin + Et ₂ NH	—	—	"	470–480 ^d	—	108
$\text{ArNHAc}^* + \text{B} \longrightarrow \text{ArNAc}^{*-} + \text{BH}^+$						
Sodium 8-acetylaminopyrene-1,3,6-trisulfonate + NaOH	—	—	Water	566–574 ^{a, b}	—	95
$\text{ArNH}_3^+ + \text{B} \longrightarrow \text{ArNH}_2^* + \text{BH}^+$						
1,3-Disulfo-7-naphthylammonium	19	56	Water, pH 1	450–484 ^b	—	22
hydrogensulfate + H ₂ O	10	56	Water, pH 0.5	Blue radiation ^c	—	22
	10	56	Water	459 ^c	—	109
3,3-Dimethyl-2-(5-(7-R-3,3-dimethyl-2,3-dihydropyrrolo[2,3- <i>b</i>]-pyridinio-2-yliden)-penta-1,3-dienyl)-7R-2,3-dihydropyrrolo[2,3- <i>b</i>]pyridinium + OH ⁻	—	—	EtOH	730 ^f	10	110

Table 4 (continued).

Reagents	c_1 /mmol litre ⁻¹	c_2 /mol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
$\text{>C=O}^* + \text{HA} \longrightarrow \text{>C=OH}^{+*} + \text{A}^-$						
3-Methoxybenzanthrone + HClO ₄	30	0.02	EtOH	540–660 ^d	–	111
3-Methoxybenzanthrone + AcOH	2.5	17.5	AcOH	563–586 606–627 ^d	– 0.9	33
7-Ethyl-4-methylcoumarin + HCl	1	–	EtOH	485 ^a	–	112
4,6-Dimethyl-7-methylamino- coumarin + HCl	1.5 –	– 0.1	" EtOH, water (24 : 1)	430–525 ^a 484 ^c	5 –	113 115
7-Ethylamino-4,6-dimethyl- coumarin + HCl	–	0.1	Ditto	487 ^c	–	114
2,3,6,7-Tetrahydro-1 <i>H</i> ,5 <i>H</i> -benzo- pyrano[6,7,8- <i>ij</i>]quinolizin-11-one + H ₂ SO ₄	2	0.2	"	474–548 ^a	4.8	115
9-Methyl-2,3,6,7-tetrahydro- 1 <i>H</i> ,5 <i>H</i> -benzopyrano[6,7,8- <i>ij</i>]quino- lizin-11-one + H ₂ SO ₄	2	0.15	"	525–556 ^a	10	15
<i>N</i> -Phenylacridone + CF ₃ COOH	2.5	0.14	Toluene	472 ^d	0.2	33
3-Methoxybenzanthrone + CF ₃ COOH	2.5	0.13	"	611–641 ^d	2.5	33
$\text{>N}^* + \text{HA} \longrightarrow \text{>N}^{+*} + \text{A}^-$						
5-Phenyl-2-(4-pyridyl)oxazole + AcOH	0.86 0.86 0.86 0.86 0.96	1.80 2.35 2.85 3.75 4.60	EtOH " " " "	506–520 ^a 512–522 ^a 510–520 ^a 505–517 ^a 501–515 ^a	0.4 0.6 1.0 2.0 2.6	116 116 116 116 116
5-(Methoxyphenyl)-2-(4-pyridyl)- oxazole + AcOH	0.70 0.70 0.70 0.70 0.70 0.70	0.92 1.62 2.26 2.68 3.69 4.57	" " " " " "	570–594 ^a 554–589 ^a 560–585 ^a 550–583 ^a 549–583 ^a 545–582 ^a	2.7 6.1 7.8 9.5 12 16	116 116 116 116 116 116
5-Phenyl-2-(2-quinolyl)-oxazole + AcOH	0.71	5.85	"	514–534 ^a	7.9	116
5-Phenyl-2-(4-quinolyl)-oxazole + AcOH	0.86	5.57	"	512–521 ^a	2.3	116
1,4-Bis(5-phenyloxazol-2-yl)benzene + HClO ₄	0.4	–	MeCN	479–490 ^a	3.6	42
1,4-Bis(5-phenyloxazol-2-yl)benzene + CF ₃ COOH	0.4	–	CF ₃ COOH	460–476 ^a	17.0	42
1,4-Bis(5-sulfoxyphenyloxazol-2-yl)- benzene + CF ₃ COOH	–	–	EtOH, water (3 : 1)	489–499 ^a	2.9	42
1,4-Bis(5-sulfoxyphenyloxazol-2-yl)- benzene + HClO ₄	–	–	Ditto	485–499 ^a	5.5	42
1,4-Bis(5-sulfoxyphenyloxazol-2-yl)- benzene + H ₂ SO ₄	–	–	Water	451–458 ^a	7.1	42
$\text{>N}^* \cdots \text{HA} \longrightarrow \text{>N}^{+*} \cdots \text{A}^-$						
1,4-Bis(5-phenyloxazol-2-yl)benzene + CF ₃ COOH	0.4	–	Dioxane	476–491 ^a	14.2	42
1,4-Bis(5- <i>p</i> -tolylloxazol-2-yl)benzene + CF ₃ COOH	–	–	"	487–500 ^a	4.7	42

Table 4 (continued).

Reagents	c_1 /mmol litre ⁻¹	c_2 /mol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
						
7-Hydroxycoumarin	5	—	EtOH, water 2.7% HClO ₄	487 ^b	0.9	102
7-Hydroxy-4-methylcoumarin	—	—	EtOH, water (24 : 1)	408, 487 ^b	4.0	117
	5	—	MeOH, 0.37 N HClO ₄ (3 : 2)	450–600 ^a	—	105
	5	—	EtOH, water 2.7% HClO ₄	487 ^b	0.4	102
	—	—	EtOH, water (24 : 1)	400, 480 ^b	7.3	117
	1.8	—	EtOH	477–546 ^a	—	118
7-Hydroxy-4-trifluorocoumarin	—	—	EtOH, water (3 : 2)	437–544 ^a	—	119
	5	—	EtOH, water, 15% HClO ₄	576 ^b	1.9	102
	—	—	EtOH, water (24 : 1)	530 ^b	10.7	117
	—	—	EtOH, water (1 : 1)	513 ^b	11.8	117
	0.75	—	Ditto	506 ^c	—	120
6-Glucosyl-7-hydroxy- coumarin	—	—	Water	440–490 ^c	—	121
3-Cyano-7-hydroxycoumarin	—	—	EtOH, water (7 : 3)	490–520 ^c	—	122
3-Cyano-7-hydroxy-4-methyl- coumarin	2	—	EtOH, water (9 : 1), 2.5 mM HClO ₄	440–505 ^a	—	107
3-Cyano-7-hydroxy-4-trifluoro- methylcoumarin	—	—	EtOH, water (24 : 1)	543 ^b	12.6	117
—	—	—	EtOH, water (1 : 1)	543 ^b	6.5	117
Two reactions simultaneously						
						
7-Hydroxy-4-methylcoumarin + H ₂ O	—	—	EtOH, water	370–530 ^d	—	123
7-Hydroxy-4-trifluoromethyl- coumarin + H ₂ O	5	—	EtOH, water (50%, 35%), 15% HClO ₄	510–595 ^b	10	102
						
5 <i>H</i> -9-Diethylamino-5-imino- benzo[<i>a</i>]phenoxazine + H ₂ O	0.14	3.3	EtOH, KOH (3 mmol litre ⁻¹)	610–715 ^f	—	38

Note. The following designations are adopted. c_1 and c_2 are concentrations of the first and second components, respectively.

Excitation source : ^a nitrogen laser (337 nm); ^b excimer laser (308 nm); ^c pulse lamp; ^d the second harmonic of a ruby laser (347.1 nm). ^e Cross-section of stimulated emission estimated according to the equation $\sigma_{34} = I_{1/2}\tau'$,¹⁰¹ where $I_{1/2}$ is the intensity of light leading to half the fluorescence intensity, τ' was taken from Ref. 26. ^f The second harmonic of a YAG: Nd³⁺-laser (532 nm).

Table 5. Characteristics of photochemical lasers based on intramolecular proton phototransfer reactions of organic compounds.

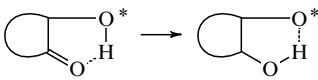
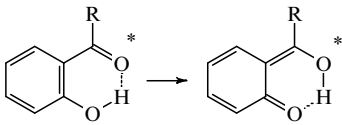
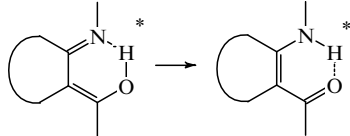
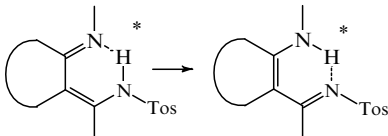
Reagent	c /mmol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
					
3-Hydroxyflavone	1.64	Methylcyclohexane	518–545 ^a	1.2 ^b	53
	1.64	Dioxane	535 ^a	—	53
	3.0	MeCN	526 ^a	—	124
	3.0	Acetone	526 ^a	—	124

Table 5 (continued).

Reagent	c /mmol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
3,3',4',7-Tetrahydroxyflavone	2.0	Dioxane	544–570 ^a	0.14 ^b	124
					
Sodium salicylate	1	EtOH	395–417 ^a	—	96
	1	Dioxane	390–411 ^c	7	125
Salicylamide	1	DMF	439 ^c	5	126
					
2-(Benzimidazol-2-yl)phenol	2.1	Dioxane	460–490 ^c	14.5	56
	2.0	MeOH	450–480 ^c	6.0	56
	1.9	EtOH	454–480 ^c	3.0	56
	2.6	MeCN	459–489 ^c	9.0	56
	1.9	DMF	463–495 ^c	11.5	56
2-(Benzimidazol-2-yl)-4-methylphenol	1.2	Dioxane	475–522 ^a	15.5	56
2-(Benzimidazol-2-yl)-4-fluorophenol	0.7	MeCN	465–510 ^a	10	56
	1	Polymethylmethacrylate	487–499 ^a	1	127
2-(Benzimidazol-2-yl)-4-methoxyphenol	1	Cyclohexane, Dioxane	509–537 ^a	5.5	56
	1.4	"	514–552 ^a	9.0	56
2,5-Bis(benzimidazol-2-yl)hydroquinone	1	Cyclohexane, Dioxane	509–542 ^a	8.0	56
	1	MeCN	507–540 ^a	10.0	56
	1.4	Dioxane	515–549 ^a	13.5	56
	1.5	DMF	515–553 ^a	7.0	56
Methyl 2-(2-hydroxyphenyl)benzimidazole-5(6)-carboxylate	0.5	Polymethylmethacrylate	489–499 ^a	0.5	128
Methyl 2-(5-fluoro-2-hydroxyphenyl)benzimidazole-5(6)-carboxylate	0.5	"	499–517 ^a	1.8	128
Copolymer of allyl-2-(2-hydroxyphenyl)benzimidazole-5(6)-carboxylate and methyl methacrylate	0.5	"	490–504 ^a	1.4	128
Copolymer of allyl-2-(5-fluoro-2-hydroxyphenyl)benzimidazole-5(6)-carboxylate and methyl methacrylate	0.5	"	502–521 ^a	11.3	128
3,6-Bis(benzoxazol-2-yl)hydroquinone	—	THF	650 ^a , 620–690 ^d	—	129
4-Methoxy-3,6-bis(benzoxazol-2-yl)phenol	—	"	615 ^a , 590–690 ^d	—	129
3,6-Bis(benzoxazol-2-yl)pyrocatechol	—	"	560 ^a , 540–610 ^d	—	129
2,2'-Bipyridyl-3,3'-diol	3	{ Dioxane Benzene Dioxane Cyclohexane	490–573 ^a	12	130
			495–567 ^a	3	63
			494–567 ^a	2	63
			492–572 ^a	4	63
5-Methyl-2,2'-bipyridyl-3,3'-diol	3	Dioxane	503–564 ^a	6.5	130
5,5'-Dimethyl-2,2'-bipyridyl-3,3'-diol	3	"	503–573 ^a	7.2	130

 $\varepsilon c = 20 \text{ cm}^{-1}$

Table 5 (continued).

Reagent	c /mmol litre ⁻¹	Solvent	Radiation range /nm	Laser efficiency (%)	Ref.
	—	EtOH	530 ^a	—	98
<i>N</i> -[2-(benzoxazol-2-yl)phenyl]toluene- <i>p</i> -sulfamide	—	"	530 ^a	—	98

Note. ^a Excitation by a nitrogen laser (337 nm). ^b The ratio of peak power to peak power of laser radiation of Rhodamine 6G. ^c Excitation by an excimer laser (308 nm). ^d Spectral range of amplification.

V. Losses in photochemical lasers

The efficiency of dye lasing is determined by the relationship between the light amplification and losses. The losses are classified as constant and induced losses. The former are the losses in the resonator and at the mirrors. In dye lasers overabsorption of the laser radiation by the dye in the ground state (for a photochemical laser, by the components of acid-base interaction) belong to the constant losses in addition to those mentioned above. The constant losses are time independent. The induced losses in dye lasers are related to the absorption of lasing by short-living intermediate species produced by the excitation light.

Induced losses in photochemical lasers unlike ordinary lasers may occur due to photoprotolytic reactions. Let us consider these induced losses.

1. Absorption of the laser radiation by the product of a photochemical reaction in the excited singlet [terms $N_3\sigma_{35}(v)$ and $N_3'\sigma_{3'5'}(v)$ in the equation (7)] and triplet [terms $N_6\sigma_{67}(v)$ and $N_6'\sigma_{6'7'}(v)$] states of the components of the acid-base interaction.

Acid-base systems with simultaneous lasing of the initial compound and the photoreaction product are the most valuable from the practical viewpoint. In the selective resonator of such a system, it is possible to attain laser radiation tuned over a wide spectral range, which exceeds the range of tuning for the individual components of the acid-base system. Lasing of the initial compound and the reaction product separately does not necessarily imply their simultaneous lasing. Thus 2-heteryloxazoles and their cations fluoresce efficiently and lase separately.⁴⁰ However, solutions with simultaneous efficient fluorescence of both the initial heteryloxazole and cation, do not lase at certain ratio of the components. As the concentration of a proton donor (acetic acid) in ethanolic solutions of 2-heteryloxazoles is increased, the quantum yields of fluorescence of the initial form are decreased, and a band of fluorescence of a protonated form resulting from the proton phototransfer appears in the longwave region of the spectrum,³⁰ and the efficiency of laser radiation of the initial form drops to zero at low concentrations of acetic acid. At certain concentrations, both forms do not lase. At higher acetic acid concentrations, the laser radiation of the photoreaction product appears and the efficiency of this radiation increases with the increase in the acid concentration.¹¹⁶ Both the neutral and the protonated forms of 2-heteryloxazoles cause additional losses, which decrease stimulated emission by the corresponding conjugated acid-base form. For this reason, it is impossible to produce two-band laser radiation in solutions of 2-heteryloxazoles. The losses due to the neutral form in the lasing by the cations result from the $S_n \leftarrow S_1$ absorption of the neutral forms. The losses due to the cations in the lasing by the neutral forms, in addition to $S_n \leftarrow S_1$

absorption in the region of stimulated emission of the neutral forms, may result from slow dissociation of the cations in the ground state.¹¹⁶

2. Light absorption by decay products of a lasing species.

Reactions of electron photosplitting are typical of the aromatic compounds with the electron-donor group (OR, NR₂, O⁻). The thus formed solvated electron has a broad absorption spectrum,¹³¹ which can overlap with that of laser radiation of a photochemical laser. Thus flash lamp excitation of an aqueous solution of sodium 8-hydroxypyrene-1,3,6-trisulfonate (SHPTS) induced losses in the photochemical laser that are related to the absorption of the laser radiation from the deprotonated form of SHPTS by the hydrated electron produced from this excited form.¹³² The light absorption by the hydrated electron leads to a decrease in the efficiency and narrows the lasing spectrum of SHPTS. In the laser excitation, the induced losses in this laser are small.¹⁰¹ A decrease in the hydrated electron concentration due to its interaction with electron acceptors results in a decrease in these induced losses and an increase in the laser radiation efficiency of SHPTS in the lamp excitation.¹³²

If the 7-aminonaphthalene-1,3-disulfonate dianion is formed in acidic solutions by the reaction of an acid photodissociated monoanion with the protonated amino group, the efficiency of the lasing upon pulse photoexcitation is considerably higher compared to that upon direct excitation from the ground state in neutral solutions.²² This increase in efficiency is rationalised as a decrease in losses, due to the induced $T_n \leftarrow T_1$ absorption of light by the 7-aminonaphthalene-1,3-disulfonate dianion upon protonation of the amino group of the dianion triplet ($\sigma_{67} < \sigma_{6'7'}$) in acidic solutions and a decrease in losses, caused by the light absorption by the hydrated electron, as a result of the effective reaction of the electron with the proton.

VI. Tunable photochemical lasers

Systems with intermolecular relaxation processes that allow excitation of two or several different lasing species are promising for designing lasers tunable over a wide spectral range. This can be achieved in systems with electron energy transfer if both the donor and acceptor lase and in systems with fast reversible photochemical reactions provided both the initial species and the reaction product lase simultaneously.⁹ Favourable relative disposition of the spectra of laser radiation of the components in binary systems with energy transfer and in systems with photoprotolytic reactions enables generation of laser radiation over a wide spectral range in a selective resonator.

The acid-base systems with simultaneous laser radiation of both photoprotolytic forms are few. In the majority of photo-

Table 6. Characteristics of photochemical lasers based on binary dye systems.

Binary dye system	c_1 /mmol litre ⁻¹	c_2 /mmol litre ⁻¹	$\lambda_1 - \lambda_2$ or λ /nm
7-Hydroxy-4-methyl-coumarin ^a + sodium	2.4	0	426–515
8-hydroxypyrene-1,3,6-trisulfonate ^a in EtOH – water solution (3:7)	2.4	0.15	440–523
	0	0.5	507–534
6-Glucosyl-7-hydroxy-coumarin ^a + sodium	2.4	0	436–516
8-hydroxypyrene-1,3,6-trisulfonate ^a in water	2.4	0.15	441–527
	0	1.0	506–533
7-Diethylamino-4-methyl-coumarin ^a + sodium	1.6	0	450–510
8-hydroxypyrene-1,3,6-trisulfonate ^a in EtOH – water solution	1.6	0.12	453–525
	0	0.7	510–535
1,4-Bis(5-phenyl-1-propionyl- Δ^2 -pyrazolin-3-yl)benzene + 7-hydroxy-4-methyl-coumarin ^a in EtOH – water solution, (9:1), 0.05 mol litre ⁻¹ AcONa	0.5	0	404–418
	0.5	4	416–470
	0	2	429–497
1,4-Bis(5-phenyl-1-propionyl- Δ^2 -pyrazolin-3-yl)benzene + 7-diethylamino-4-methyl-coumarin ^b in dioxane – water solution, (19:1)	0.5	0	405–417
	0.5	1	413–457
	0	2	435–473
3-Hydroxyflavone ^a + 1,1,4,4-tetraphenylbutadiene in methylcyclohexane	0	1.64	528–540
	3.5	1.64	509–540
	4.5	1.64	500–534
	4.5	1.24	496–528
	4.5	0	490–525
2-(Benzimidazol-2-yl)-4-methylphenol ^a + 2,5-bis-(benzimidazol-2-yl)hydroquinone ^a in dioxane	1.3	0	495
	1.2	0.1	502
	1.1	0.2	505
	0.9	0.4	509
	0.8	0.5	511
	0.7	0.6	515
	0.6	0.7	516
	0.4	0.9	519
	0.2	1.1	525
	0	1.3	527
2-(Benzimidazol-2-yl)-4-methylphenol ^a + 2,5-bis-(benzimidazol-2-yl)hydroquinone ^a in acetonitrile	2.6	0	474
	2.2	0.1	478
	2.0	0.3	488
	1.6	0.5	496
	1.3	0.5	503
	0.9	0.7	512
	0.4	0.9	520
	0	1.0	524

Note. The following designations are adopted: c_1 is the concentration of the first component of the binary dye system, c_2 is the concentration of the second component of the binary dye system, $\lambda_1 - \lambda_2$ is the range of tuning of lasing, λ is the wavelength of spectral maximum of laser radiation. The data for the first five binary dye systems are taken from Ref. 134, for the next system from Ref. 133, and for the two last systems from Ref. 56. ^a The component that undergoes proton phototransfer reaction. ^b The component that forms a hydrogen-bond complex in the excited state.

chemical lasers (see Tables 4 and 5), stimulated light emission by the reaction product only is observed. This narrows substantially the possibility for creation of an increased range of tunable radiation in dye lasers. Binary mixtures were suggested to overcome this difficulty. In these mixtures, one or both components participate in photoprotolytic reactions.^{133,134} Realisation of a large Stokes' shift of fluorescence, due to adiabatic reactions of proton phototransfer allows the selection of binary solutions where the fluorescence band of one of the components lies in the spectral range between the absorption band and the fluorescence band of the second component. This allows one to create active media of lasers with an expanded range of the laser radiation tuning within the limits of the total luminescence band of the binary mixture components.

To increase substantially the tuning range of laser radiation in binary mixtures with photoprotolytic reactions it is necessary that first, the fluorescence bands are shifted relative to each other to make the total amplification band noticeably wider than the amplification bands of the individual components. Second, the energy transfer between components should not occur, that is, the absorption band of one component should not overlap with the fluorescence band of the other component. These requirements can be met if systems with a high Stokes' shift of fluorescence are used, e.g. systems with photoprotolytic reactions.¹³⁴ In coherent excitation, compounds should possess substantial absorption at the excitation wavelength. In lamp excitation the absorption spectra of the components should have minimum overlap to utilise efficiently the pump energy. For some binary mixtures of this type, broadening of the tuning range or shift of the maximum of laser radiation is observed at a certain ratio of the components (Table 6).

The spectrum of stimulated emission of 2,2'-bipyridyl-3,3'-diol in which intramolecular proton phototransfer occurs exhibits a blue shift in dioxane upon addition of 7-ethylamino-6-methyl-4-trifluoromethylcoumarin.⁶³ This effect depends on the relative concentration of the components. If spectra of laser radiation of components of a binary mixture are far removed from each other, the mutual influence of the components on the spectral position of their laser radiation is absent. The spectrum of stimulated emission of a mixture of 1,4-bis(2-methylstyryl)benzene (0.8×10^{-3} mol litre⁻¹) and 3-hydroxyflavone (3×10^{-3} mol litre⁻¹) which undergoes intramolecular proton phototransfer, exhibits two peaks at 420 and 535 nm in dioxane.¹³³ These maxima coincide with those of stimulated emission of the individual components in the same solvent and their relative intensities depend on the relative concentrations of the components. A similar picture is observed for a solution of 4,4'-diphenylstilbene (1.2×10^{-3} mol litre⁻¹) and 3-hydroxyflavone (1.64×10^{-3} mol litre⁻¹) in dioxane. Two maxima at 408 and 535 nm,¹³³ which correspond to the stimulated emission of individual components, are observed in the spectrum of stimulated emission of a mixture.

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Types of cationic complexes based on oxocentred tetrahedra [OM₄] in the crystal structures of inorganic compounds

S V Krivovichev, S K Filatov, T F Semenova

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Abstract. The crystal structures of inorganic compounds comprising cationic complexes containing oxygen atoms coordinated tetrahedrally to metal atoms, or oxocentred groups [OM₄], are considered. The linking of the [OM₄] tetrahedra in the structures has been analysed and cationic complexes of different structures have been identified. The rules governing the linking of the [OM₄] tetrahedra have been formulated and the cationic complexes have been subjected to a detailed systematic treatment on their basis. Data on the statistics of the bond lengths and bond angles in the [OM₄] tetrahedra are presented. The bibliography includes 317 references.

I. Introduction

One of the approaches to the description of crystal structures is the identification in the latter of cations as the central atoms and of anions as ligands. However, a number of crystal structures can also be considered from the standpoint of the coordination of anions^{1–7} and in particular of oxygen atoms (Al₂O, Al₃O,^{8,9} Mg₂O, Mg₃O,^{10–13} Li₃O, Li₄O, Li₅O,^{14,15} Na₃O, Na₄O, K₃O, K₄O,^{16,17} *etc.* clusters). Some workers^{18–21} have used this approach for the description of crystal structures, identifying in the latter individual atomic groups formed by anions as the central atoms and by cations as the ligands. The development of this approach constitutes the subject of the crystal chemistry of compounds with oxocentred complexes, within the framework of which one considers ‘additional’ oxygen atoms — atoms which do not enter into the composition of the traditional anionic complexes [T_mO_m] (T = Si, Ge, B, S, P, V, As, Se, *etc.*) and water molecules — as the coordination centres. We emphasise that the proposed method applies only to cationic complexes and does not alter the classification of structures based on the type of anionic groups. In most cases, the ‘additional’ oxygen atoms are involved in the tetrahedral coordination of metal atoms and oxygen is thus

the central atom in cationic [OM₄]ⁿ⁺ complexes. We may note that the coordination of the ‘additional’ oxygen atom in the complex originally studied structurally was not as a rule analysed, but sometimes an oxocentred complex based on [OM₄] groups was identified in connection with the main alternative description of the structure. For example, Sahl²² described the structure of lanarkite Pb₂O(SO₄) on the basis of chains of [OPb₂], consisting of edge-linked [OPb₄] tetrahedra and sulfate groups [SO₄]. Apparently the first systematic study on this topic is that of Bergerhoff and Paeslack,¹⁹ where the authors specified only ‘additional’ oxygen atoms as the centres for a series of tetrahedral complexes based on [OM₄] groups. The calculation of the stoichiometric cation/additional oxygen atom ratios, which are sometimes appreciably greater than unity, serves as the crystal-chemical basis for this approach. Thus in the structure of dolerophanite Cu₂O(SO₄),^{23,24} the ratio is 2, which provides grounds for considering the ‘additional’ oxygen atom as the coordination centre. Six oxocentred complexes based on [OM₄] tetrahedra have been identified:¹⁹ a single tetrahedron, a chain, three types of layers, and one framework. Such a small structural diversity of [OM₄] complexes is due to the fact that at the time when the above communication was written¹⁹ (1968) few structures with ‘additional’ oxygen atoms were known. Later Carre *et al.*²⁰ analysed a series of compounds with complexes based on oxocentred [OLa₄] tetrahedra. They specified²⁰ five different types of complexes considered as derivatives of the oxocentred [OLa] layer. Bengtsson and Holmberg²¹ published a review on the structural chemistry of crystalline and amorphous media containing [OPb₄] tetrahedra. Oxocentred [OPb₄] tetrahedra have been found in glasses of the PbO–PbF₂ system.^{25–27} They produce a three-dimensional framework made up of O–Pb–O linkages and performing in essence a function analogous to that of the [SiO₄] tetrahedra in silicate glasses. The [OCu₄] tetrahedra are well known in organometallic chemistry as the central groups in copper(II) μ_4 -oxo-complexes.^{28–37} Ten types of [OCu₄] complexes have been identified^{38–41} and their characteristic features have been noted: the cationic nature of [OM₄] tetrahedral complexes; owing to the large size of the central atom and its relatively low charge (2–), the tetrahedra are linked to one another not only *via* common corners but also *via* their edges and there is also a possibility of corners common to more than two tetrahedra (this accounts for the exceptional diversity of the types of complexes).

S V Krivovichev, S K Filatov, T F Semenova St.-Petersburg State University, Universitetskaya naberezhnaya 7/9, 199034 St.-Petersburg, Russian Federation. Fax (7-812) 218 13 44. Tel. (7-812) 218 96 47. E-mail: flt@cryst.geol.pu.ru (S V Krivovichev)

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Inorganic compounds incorporating an oxygen atom with tetrahedral coordination involving metal atoms are examined in the present review and a systematic crystal-chemical description of the ways in which the oxocentred $[\text{OM}_4]$ groups are linked together to form cationic $[\text{OM}_n]$ complexes is given.

II. The bond lengths in $[\text{OM}_4]$ complexes and the physical properties of compounds with $[\text{OM}_4]$ tetrahedra

The identification of the oxocentred cationic $[\text{OM}_4]$ complexes as structural units of a special type arose because of the high strength of the O–M bonds in these groups. Table 1 presents the average M–O distances (M = Cu, Sn, Pb, La) in structures with tetrahedrally coordinated ‘additional’ oxygen atoms O_A and the anionic $[\text{TO}]_n$ complexes formed by the central atom T and the oxygen atoms O_T as the ligands $\{[\text{TO}_3], \text{T} = \text{Se, As}; [\text{TO}_4], \text{T} = \text{S, Cr, V, P, Ge}; [\text{TO}_6], \text{T} = \text{Mo, Re}\}$. Thus the average M– O_A and M– O_T distances are 1.93 and 1.99 Å respectively for M = Cu, 2.23 and 2.42 Å for M = Sn, 2.33 and 2.69 Å for M = Pb, and 2.42 and 2.60 Å for M = La. We may note that bonds longer than 2.1 Å were not taken into account in calculating the Cu–O bond lengths.

The O_A –M bond is on average shorter than O_T –M, which suggests a high bond strength in the oxocentred tetrahedral complexes and influences the physical properties of the chemical compounds.

We shall consider as an example the crystal structure of georgbokiite $\text{Cu}_5\text{O}_2(\text{SeO}_3)_2\text{Cl}_2$ (Fig. 1). In this structure, there are isolated groups (SeO_3) with Se atoms involved in ternary

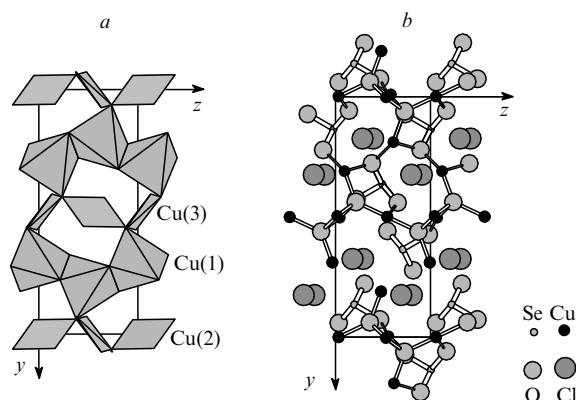


Figure 1. The crystal structure of georgbokiite $\text{Cu}_5\text{O}_2(\text{SeO}_3)_2\text{Cl}_2$ in projection onto the yz plane.⁴² (a) Representation in terms of the coordination polyhedra of copper; (b) ‘ball-and-stick’ representation.

‘pyramidal’ coordination. According to traditional crystal-chemical ideas, this structure is considered from the standpoint of the coordination of copper and selenium atoms. Three crystallographically nonequivalent copper atoms form coordination polyhedra with different structures and compositions: $\text{Cu}(1)\text{O}_3\text{Cl}_2$ — trigonal bipyramid; $\text{Cu}(2)\text{O}_4\text{Cl}_2$ and $\text{Cu}(3)\text{O}_5\text{Cl}$ — octahedra. Only the equatorial CuO_4 fragments are indicated in Fig. 1a for the octahedra as the most stable groups. The $\text{Cu}(3)\text{O}_4$ squares are linked *via* their edges, forming infinite CuO_2 chains, extended

Table 1. The M–O bond lengths for the ‘additional’ oxygen atom O_A in the $[\text{OM}_4]$ tetrahedra and the O_T oxygen atom in the $[\text{TO}_3]$ triangular groups, $[\text{TO}_4]$ tetrahedra, or $[\text{TO}_6]$ octahedra.

Compound	M– O_A / Å	M– O_T / Å	Ref.	Compound	M– O_A / Å	M– O_T / Å	Ref.
M = Cu				M = Pb			
$\text{Cu}_5\text{O}_2(\text{SeO}_3)_2\text{Cl}_2$	1.95 (1.93–1.98)	2.00 (1.94–2.05)	42	$\text{Pb}_2\text{O}(\text{SO}_4)$	2.30 (2.27–2.33)	2.66 (2.46–2.85)	22
$\text{KCu}_3\text{OCl}(\text{SO}_4)_2$	1.92 (1.86–1.98)	2.01 (1.93–2.08)	43, 44	$\text{Pb}_3\text{O}_2(\text{SO}_4)$	2.32 (2.18–2.43)	2.80 (2.69–2.95)	57, 58
$\text{Cu}_2\text{O}(\text{SO}_4)$	1.92 (1.88–2.00)	1.99 (1.91–2.07)	23, 24	$\text{Pb}_3\text{O}_2(\text{SO}_4)$	2.36 (2.32–2.39)	2.62 (2.55–2.70)	59
$\text{NaKC}_3\text{O}(\text{SO}_4)_3$	1.93 (1.91–1.94)	1.97 (1.92–2.03)	45	$\text{Pb}_3\text{O}_2(\text{SO}_4)$	2.32 (2.12–2.49)	2.76 (2.55–2.97)	60
$\text{K}_2\text{Cu}_3\text{O}(\text{SO}_4)_3$	1.93 (1.92–1.96)	1.97 (1.93–2.03)	46, 47	$\text{Pb}_5\text{O}_3(\text{GeO}_4)$	2.32 (2.19–2.68)	2.54 (2.14–2.92)	61
$\text{Na}_2\text{Cu}_4\text{O}(\text{PO}_4)_2\text{Cl}$	1.88 (1.85–1.91)	2.00 (1.92–2.03)	48	$\text{Pb}_{19}(\text{VO}_4)_2\text{O}_9\text{Cl}_4$	2.32 (2.18–2.59)	2.77 (2.36–3.10)	62, 63
$\text{Cu}_4\text{O}(\text{PO}_4)_2$	1.91 (1.90–1.92)	1.98 (1.92–2.09)	49, 50	$\text{Pb}_2\text{O}(\text{CrO}_4)$	2.30 (2.28–2.31)	2.78 (2.46–2.93)	64–66
$\text{Cu}_2\text{O}(\text{SeO}_3)$	1.96 (1.93–1.97)	1.97 (1.93–2.02)	51	$\text{Pb}_8\text{Cu}(\text{AsO}_3)_2\text{O}_3\text{Cl}_3$	2.40 (2.18–2.57)	2.57 (2.34–2.89)	67
$\text{Cu}_2\text{O}(\text{SeO}_3)$	1.94 (1.92–.97)	2.02 (1.98–2.08)		M = La			
$\text{Cu}_5\text{O}_2(\text{PO}_4)_2$	1.93 (1.91–1.94)	1.96 (1.90–2.06)	52	$\text{La}_3\text{O}_2(\text{ReO}_6)$	2.38 (2.32–2.45)	2.60 (2.42–2.86)	68
$\text{Cu}_4\text{O}(\text{AsO}_4)_2$	1.91 (1.90–1.93)	1.97 (1.93–2.02)	53	$\text{La}_4\text{O}_2(\text{Re}_2\text{O}_8)$	2.41 (2.41)	2.57 (2.54–2.60)	69
$\text{Cu}_5\text{O}_2(\text{VO}_4)_2$	1.94 (1.90–2.10)	1.98 (1.89–2.05)	54, 55	$\text{La}_4\text{O}(\text{Mo}_2\text{O}_{10})$	2.40 (2.39–2.41)	2.56 (2.37–2.90)	70
M = Sn				$\text{La}_3\text{O}_2(\text{ReO}_6)$	2.39 (2.32–2.50)	2.60 (2.24–3.00)	71
$\text{Sn}_2\text{O}(\text{SO}_4)$	2.23 (2.14–2.35)	2.42 (2.23–2.56)	56	$\text{La}_4\text{O}(\text{Re}_6\text{O}_{18})$	2.52 (2.52)	2.65 (2.51–2.93)	72

Note. The space group is indicated for compounds existing in several polymorphic modifications. The table presents the average bond lengths and the limits of their variation (in brackets) in the crystal structure. The error in the determination of the bond lengths does not exceed 0.01 Å.

along the x axis and joined together into a layer parallel to the xz plane. The layers are combined into a framework *via* the Cu(1)O₃Cl₂ polyhedra. Thus, from the standpoint of traditional ideas, the most stable fragment in the structure of georgbokiite is a chain, parallel to the x axis, made up of edge-linked CuO₄ squares. However, in the study of thermal deformations of georgbokiite it was found that the z and y axes are respectively the directions of minimum and maximum thermal expansions, the average expansion occurring along the x axis.⁷³ Furthermore, one of the cleavage planes (yz) in the test compound is perpendicular to the direction of the CuO₂ chains.

Analysis of this structure from the standpoint of the crystal chemistry of oxocentred complexes showed that the 'additional' oxygen atoms are tetrahedrally coordinated to copper atoms (Fig. 1b). By being alternately corner- and edge-linked, the [OCu₄] groups form oxocentred [O₂Cu₅] chains extended parallel to the z axis (Fig. 2). The thermal expansion is a minimum precisely along this direction and both cleavage systems (xz and yz) are parallel to the latter. The maximum refractive index, corresponding as a rule to the direction of the densest rows of atoms, corresponds also to the direction of the z axis.^{74, 75}

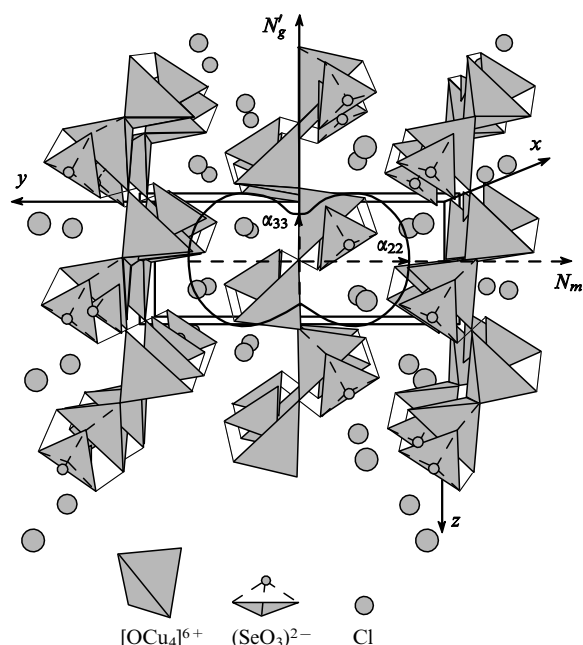


Figure 2. The oxocentred [O₂Cu₅] chains in the structure of georgbokiite and the figure representing its thermal expansions.

α_{22} and α_{33} are the axes of the figure representing the thermal expansion coefficients; N_g' and N_m are the axes of the optical indicatrix in the yz plane.

Thus the identification of oxocentred groups in the structures makes it possible to treat more clearly the anisotropy of the thermal expansion and of other physical properties of georgbokiite than in the traditional approach. Henceforth, in numerating the ways in which the [OM₄] groups can be linked together to form a cationic complex, we shall make use of polyhedral images similar to that presented in Fig. 2. Images of the structures from the point of view of the classical approach (Fig. 1) may be found in the original studies indicated in the references.

III. Systematic treatment of cationic complexes based on [OM₄] tetrahedra and the principles governing their descriptions

In traditional crystal chemistry, [TO₄] tetrahedra are as a rule corner-linked and one corner belongs to not more than two

tetrahedra.^{76, 77} The linking together of the tetrahedra *via* their edges (let alone faces) is encountered very rarely. For example, edge-linking of the tetrahedra in silicate anions has been established in the fibrous modification of silicon dioxide⁷⁶ and in certain beryllsilicates.⁷⁸ The formation of 'knotted' linkages,^{77, 78} i.e. the linking together of several tetrahedra by one corner, is also an exceptional case and the 'knot' consists as a rule of not more than four highly distorted tetrahedra.

In describing the crystal structure using [OM₄] tetrahedra, the possibility of their edge-linking is postulated and one M corner can belong to more than two tetrahedra.

In the present review, oxocentred [OM_x] complexes are represented as an assembly of [OM₄] tetrahedra.

There are several classifications of polyhedral structural units.^{76, 79, 80} The classification based on Liebau features,⁷⁶ constructed on the basis of a traditional systematic treatment of silicates devised by Machatschki, Bragg, *etc.*, is the most general. The Liebau classification involves both different geometrical types of coordination polyhedra and various ways of linking them together (*via* corners, edges, and n -corner faces). However, it bears features of the structure of silicate anions, for the classification of which it has in fact been created. For a more complete classification of polyhedral edge-linked and face-linked structural units, this system requires a series of amplifications, which are unimportant for silicates. The principal characteristics of the systematic treatment employed are described briefly below and an account is given of the main principles governing this description of structures made up of oxocentred fragments. The problems of the classification of polyhedral structures have been described in greater detail in another communication.⁸¹

Features of the systematic treatment. 1. The coordination of the central atom is a parameter which includes both the coordination number of the central atom and the geometry of the coordination polyhedron. The recommendations given by Parthé and coworkers^{79, 80, 82} are employed in the determination of the values of the parameters. In particular, the designation $4t$ was adopted for tetrahedral groups.

2. The dimensionality of the complex D is the number of dimensions in which the complex is of infinite extent. The following values are possible: 0 (finite complexes), 1 (chain complexes), 2 (layered complexes), 3 (framework complexes).

3 and 4. The linkedness of the tetrahedra in the complex ML and the linkedness of the tetrahedron L .

The parameter ML indicates the way in which it is possible to construct the specified complex by adding individual single polyhedra. It is determined as the following hierarchical series of values: $3 > 2$, $3 > 1$, 2 , $3 > 2 > 1$, $2 > 1 > 0$. Here it is necessary to make use of Wells's rule: if an edge (or face) is shared by two tetrahedra, then its corners (and edges) are not considered to be shared by these two tetrahedra. The value of L reflects all the ways of linking together the polyhedra in the complex. The linkedness L is equal to the number of corner atoms shared by two coordination polyhedra:¹⁰ $L = 0$ for an isolated polyhedron, $L = 1$ for corner-linking, $L = 2$ for edge-linking, and $L = 3$ and above for face-linking.

5. The connectedness s of the polyhedra of a coordination polyhedron is equal to the number of polyhedra with which the given polyhedron shares corners, regardless of their linkedness.^{76, 82}

6. The branchedness of the complex B . The finite structural units and single chains[†] are called unbranched if they contain no subunits linked to more than two other subunits.⁸² Otherwise they are called branched. Furthermore, complex structural complexes, which may be regarded as made up of unbranched (branched) finite fragments or unbranched (branched) single chains, are described as unbranched (branched). The branchedness B of a cationic complex of infinite extent (*i.e.* with $D > 0$) is a property of its fundamental chain. The fundamental chain is defined as the

[†] A chain consisting of secondary tetrahedra is called single.

chain from which the cationic complex may be constructed by its successive addition.⁸² The fundamental chain consists of a single chain (made up of only secondary polyhedra) and branches. Liebau⁷⁶ suggested that unbranched, open-branched, loop-branched, mixed-branched, and hybrid complexes, designated respectively by the symbols uB , oB , lB , olB , and hB , be distinguished.

7. The periodicity P . The term periodicity of a structural fragment of infinite extent is the number of structural subunits (excluding branches) constituting the period of the chain from which this fragment may be constructed by the successive addition of subunits to one another.⁸² For finite ring complexes, the number of polyhedra constituting the ring is specified as the periodicity. Liebau⁷⁶ calls this parameter the ring periodicity.

8. The multiplicity M of the complex is the term given to the number of single polyhedra, chains, or layers, which, by linking to one another, form a complex with the same dimensionality as the initial complexes.⁸²

9. The ratio $n:m$ for the complex $[A_nB_m]$, where A is the central atom and B is the ligand.

Formula and diagram of connectedness. The following is the connectedness formula: $(s: L_1 - s_1; L_2 - s_2 \dots L_n - s_n)$, where $L_1, L_2, \dots, L_n$ are specific values of linkedness, while $s_1, s_2, \dots, s_n$ are specific values of connectedness for the given polyhedron with others in accordance with the values of linkedness indicated ahead of them. The formula of the connectedness of this polyhedron shows how many polyhedra are linked to the given polyhedron and in what way. It is convenient to employ the so called diagram of connectedness constructed on the basis of the Schlegel diagram for the given polyhedron. The latter represents a planar image of the edge network of any kind of convex polyhedron. For the tetrahedron, the Schlegel diagram represents the view from above on to a regular tetrahedron placed on one of its triangular bases. The Schlegel diagrams were first introduced into crystal chemistry by Hoppe and Köhler.⁸³

Henceforth we shall use the following ways of representing the elements of connectedness.

1. The corner designated by a circle links the given polyhedron to another. If the corner links the given polyhedron to more than one other polyhedron, then the number of such polyhedra is indicated next to the corner.

2. The edge identified by a semibold line is common to two polyhedra.

The connectedness diagrams will be referred to as equivalent if the relative disposition of the linkage corners and/or edges in them is the same (or is mirror-symmetrical).

Classification of the polyhedra in a polyhedral complex. For the crystal-chemical description of the coordination polyhedra, constituting the given complex it is necessary not only to indicate the geometrical characteristics but also to define the way in which they are joined together. Wells^{84–86} suggested that polyhedra with the same relative disposition as the elements of connectedness be referred to as topologically equivalent. Within the framework of the approach employed, this means that polyhedra with equivalent connectedness diagrams are referred to as topologically equivalent polyhedra in the complex.

It is essential to note that the description of the disposition of the elements of connectedness in the polyhedron (with the aid of the connectedness diagram) is still insufficient to define the position of the polyhedron in the complex. In the same structure, topologically equivalent polyhedra may have different environments comprising polyhedra with which they have common linkage corners. In such cases we speak of configurationally nonequivalent polyhedra (more rigorous definitions have been given elsewhere⁸¹).

Configurationally equivalent polyhedra are always topologically equivalent, but topologically equivalent polyhedra may be configurationally nonequivalent. Crystallographically equivalent polyhedra are always topologically and configurationally equivalent.

Thus, from this standpoint, a polyhedral cationic complex consists of n types of configurationally equivalent and m classes of topologically equivalent polyhedra. In the general case, we have $m < n$. The classification of the polyhedra in the structure is based on the order of hierarchical equivalence ratios: configurational – topological – crystallographic.

Additional features of the systematic treatment. 10. The number of configurational types of polyhedra in the complex and their ratio.

11 and 12. The diagrams and formulae of the connectedness of the configurational types of polyhedra.

Crystal-chemical formulae. When the formula of the complex is written, the system recommended by Liebau *et al.*^{76, 82} is used to characterise it structurally. The following parameters are indicated in braces before the chemical formula of the complex written in square brackets: $\{B, M_\infty^D\}$. The following designations are adopted for finite structures ($D = 0$): $\{f\}$ — for a chain of finite length, $\{r\}$ — for a ring polyion, $\{c\}$ — for a cage.^{79, 82}

IV. Types of cationic [OM₄] complexes

1. General remarks

The structures of oxocentred complexes are described in terms of the [OM₄] tetrahedra in accordance with the following main principles. Taking into account the features of the classification formulated in the previous section, the type units of oxocentred [OM₄] structural units are treated systematically. All the known crystal structures in which the complex has been found are indicated for complexes of each type. Some of these structures are considered as examples and are described from the standpoint of the crystal chemistry of compounds with oxocentred groups.

For convenience we introduced a numbering of the types of structural units within each dimensionality. A capital Latin letter is placed before the number of the complex indicating its dimensionality: I — finite (*islands*), C — one-dimensional or chain (*chains*), L — two-dimensional or layered (*layers*), F — three-dimensional or framework (*frameworks*).

2. Finite oxocentred complexes.

Tables 2 and 3 as well as Fig. 3 present the main types of finite oxocentred complexes, the crystal structures in which these complexes have been found, and a topological description of the latter.

1I. The individual [OM₄] tetrahedron. The oxocentred [OM₄] tetrahedron is known in organic crystal chemistry,^{28–37} for example $M = \text{Cu}$, Be , or Zn . Among inorganic compounds, a single [OM₄] tetrahedron can be identified, in particular, in the crystal structure of ponomarevite $\text{K}_4\text{Cu}_4\text{OCl}_{10}$,^{87–89} which con-

Table 2. Classification of the types of finite oxocentred complexes based on the [OM₄] tetrahedron.

Num- ber	L	Para- meter	n	O:M	Type of complex	m	p	Connect- edness formula
$I1$	0	—	1	1:4	[OM ₄]	1	1	(0)
$I2$	1	$\{f\}$	2	2:7	$\{f\}[\text{O}_2\text{M}_7]$	1	1	(1: 1–1)
$I3$	1	$\{f\}$	4	4:3	$\{f\}[\text{O}_4\text{M}_{13}]$	2	A1 B1	(1: 1–1) (2: 1–2)
$I4$	2	$\{f\}$	2	1:3	$\{f\}[\text{O}_2\text{M}_6]$	1	1	(1: 2–1)
$I5$	2	$\{f\}$	4	2:5	$\{f\}[\text{O}_4\text{M}_{10}]$	2	A1 B1	(1: 2–1) (2: 2–2)
$I6$	2	$\{c\}$	4	1:2	$\{c\}[\text{O}_4\text{M}_8]$	1	1	(3: 2–3)

Note. The following designations have been adopted here and in the subsequent tables: n = number of tetrahedra in the complex, m = number of topological types of tetrahedra in the complex, p = number of tetrahedra of the given topological type (A and B) in the complex.

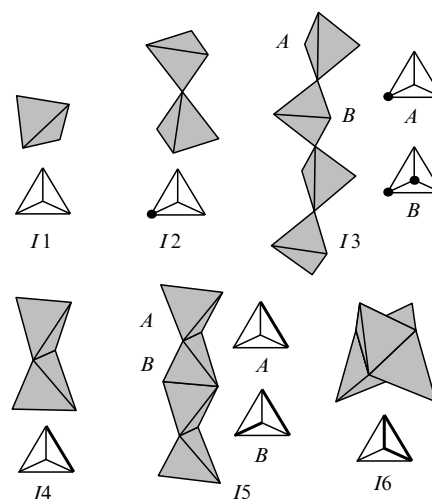
Table 3. Finite oxocentred [OM₄] complexes in the crystal structures of inorganic compounds.

Num-ber	Type of complex	Chemical formula of complex	Chemical compound	Ref.
I1	[OM ₄]	[OCu ₄]	K ₄ Cu ₄ OCl ₁₀ (ponomarevite)	87–89
			Cu ₄ (PO ₄) ₂ O	49–50
			CuO(Cu,Mg) ₃ (As _x P _{1-x} O ₄) ₂ (<i>x</i> = 0.3)	90
			Cu ₄ (AsO ₄) ₂ O, <i>P1</i>	53
			Cu ₄ (AsO ₄) ₂ O, <i>Pnma</i>	91
			KCu ₅ V ₃ O ₁₃	92
			Cu ₁₁ O ₂ (VO ₄) ₆ (fingerite)	93
		[OZn ₄]	Zn ₄ O(BO ₂) ₆	94
		[OPb ₄]	Pb ₄ O(Pb ₂ (BO ₃) ₃ Cl)	95
			Pb ₈ Bi ₂ (PO ₄) ₆ O ₂	96
		[OKBi ₃]	K ₂ Bi ₃ (PO ₄) ₂ O	97
		[OYb ₄]	Yb ₄ OCl ₆	98
		[OSm ₄]	Sm ₄ OCl ₆	99
		[OEu ₄]	Eu ₄ OCl ₆	100
		[OLa ₄]	(La ₄ O)(Re ₆ O ₁₈)	72
			La ₄ Mo ₂ O ₁₁	70
		[OCa ₄]	Ca ₄ OCl ₆	101
			Ca ₄ (PO ₄) ₂ O	102
		[OF ₄]	Fe ₁₅ Ge ₈ O ₃₆	103
		[OCe ₄]	Ce ₄ OS ₄ Cl ₂	104
		[OM ₄]	M ₄ OS ₄ Cl ₂ (M = La–Nd)	105
I1	[OM ₄]	[OLa ₂ Ga ₂]	La ₂ ZnGa ₂ S ₆ O	106
		[OCaLaGa ₂]	CaLaGa ₃ S ₆ O	106
		[OSrLaGa ₂]	SrLaGa ₃ S ₆ O	106
		[OSr ₂ Ge ₂]	Sr ₂ ZnGe ₂ S ₆ O	106
				106
I2	{ <i>f</i> }[O ₂ M ₇]	[O ₂ Pb ₇]	Pb ₉ Al ₈ O ₂₁	107
			Pb ₉ Ga ₈ O ₂₁	108, 109
		[O ₂ Pb ₆ Sb]	Pb ₆ Cu ₄ AlSbO ₂ (OH) ₁₆ Cl ₄ · (SO ₄) ₂ (mammothite)	110
		[O ₂ Cu ₇]	Cu ₉ O ₂ (PO ₄) ₄ (OH) ₂	111
		[O ₂ TiFe ₃ Ba ₃]	Ba ₄ Fe ₃ Ti(B ₂ Si ₈ O ₂₇)O ₂ Cl _{0.89} (taramellite)	112, 113
I3	{ <i>f</i> }[O ₄ M ₁₃]	[O ₄ Cu ₁₃]	Cu(Cu ₁₃ O ₄)(SeO ₃) ₂ Cl ₁₆	114
I4	{ <i>f</i> }[O ₂ M ₆]	[O ₂ Zn ₆]	Zn ₄ V ₂ O ₉	115
		[O ₂ Pb ₆]	Pb ₃ MO ₁₂ F ₂ (M = Nb, Ma)	116
		[O ₂ Fe ₆]	Fe _{3.2} Ge _{1.8} O ₈	117
		[O ₂ Cu ₆]	K ₂ Cu ₃ O(SO ₄) ₃ (fedotovite)	46, 47
			NaKCu ₃ O(SO ₄) ₃ (euchlorine)	45
			Cu ₄ O(SeO ₃) ₃ -I,II	51
I5	{ <i>f</i> }[O ₄ M ₁₀]	[O ₄ Sr ₄ Bi ₆]	Sr ₂ Bi ₃ V ₃ O ₁₄	118
I6	{ <i>c</i> }[O ₄ M ₈]	[O ₄ Pb ₈]	Pb ₉ O ₄ Br ₉	119
			TiPb ₈ O ₄ Br ₉	120
		[O ₄ Sn ₈]	Sn ₂ O(SO ₄)	56
			TiPb ₈ O ₄ Br ₉	120
			Sn ₂₁ Cl ₁₆ (OH) ₁₄ O ₆	122, 123
			HgPb ₂ O(OH)Br ₃	121
			Pb ₄ (OH) ₄ (ClO ₄) ₄ · 2H ₂ O	124
			[Pb ₄ (OH) ₄] ₃ (CO ₃)(ClO ₄) ₁₀ · 2H ₂ O	125
			Pb ₇ Ca ₂ Al ₁₂ Si ₃₆ (O,OH) ₁₀₀ · <i>m</i> (H ₂ O,OH)	126, 127

tains tetranuclear clusters [Cu₄OCl₁₀] formed by oxygen as the central atom involved in tetrahedral coordination.

I2. The binary group {*f*}[O₂T₇]. This oxocentred complex consists of two [OM₄] tetrahedra linked by one common corner and it is therefore ‘reverse’ analogue of the diorthosilicate group [Si₂O₇].

I3. The chain fragment {*f*}[O₄M₁₃] made up of four tetrahedra and discovered in the crystal structure of the compound Cu(Cu₁₃O₄)(SeO₃)₂Cl₁₆.¹¹⁴ The fragment consists of four [OCu₄] tetrahedra linked in succession *via* their corners. In the structure of

**Figure 3.** The types of finite oxocentred complexes. A, B — tetrahedra belonging to different topological types.

the given compound, there are copper atoms which do not enter into the oxocentred tetrahedra.

I4. The binary group {*f*}[O₂M₆] consists of two tetrahedra having one common edge. The presence of the complex [O₂Cu₆] having this structure has been established in the crystal structure of the exhalation mineral fedotovite K₂Cu₃O(SO₄)₃.^{46, 47}

I5. We identified the chain fragment {*f*}[O₄M₁₀] with an edge-linkage made up of four tetrahedra in the crystal structure of Sr₂Bi₃V₃O₁₄ solved by Boje and Müller-Buschbaum.¹¹⁸ From the standpoint of the approach employed, the formula of this compound is written as Sr₂Bi₃O₂(VO₄)₃.

I6. An oxocentred complex made up of four [OM₄] tetrahedra in which each tetrahedron is edge-linked to three others, was first noted by Keller in the compounds Pb₉O₄Br₉¹¹⁹ and TiPb₈O₄Br₉.¹²⁰ Later Riebe and Keller¹²¹ noted that in a complex having this structure the M atoms not involved in the linking of the tetrahedra may be replaced by hydrogen.

It is of interest that the complex [O₄Pb₄], having a similar structure but incorporating only Pb atoms participating in the linking of the tetrahedra, has been discovered in the gas phase,^{128, 129} while the complexes [(OH)₄M₄] (M = Mg, Co, Ni, Cd, Pb) have been found in aqueous solutions.^{130–132}

Table 4 presents the finite complexes formed from the complex I6 for different degrees of substitution *n*.

Table 4. Finite oxocentred complexes formed from complex I6 as a result of the substitution *n*(O + M) → *n*(OH).

<i>n</i>	Type of complex	Chemical formula of complex	Chemical compound	Ref.
0	{ <i>c</i> }[O ₄ M ₈]	[O ₄ Pb ₈]	Pb ₉ O ₄ Br ₉	119
			TiPb ₈ O ₄ Br ₉	120
			Sn ₂ O(SO ₄)	56
1	{ <i>c</i> }[O ₃ (OH)M ₇]	[O ₃ (OH)Sn ₇]	Sn ₂₁ Cl ₁₆ (OH) ₁₄ O ₆	122, 123
			HgPb ₂ O(OH)Br ₃	121
2	{ <i>c</i> }[O ₂ (OH) ₂ M ₆]	[O ₂ (OH) ₂ Pb ₄ Hg ₂]	HgPb ₂ O(OH)Br ₃	121
4	{ <i>c</i> }[O ₂ (OH) ₂ M ₆]	[(OH) ₄ Pb ₄]	Pb ₄ (OH) ₄ (ClO ₄) ₄ · 2H ₂ O	124
			[Pb ₄ (OH) ₄] ₃ (CO ₃)(ClO ₄) ₁₀ · 2H ₂ O	125
			Pb ₇ Ca ₂ Al ₁₂ Si ₃₆ (O,OH) ₁₀₀ · <i>m</i> (H ₂ O,OH)	126, 127

3. Oxocentred chain complexes

Oxocentred chains can be conveniently classified in terms of the types of single chains from which they are constructed. The linking of single chains leads to the formation of multiple structural units. All the oxocentred chains can be divided into families in terms of their multiplicity and linkedness. Tables 5 and 6 present the types of oxocentred chain complexes based on the $[\text{OM}_4]$ tetrahedra and the chemical compounds in the structures of which such complexes have been found.

Table 5. Classification of the types of oxocentred chain complexes based on the $[\text{OM}_4]$ tetrahedron.

Num-ber	ML	L	P	B	M	O:T	n	m	p	Connectedness formula
C1	1	1	1	<i>uB</i>	1	1:3	1	1	1	(2: 1-2)
C2	1	1	1	<i>uB</i>	2	2:5	1	1	1	(3: 1-3)
C3	2	1, 2	1	<i>uB</i>	2	1:2	1	1	1	(4: 1-2; 2-2)
C4	2	1, 2	1	<i>uB</i>	3	3:5	2	2	A2	(5: 1-3; 2-2)
									B1	(6: 1-2; 2-4)
C5	1	1	2	<i>uB</i>	1	1:3	1	1	1	(2: 1-2)
C6	1, 2	1, 2	2	<i>uB</i>	2	2:5	2	2	A1	(3: 1-3)
									B1	(4: 1-3; 2-1)
C7	2	2	2	<i>uB</i>	1	1:2	1	1	1	(2: 2-2)
C8	2	1, 2	2	<i>uB</i>	2	2:3	1	1	1	(5: 1-2; 2-3)
C9	2	1, 2	2	<i>uB</i>	3	3:4	2	2	A1	(5: 1-2; 2-3)
									B2	(8: 1-4; 2-4)
C10	2	1, 2	2	<i>uB</i>	6	6:7	3	3	A1	(7: 1-4; 2-3)
									B1	(9: 1-6; 2-3)
									C1	(13: 1-8; 2-5)
C11	2	1, 2	2	<i>uB</i>	6	6:7	5	4	A1	(5: 1-2; 2-3)
									B1	(12: 1-8; 2-4)
									C2	(9: 1-6; 2-3)
									D1	(18: 1-12; 2-6)
									E1	(9: 1-6; 2-3)
C12	1, 2	1, 2	2	<i>uB</i>	1	2:5	1	1	1	(2: 1-1; 2-1)
C13	1, 2	1, 2	2	<i>uB</i>	2	1:2	2	2	A1	(3: 1-2; 2-1)
									B1	(4: 1-2; 2-2)
C14	1, 2	1, 2	4	<i>uB</i>	1	2:5	1	1	1	(2: 1-1; 2-1)
C15	1, 2	1, 2	6	<i>uB</i>	1	3:8	2	2	A1	(2: 1-2)
									B2	(2: 1-1; 2-1)
C16	1	1	1	<i>lB</i>	2	1:2	3	3	A1	(4: 1-1; 2-3)
									B2	(3: 1-2; 2-1)
									C1	(4: 1-3; 2-1)

C1. The single-period chain $\{uB, 1^1_\infty\}[\text{OM}_3]$ (Fig. 4). In this chain, the tetrahedra are linked only *via* the corners with a periodicity 1. This polyion is an analogue of the metagermanate chain $[\text{GeO}_3]$.

C2. The $\{uB, 2^1_\infty\}[\text{O}_2\text{M}_5]$ double chain. The linking of two C1 chains *via* free corners leads to the formation of the C2 double chain. Such a fragment can be identified in chemical compounds belonging to the ludwigite structural type. In the crystal structures of these compounds, there is also an 'additional' oxygen atom with a tetragonal-pyramidal coordination, as well as metal atoms which do not enter into the tetrahedral oxocentred complex.

C3. The $\{uB, 2^1_\infty\}[\text{OM}_2]$ double chain. The linking of two C1 chains to one another *via* the edges leads to the formation of a type C3 oxocentred chain. The main type of linkedness *ML* for this double chain is 2, although for the fundamental chain *ML* = 1. The C3 chain may be identified in oxoborates with the warwickite structural type. In contrast to ludwigite, in the warwickite structural type all the 'additional' oxygen atoms are involved in tetrahedral coordination and all the metal atoms enter into the oxocentred complex. Chains of analogous structure have been found in the structures of the diorthosilicates of the cuspidine and epistilite groups (innelite, lomonosovite, murmanite, *etc.*). In such compounds, the 'additional' oxygen, not entering into

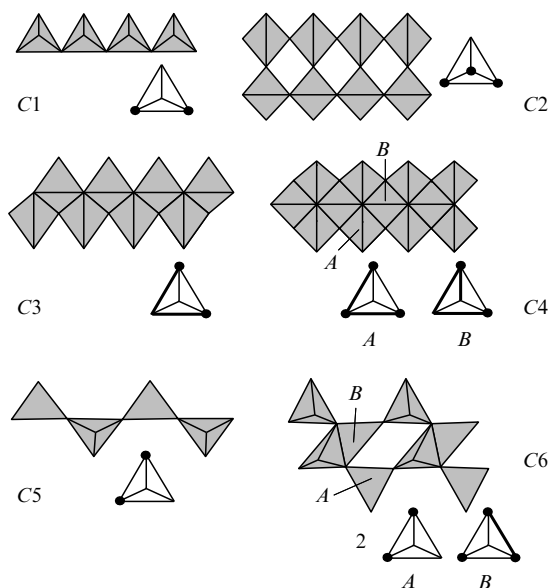


Figure 4. The types of oxocentred chain complexes (C1–C6). *A, B* — tetrahedra belonging to different topological types.

anionic complexes, may be substituted by fluorine with its similar properties. The nature of the substitution can be both statistical and ordered. The structural similarity of oxoborates and the cuspidine-group diorthosilicates was first pointed out by Belov.⁷⁷

C4. The $\{uB, 3^1_\infty\}[\text{O}_3\text{M}_5]$ triple chain. As a result of the addition of yet another single C1 chain to a C3 chain, a triple oxocentred C4 chain is formed. Such a chain was first identified by Carre *et al.*²⁰ in the crystal structure of $\text{In}_6\text{La}_{10}\text{O}_6\text{S}_{17}$.¹⁸⁰

The C1, C3, and C4 chains may be assigned to a single family with the general formula $\{uB, n^1_\infty\}[\text{O}_n\text{M}_{n+2}]$, where *n* is the multiplicity of the chain.

C5. The $\{uB, 1^1_\infty\}[\text{O}_2\text{M}_6]$ single chain. This chain is topologically equivalent to the C1 chain, different from the latter by the periodicity (*P* = 2). In terms of its structure, the C5 chain is a reverse analogue of the pyroxene chain in the silicate. The difference consists in the fact that the corners not involved in the linking of the tetrahedra into the C5 chain are turned in opposite directions relative to the plane of the chain, whereas in pyroxenes they are turned in one direction. A C5 complex has been detected, in particular, in the crystal structure of the exhalation mineral kamchatkite $\text{KCu}_3\text{O}(\text{SO}_4)_2\text{Cl}$ (Fig. 5).^{43, 44}

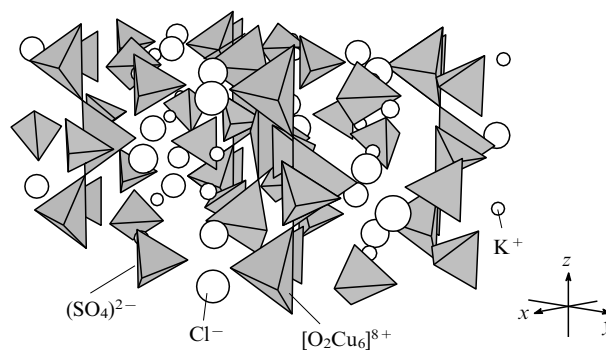


Figure 5. The crystal structure of kamchatkite $\text{KCu}_3\text{O}(\text{SO}_4)_2\text{Cl}$.

C6. The $\{uB, 2^1_\infty\}[\text{O}_2\text{M}_5]$ double chain consists of two edge-linked C5 chains. A complex with this structure may be identified in stoiberite $\text{Cu}_5\text{O}_2(\text{VO}_4)_2$,^{54, 55} the structure of which was not previously considered in terms of this aspect.

Table 6. Oxocentred [OM₄] chain complexes in the crystal structures of inorganic compounds.

Number	Type of complex	Chemical formula of complex	Chemical compound	Ref.
C 1	{ <i>uB</i> , 1 _∞ ¹ }[OM ₃]	[OPb ₃]	Pb ₃ Ta ₅ O ₉ F ₁₃ (Pb ₃ O(Ta ₅ O ₈)F ₁₃)	133
		[OY ₃]	Y ₃ OCl ₂ (OH) ₅	134
		[OGd ₃]	Gd ₃ O(OH) ₅ Br ₂	135
		[OCu ₂ Zn]	Cu ₂ Zn(B ₂ O ₅)O	136
		[OCu ₂ Cd]	Cu ₂ Cd(B ₂ O ₅)O	137
		[OCu ₂ Co]	Cu ₂ Co(B ₂ O ₅)O	138
C 2	{ <i>uB</i> , 2 _∞ ¹ }[O ₂ M ₃]	[O ₂ M ₃] (M = Fe, Mg, Ti, Sb, Sn, Ni, Cr, Mn, Al, Mo, Zn)	(Mg,Fe ²⁺) ₂ Fe ³⁺ O ₂ (BO ₃) (ludwigite)	139–143
			Fe ₃ O ₂ (BO ₃) (vonsenite)	144, 145
			Mg _{1.7} Mn _{1.29} O ₂ (BO ₃) (takeuchiite)	146
			(Mg,Mn) ₂ (Mn,Fe)O ₂ (BO ₃) (orthopinakiolite)	147
			(Sn,Fe,Mg)(Fe,Mg) ₂ O ₂ (BO ₃) (hulsite)	148, 149
			Ni ₂ CrO ₂ (BO ₃)	140
			Ni ₂ VO ₂ (BO ₃)	140
			Ni ₂ MO ₂ (BO ₃) (M = Ga, Fe, Al, Cr)	150
			Ni ₂ FeO ₂ (BO ₃)	151
			Mg ₂ MnO ₂ (BO ₃) (fredrikssonite)	152
			Zn ₅ Mn(BO ₃) ₂ O ₄	153
C 3	{ <i>uB</i> , 2 _∞ ¹ }[OM ₂]	[OLa ₂]	(La ₂ O)(LaGaS ₅)	154
			Pb ₁₁ Si ₃ O ₁₇	155
		[OPb ₂]	Pb ₁₁ Ge ₃ O ₁₇	156
			LaCrOS ₂	157
		[OLaCr]	Y ₂ O(BeO ₃)	158, 159
		[OY ₂]	Fe ₂ O(BO ₃)	160
		[OF ₂]	FeCoO(BO ₃)	158
		[OF ₂ Co]	Mg(Mg _{0.5} Ti _{0.5})O(BO ₃) (warwickite)	161–163
		[OMg _{1.5} Ti _{0.5}]	Mn ₂ O(BO ₃)	164
		[OMn ₂]	MnFeO(BO ₃)	165
		[OMnFe]	MnAl _{0.5} Y _{0.5} O(BO ₃)	165
		[OMn(Al,Y)]	Co _{1.5} Mo _{0.5} O(BO ₃) (M = Ti, Zr)	166
		[OC _{0.5} Mo _{0.5}] (M = Ti, Zr)	ZnFeO(BO ₃)	153
		[OZnFe]	Na ₅ Ti ₂ (Si ₂ O ₇)(PO ₄)O ₂ (lomonosovite, β-lomonosovite)	167–170
		[OTiNa]	Na ₂ Ti ₂ (Si ₂ O ₇)O ₂ (murmanite)	171, 172
		[O ₃ FCa ₇ Nb]	Ca ₇ Nb(Si ₂ O ₇) ₂ O ₃ F (niocalite)	173, 174
		[(O,F) ₂ Ca ₂ NaZr]	Ca ₂ Na(Zr,Nb)(Si ₂ O ₇)(O,F) ₂ (woehlerite)	175
		[(OH,F)Ca ₂]	Ca ₄ (Si ₂ O ₇)(OH,F) ₂ (cuspidine)	176, 177
		[OF(Na,Ca) ₃ Zr]	(Na,Ca,Mn) ₃ (Zr,Ti)(Si ₂ O ₇)OF (lavenite)	178, 179
C 4	{ <i>uB</i> , 3 _∞ ¹ }[O ₃ M ₅]	[O ₃ La ₅]	In ₆ La ₁₀ O ₆ S ₁₇	180
C 5	{ <i>uB</i> , 1 _∞ ¹ }[O ₂ M ₆]	[O ₂ Cu ₆]	KCu ₃ O(SO ₄) ₂ Cl (kamchatkite)	43, 44
			Cu ₃ V ₂ O ₈ (H ₂ O)	181
			Cu ₈ ZnO ₂ (SeO ₃) ₄ Cl ₆	182
			Cu ₃ Mo ₂ O ₉	183, 184
			Na ₂ Cu(Cu ₃ O)(PO ₄) ₂ Cl	48
			Zn ₃ O(SO ₄)	185
C 6	{ <i>uB</i> , 2 _∞ ¹ }[O ₂ M ₅]	[O ₂ Ti ₂ Y ₄]	Y ₂ (Y ₂ TiO)(SiO ₄) ₂ F ₆	186
			Cu ₅ V ₂ O ₁₀ (stoiberite)	54, 55
C 7	{ <i>uB</i> , 1 _∞ ¹ }[OM ₂]	[OPb ₂]	Pb ₂ OFX (X = Cl, Br, I)	187
			Pb ₂ O(SO ₄) (lanarkite)	22
		[O ₂ Cu ₃ (Al,Fe)]	Pb ₂ O(WO ₄)	188
			Pb ₂ O(CrO ₄) (phoenicochroite)	64–66
		[O ₂ Cu ₃ Al]	Pb ₂ O(XO ₄) (X = S, Cr, Mo)	66
			K ₃ Cu ₃ (Al,Fe)O ₂ (SO ₄) ₂ (kljuchevskite)	189, 190
		[OCu ₂]	K ₃ Cu ₃ AlO ₂ (SO ₄) ₂ (alumokljuchevskite)	191
			K ₂ Cu ₂ O(SO ₄) (piypite)	192, 193
		[OBi ₂]	Cu ₄ O ₂ (VO ₄)Cl	194
			(UO ₂)Bi ₄ O ₄ (AsO ₄) ₂ · 2H ₂ O (walpurgite, orthowalpurgite)	195–197
		[OPbGe]	PbGeO(Ge ₂ O ₆)	198
			CaBiVO ₅	199
		[OLa ₂]	La ₄ Re ₂ O ₁₀	69
			Nd ₄ Re ₂ O ₁₁	200
		[ONd ₂]	Na ₂ (Pr ₄ O ₂)Cl ₉	201
		[O ₂ Pr ₄]		

Table 6 (continued).

Number	Type of complex	Chemical formula of complex	Chemical compound	Ref.
C8	$\{uB, 2_{\infty}^1\}[\text{O}_2\text{M}_3]$	$[\text{O}_2\text{Pb}_3]$	$\text{Pb}_3\text{O}_2(\text{SO}_4)$ ($P2_1/m$) $\text{Pb}_3\text{O}_2(\text{SO}_4)$ ($Cmcm$) $\text{Pb}_3\text{O}_2(\text{SO}_4)$ ($P1$) $\text{Pb}_3\text{O}_2\text{Cl}_2$ (mendipite) $\text{Pb}_3\text{O}_2\text{I}_2$ $\text{Pb}_3\text{CuO}_2(\text{OH})_2\text{Cl}_2$ (chloroxiphite) $\text{BiMg}_2\text{O}_2(\text{PO}_4)$ $\text{BiMg}_2\text{O}_2(\text{AsO}_4)$	57, 58 59 60 202, 203 204 205 206
		$[\text{O}_2\text{BiMg}_2]$		
		$[\text{O}_2\text{La}_3]$	$\text{La}_3\text{O}_2(\text{ReO}_6)$ ($P2_1/m$) $\text{La}_3\text{O}_2(\text{ReO}_6)$ ($C2$)	68 69
		$[\text{O}_2\text{Y}_3]$	$\text{Y}_3\text{O}_2(\text{ReO}_6)$	207
		$[\text{O}_2\text{Sm}_3]$	$\text{Sm}_3\text{O}_2(\text{ReO}_6)$	208
		$[\text{O}_2\text{Ce}_2\text{Ti}]$	$\text{Na}_2\text{Ce}_2\text{TiO}_2(\text{SiO}_4)(\text{CO}_3)_2$ (tundrite)	209, 210
C9	$\{uB, 3_{\infty}^1\}[\text{O}_3\text{M}_4]$	$[\text{O}_3\text{La}_4]$	$\text{La}_4\text{O}_3(\text{AsS}_3)_2$	211
C10	$\{uB, 6_{\infty}^1\}[\text{O}_6\text{M}_7]$	$[\text{O}_6\text{Bi}_7]$	$\text{Bi}_{14}\text{O}_{16}(\text{SO}_4)_5$	212
C11	$\{uB, 6_{\infty}^1\}[\text{O}_6\text{M}_7]$	$[\text{O}_6\text{Bi}_7]$	$\gamma\text{-Bi}_2\text{MoO}_6$	213
C12	$\{uB, 1_{\infty}^1\}[\text{O}_2\text{M}_5]$	$[\text{O}_2\text{Cu}_5]$	$\text{Cu}_2\text{O}_5(\text{SeO}_3)_2\text{Cl}_2$ $\text{Cu}_5\text{O}_2(\text{PO}_4)$	42 52
		$[\text{O}_2\text{M}_5]$ ($\text{M} = \text{Pb, Ge, Ga, Ba, Al, Sn, Fe, Ti}$)	$\text{Pb}_3\text{GeGa}_{10}\text{O}_{20}$ $\text{Ba}_3\text{SnFe}_{10}\text{O}_{20}$ $\text{Pb}_3\text{GeAl}_{10}\text{O}_{20}$ $\text{Pb}_3\text{SiAl}_{10}\text{O}_{20}$ $\text{Ba}_3\text{TiAl}_{10}\text{O}_{20}$ $\text{BaSrPbMn}_2\text{Al}_9\text{O}_{20}$	214 214 215 215 216 217
C13	$\{uB, 2_{\infty}^1\}[\text{OM}_3]$	$[\text{OAl}_2]$ $[\text{OFe}_2]$	$\text{Al}_2\text{O}(\text{SiO}_4)$ (kyanite) $\text{Fe}_2\text{O}(\text{GeO}_4)$	218, 219 220
C14	$\{uB, 1_{\infty}^1\}[\text{O}_2\text{M}_5]$	$[\text{O}_2(\text{Mg, Fe})_5]$ $[\text{O}_2(\text{Mg, Cr})_5]$ $[\text{O}_2(\text{Mg, Al})_5]$ $[\text{O}_2(\text{Fe, Ti})_5]$ $[\text{O}_2(\text{Mg, Ti, Al, Fe})_5]$	$\text{Na}_2(\text{Mg, Fe})_6[(\text{Ge, Fe})_6\text{O}_{18}]\text{O}_2$ $\text{NaMg}_2\text{Cr}(\text{Si}_3\text{O}_9)\text{O}$ (krinovite) $\text{Ca}_2(\text{Mg, Al})_6\text{O}_2[(\text{Si, Al, B})_6\text{O}_{18}]$ (serendibite) $\text{Na}_2\text{Fe}_5\text{TiO}_2(\text{Si}_6\text{O}_{18})$ (aenigmatite) $\text{Ca}_2(\text{Mg, Ti, Al, Fe})_6\text{O}_2(\text{Si}_6\text{O}_{18})$ (rhoenite) $(\text{Ca, Na})_2(\text{Mg, Al, Fe})_6\text{O}[(\text{Si, Al, Be})_6\text{O}_{18}]$ (makarochkinite)	221 222 223–225 226 227 228
C15	$\{uB, 1_{\infty}^1\}[\text{O}_3\text{M}_8]$	$[\text{O}_3\text{Pb}_8]$	$\text{Pb}_8\text{Cu}(\text{AsO}_3)_2\text{O}_3\text{Cl}_5$ (freedite)	67, 229
C16	$\{lB, 2_{\infty}^1\}[\text{OM}_2]$	$[\text{O}_3\text{Cu}_4\text{Ti}_2]$	$\text{Cu}_9\text{Ti}(\text{B}_2\text{O}_3)(\text{BO}_3)_2\text{O}_6$	230

C7. The $\{uB, 1_{\infty}^1\}[\text{OM}_2]$ fundamental chain (Fig. 6). A single oxocentred chain, consisting of secondary tetrahedra edge-linked in succession, was first identified by Sahl²² in the crystal structure

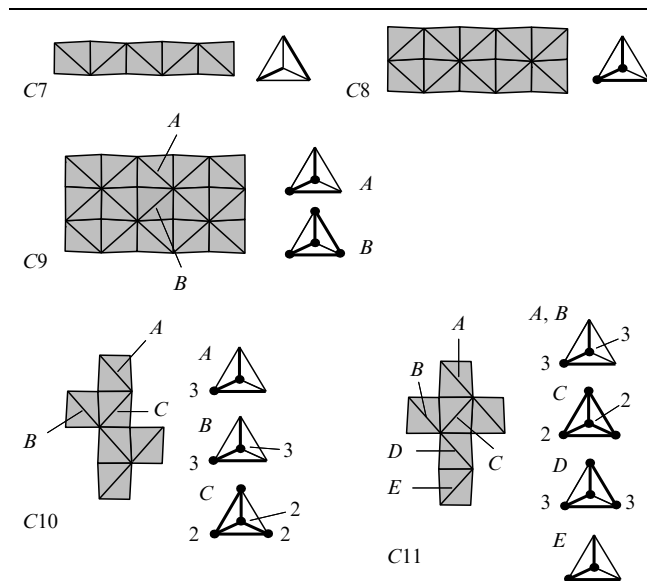


Figure 6. The types of oxocentred chain complexes (C7–C11). A, B, C, D, E — tetrahedra belonging to different topological types.

of lanarkite $\text{Pb}_2\text{O}(\text{SO}_4)$. This one-dimensional structural unit based on $[\text{OM}_4]$ tetrahedra is one of the commonest in oxocentred complexes. Thus it has been detected in three new minerals of exhalation origin in the Tolbachick volcano: klyuchevskite,^{189, 190} aluminoklyuchevskite,¹⁹¹ and piypite.^{192, 193}

C8. The $\{uB, 2_{\infty}^1\}[\text{O}_2\text{M}_3]$ double chain. The edge-linking of two C7 chains leads to the formation of the C8 double chain.

C9. The $\{uB, 3_{\infty}^1\}[\text{O}_3\text{M}_4]$ triple chain is formed by the linking of three C7 chains. A similar complex with the formula $[\text{O}_3\text{La}_4]$ has been identified by Carre *et al.*²⁰ in the crystal structure of $\text{La}_4\text{O}_3\text{As}_3\text{S}_9$.²¹¹

The C7, C8, and C9 chains form a family with the general formula $\{uB, n_{\infty}^1\}[\text{O}_n\text{M}_{n+1}]$, where n is the multiplicity of the chain. It may be postulated that a chain belonging to the same family with $n = 4$ occurs in the crystal structure of $\text{Pb}_5\text{O}_4[\text{SO}_4]$, which could not be fully solved. This hypothesis is based on the existence of oxocentred chains of type C7 ($n = 1$) and C8 ($n = 2$) in the compounds $\text{Pb}_2\text{O}(\text{SO}_4)$ ²² and $\text{Pb}_3\text{O}_2(\text{SO}_4)$ ^{57–60} respectively, which have similar compositions.

C10, C11. The six-fold chains having the general formula $\{uB, 6_{\infty}^1\}[\text{O}_6\text{M}_7]$ consist of six type C7 chains linked in different ways. The possibility of identifying the C10 polyion in the $\text{Bi}_{14}\text{O}_{16}(\text{SO}_4)_5$ structure and of representing it by a block cut out of a type PbO layer was pointed out by Aurivillius.²¹² The C11 chain may be identified in the structure of the high-temperature modification of bismuth oxomolybdate $\gamma\text{-Bi}_2\text{MoO}_6$ tentatively determined on the basis of high-resolution electron microscopy data.²¹³ The difference between the C10 and C11 chains is reflected in the configurational and topological properties of the tetrahedra constituting

them. There are three configurational types of tetrahedra in the C10 polyion, each of which constitutes a topological equivalence class. The C11 chain consists of tetrahedra with five different configurations, two of which are of the same topological type. The example of these chains shows that the use of the configurational and topological properties of the tetrahedra is important for the classification of structural units.

C12. The $\{uB, 1_{\infty}^1\}[O_2M_5]$ single chain (Fig. 7). In this chain, links *via* corners and edges alternate. An example of a compound with such a chain is provided by georgbokiite $Cu_5O_2(SeO_3)_2Cl_2$ (in the original study,⁴² the coordination of the additional oxygen atom was not considered).

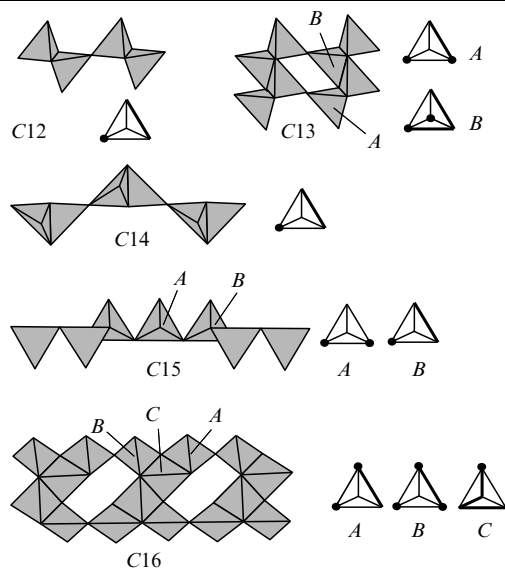


Figure 7. The types of oxocentred chain complexes (C12–C16). A, B, C — tetrahedra belonging to different topological types.

C13. The $\{uB, 2_{\infty}^1\}[OM_2]$ double chain, consisting of two type C12 chains, was first identified by Bergerhoff and Paeslack¹⁹ in kyanite $Al_2O(SiO_4)$.²¹⁸

C14. The oxocentred $\{uB, 1_{\infty}^1\}[O_2M_5]$ chain, which may be found in compounds of the aenigmatite structural type, is a topological analogue of the C12 chain but with a periodicity of 4.^{221–228}

C15. The $\{uB, 1_{\infty}^1\}[O_6M_{16}]$ single chain with a periodicity of 6 is an interesting example of the alternation of two bonds *via* neighbouring corners with a single bond *via* the edge. This remarkable polyion, with the formula $[O_3Pb_8]$, may be identified in the structure of freedite $Pb_8Cu(AsO_3)_2O_3Cl_5$, solved by Pertlik,⁶⁷ who did not, however, consider it within the framework of the approach which we are employing.

C16. The $\{lB, 1_{\infty}^1\}[OM_2]$ loop-branched chain has been detected in the structure of copper titanium oxoborate $Cu_9Ti(B_2O_5)_2(BO_3)_2O_6$. This consists of two types of C1 chains linked by two additional tetrahedra adjoining them *via* two edges each. It is essential to note that this compound contains also ‘additional’ oxygen atoms involved in nontetrahedral (ternary) coordination and copper atoms which do not enter into the complex under consideration. The C16 chain is the only example of a branched complex involving oxocentred chains.

4. Layered oxocentred complexes

A series of layers may be described as derivative of the type PbO tetrahedral layer. Carre *et al.*²⁰ suggested that certain chains based on the [OLa₄] tetrahedron be also considered in terms of this aspect. However, the above principle is subject to limitations, since there are many structural units which cannot be detected among derivatives of the PbO layer regardless of the way in which

it is ‘sliced’. We therefore use this approach only for certain layered structures. Tables 7 and 8 present the characteristics of the types of layered oxocentred complexes based on [OM₄] tetrahedra and the chemical compounds in the structures of which these complexes have been detected.

Table 7. Classification of the types of oxocentred layered complexes based on the [OM₄] tetrahedron.

Num-ber	ML	L	P	B	M	O:T	m	n	p	Connectedness formula
L1	1	1	2	uB	1	2:5	1	1	1	(3: 1–3)
L2	1	1	2	uB	1	2:5	1	1	1	(3: 1–3)
L3	2	1, 2	1	uB	2	1:1	1	1	1	(9: 1–6; 2–3)
L4	2	1, 2	1	uB	4	4:3	2	2	A1	(13: 1–10; 2–3)
									B1	(18: 1–12; 2–6)
L5	1, 2	1, 2	2	uB	1	4:5	1	1	1	(7: 1–4; 2–3)
L6	1, 2	1, 2	2	uB	1	6:7	2	2	A1	(7: 1–4; 2–3)
									B1	(8: 1–4; 2–4)
L7	1, 2	1, 2	2	uB	1	8:9	2	2	A1	(7: 1–4; 2–3)
									B1	(8: 1–4; 2–4)
L8	1, 2	1, 2	4	lB	1	1:2	1	1	1	(5: 1–4; 2–1)
L9	1, 2	1, 2	4	uB	1	2:3	1	1	1	(5: 1–3; 2–2)
L10	1, 2	1, 2	2	uB	1	1:2	1	1	1	(3: 1–2; 2–1)
L11	1, 2	1, 2	2	uB	1	1:2	1	1	1	(6: 1–5; 2–1)
L12	2	1, 2	2	uB	1	1:1	1	1	1	(8: 1–4; 2–4)
L13	2	1, 2	4	uB	1	1:1	1	1	1	(8: 1–4; 2–4)
L14	2	1, 2	3	lB	1	4:5	1	1	1	(6: 1–3; 2–3)
L15	1, 2	1, 2	4	lB	1	3:5	2	2	A2	(4: 1–2; 2–2)
									B1	(5: 1–2; 2–3)
L16	2	1, 2	2	lB	1	9:14	6	4	A1	(4: 1–2; 2–2)
									B1	(4: 1–2; 2–2)
									C1	(5: 1–2; 2–3)
									D1	(5: 1–2; 2–3)
									E1	(5: 1–3; 2–2)
									F1	(6: 1–2; 2–4)
L17	2	1, 2	2	lB	1	7:8	5	3	A2	(7: 1–4; 2–3)
									B2	(7: 1–4; 2–3)
									C1	(6: 1–2; 2–4)
									D1	(7: 1–3; 2–4)
									E1	(7: 1–3; 2–4)
L18	1, 2	1, 2	2	hB	1	11:12	5	5	A2	(9: 1–4; 2–5)
									B4	(11: 1–8; 2–3)
									C1	(12: 1–8; 2–4)
									D2	(8: 1–8)
									E2	(9: 1–8; 2–1)
L19	1, 2	1, 2	2	lB	1	4:7	5	5	A1	(4: 1–2; 2–2)
									B1	(4: 1–2; 2–2)
									C1	(3: 1–1; 2–2)
									D1	(4: 1–3; 2–1)
									E1	(4: 1–2; 2–2)
L20	2	1, 2	2	uB	2	4:3	1	1	1	(15: 1–10; 2–5)

L1. The $\{uB, 1_{\infty}^2\}[O_2M_5]$ layer (Fig. 8) can be regarded as made up of C5 single chains. In terms of its structure, it resembles the [Si₂O₅] tetrahedral networks constituting (together with octahedral networks) the structures of layered silicates.⁷⁶ However, the topological structures of the layer considered and the silicate layer differ, since the unshared corners of neighbouring tetrahedra in the L1 layer are turned in opposite directions relative to the plane of the layer. The difference between the silicate tetrahedral network and the L1 layer is analogous to the difference between the pyroxene chain and the C5 chain. The structural unit [O₂Cu₅] of the L1 type has been detected in the crystal structure of averievite $[Cu_5O_2](VO_4)_2 \cdot MCl$ (M = K, Rb, Cs) (Fig. 9).^{232, 233} In this structure, the oxocentred layers are located exactly one under the other, the [VO₄] groups are ‘glued’ to the

Table 8. Oxocentred [OM₄] layered complexes in the crystal structures of inorganic compounds.

Number	Type of complex	Chemical formula of complex	Chemical compound	Ref.
L1	{ <i>uB</i> , 1 _∞ ² }[O ₂ M ₅]	[O ₂ Cu ₃ Pb ₂] [O ₂ Cu ₅]	Pb ₂ Cu ₃ O ₂ (NO ₃) ₂ (SeO ₃) ₂ Cu ₅ O ₂ (VO ₄) ₂ ·MCl (M = K, Rb, Cs) (averievite)	231 232, 233
L2	{ <i>uB</i> , 1 _∞ ² }[O ₂ M ₅]	[O ₂ Cu ₅]	NaCu ₅ O ₃ (SeO ₃) ₂ Cl ₃	234
L3	{ <i>uB</i> , 2 _∞ ² }[OM]	[OX] (X = La, Ce, Pu)	La ₂ O ₂ S, Ce ₂ O ₂ S, Pu ₂ O ₂ S La ₂ O ₂ Se LaOF	235 236 237
L4	{ <i>uB</i> , 1 _∞ ² }[O ₄ M ₃]	[O ₄ (Bi,Sr) ₃]	Bi _{0.765} Sr _{0.235} O _{1.383}	238
L5	{ <i>uB</i> , 1 _∞ ² }[O ₄ M ₃]	[O ₄ Cu ₃ Bi ₂]	Na ₂ [(Bi ₂ Cu ₃ O ₄ (AsO ₄) ₂)·H ₂ O K ₂ [Bi ₂ Cu ₃ O ₄ (AsO ₄) ₂]·2H ₂ O	239 239
L6	{ <i>uB</i> , 1 _∞ ² }[O ₆ M ₇]	[O ₆ Cu ₃ Bi ₄]	Cu ₃ Bi ₄ V ₂ O ₁₄	240
L7	{ <i>uB</i> , 1 _∞ ² }[O ₈ M ₉]	[O ₈ Bi ₉]	Bi ₂₀ O ₂₇ (SO ₄) ₁₂	212
L8	{ <i>uB</i> , 1 _∞ ² }[OM ₂]	[OY ₂]	Y ₂ OS ₂	241
L9	{ <i>uB</i> , 1 _∞ ² }[O ₂ M ₃]	[O ₂ Ce ₂ Cr] [O ₂ HgPb ₂]	(Ce ₂ CrO ₂)CrS ₄ HgPb ₂ O ₂ Cl ₂	242 243
L10	{ <i>uB</i> , 1 _∞ ² }[OM ₂]	[OCu ₂] [O ₂ Cu ₃ Bi]	Cu ₂ O(SO ₄) (dolerophanite) Cu ₃ Bi(SeO ₃) ₂ O ₂ Cl (franciscite)	23, 24 244
L11	{ <i>uB</i> , 1 _∞ ² }[OM ₃]	[O(Mg,Mn) ₂] [(O,F) ₄ (Ca,Na) ₆ ZrTi]	(Mg,Mn) ₂ Mn(BO ₃) ₂ Ca _{3.5} Na _{2.5} Zr(Ti,Mn,Nb)(Si ₂ O ₇) ₂ ·F ₂ O(F,O) (rosenbuschite)	142, 245 246
		[(O,F) ₂ (Na,Ca,Ce) ₃ Ti]	(Na,Ca,Ce) ₃ Ti(Se ₂ O ₇)(O,F) ₂ (mosandrite)	247
		[(O,F) ₂ (Na,Ca) ₂ (Zr,Ti,Mn) ₂]	(Na,Ca) ₂ (Zr,Ti,Mn) ₂ (Si ₂ O ₇)(O,F) ₂ (seidozerite)	248, 249
		[O ₄ Ti ₃ CaBa ₄]	Na ₂ Ba ₃ (Ba,K,Mn)(Ca,Na)Ti(TiO ₂) ₂ [Si ₂ O ₇] ₂ (SO ₄) ₂ (innelite)	250
L12	{ <i>uB</i> , 1 _∞ ² }[OM]	[(O,F) ₄ (Ti,Al) ₂ (Ca,Na) ₆] [OPb]	(Ca,Na) ₇ (Ti,Al) ₂ (Si ₂ O ₇) ₂ O(O,F) ₃ (goetzenite) PbO, <i>P4/nmm</i> PbO, <i>Cmma</i> Pb ₇ O ₈ Cl ₂ (asisite) FeO(OH) (lepidocrocite) AlO(OH) (boehmite) Bi ₂ CoO ₃ SO ₄ PbBiO ₂ Cl (perite) PbSbO ₂ Cl (nadorite) (MO)(CuSe) (M = Bi, Nd, Gd, Dy) Pb ₃ Sb _{0.6} As _{0.4} (O ₃ OH)Cl ₂ (thorikosite) Pb ₂ (O,OH) ₂ Cl (blixite) Bi ₂ O ₂ (CO ₃) (bismutite) CaBi ₂ O ₂ (CO ₃) ₂ (bayerite) BiOF (zavaritskite) BiOCl (bismoclite) Bi ₂ O ₂ (MoO ₄) (koehlinite) Bi ₂ O ₂ (WO ₄) (russellite) CaBiOF(CO ₃) (kettnerite)	251 252 252 253 254 255 256 257, 258 259 260 261 261 262 262 263, 264 265 266–268 269 270
L13	{ <i>uB</i> , 1 _∞ ² }[OM]	[OPb]	PbO, <i>Pbcm</i>	271
L14	{ <i>lB</i> , 1 _∞ ² }[O ₄ M ₅]	[O ₄ Pb ₄ Ag]	AgPb ₄ O ₄ Cl	272
L15	{ <i>lB</i> , 1 _∞ ² }[O ₃ M ₅]	[O ₃ Pb ₅]	Pb ₅ O ₃ (GeO ₄)	61
L16	{ <i>lB</i> , 1 _∞ ² }[O ₉ M ₁₄]	[O ₉ Pb ₁₄]	Pb ₁₄ (VO ₄) ₂ O ₉ Cl ₄ (komatite) Pb ₁₄ (AsO ₄) ₂ O ₉ Cl ₄ (salinite)	62, 63 273
L17	{ <i>lB</i> , 1 _∞ ² }[O ₇ M ₈]	[O ₇ Pb ₈]	Ag ₂ Pb ₈ O ₇ Cl ₄	274
L18	{ <i>hB</i> , 1 _∞ ² }[O ₁₁ M ₁₂]	[O ₈ F ₃ (Ca,Na) ₈ (Ti,Nb) ₄]	(Ca,Na) ₈ (Ti,Nb) ₄ (Si ₂ O ₇) ₂ O ₈ F ₃ (fersmanite)	275
L19	{ <i>lB</i> , 1 _∞ ² }[O ₄ M ₇]	[O ₄ Pb ₇]	Pb ₁₁ Si ₃ O ₁₇ Pb ₁₁ Ge ₃ O ₁₇	155 156
L20	{ <i>uB</i> , 2 _∞ ² }[O ₄ M ₃]	[O ₄ Ba ₂ Bi]	BaBi ₄ O ₄ I ₂	276

bases of the [OCu₄] tetrahedra and together with the layers form the fundamental electrically neutral Cu₅O₂(VO₄)₂ framework. As a consequence of the disposition of the layers one under the other, broad cavities with a radius in excess of 3.0 Å, which incorporate the alkali metal ions K⁺, Rb⁺, and Cs⁺ as well as the chloride ions Cl[−], are formed in the structure.

L2. A layer of this type is a ‘corrugated’ analogue of the L1 layer. It is distorted in such a way that the periodicity of the fundamental chain of the layer changes from 2 to 3. This layer has been detected by Shuvalov *et al.*²³⁴ in the crystal structure of NaCu₅O₂(SeO₃)₂Cl₃.

L3. The oxocentred {*uB*, 2_∞²}[OM] layer with the chemical formula [OLa] was identified by Bergerhoff and Paeslack¹⁹ in the La₂O₂S structure solved by Zachariasen.²³⁵ The multiplicity of this layer is 2, although it can be regarded as consisting of two corner-linked layers with a periodicity of 1.

L4. The [O₄M₃] structural unit of this type consists of two L3 layers ‘glued’ to one another or of four simple corner-linked single-period layers. As a result of the ‘glueing’, the O:M ratio becomes 1.333, *i.e.* greater than 1.

L5, L6, L7. The layers of these types can be regarded as a result of the successive linking of C7 chains. The C7 chains are initially linked *via* their edges into multiple chains similar to C8 and C9,

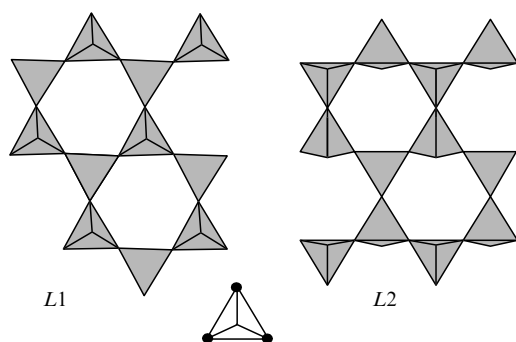


Figure 8. The types of oxocentred layered complexes *L1* and *L2*.

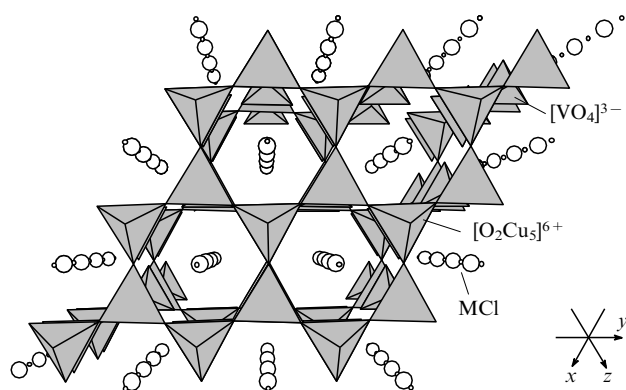


Figure 9. The crystal structure of averievite $\text{Cu}_5\text{O}_2(\text{VO}_4) \cdot \text{MCl}$.

after which these multiple chains are linked *via* lateral corners into infinite layers. Thus the *L5* and *L6* layers can be regarded as consisting of *C8* and *C9* chains respectively. The *L7* layer is formed from a *C7* four-fold chain, the individual fragments of which have not so far been detected in chemical compounds. The possibility of identifying the *L7* layer in the $\text{Bi}_{26}\text{O}_{27}(\text{SO}_4)_{12}$ crystal structure has been pointed out.²¹² The *L5* and *L6* layers were not considered in the original studies. It is of interest that the last two layers in compounds have similar chemical compositions — $[\text{O}_4\text{Cu}_3\text{Bi}_2]$ and $[\text{O}_6\text{Cu}_3\text{Bi}_4]$ respectively. In these complexes, the Bi atoms participate only in the edge-linking of the *C7* chains into multiple chains, whereas the Cu atoms are involved in corner-linking into a layer of the multiple fragments formed. Thus the functions of the cations in the topological structures of the *L5* and *L6* layers are different.

L8. The $\{uB, 1_\infty^2\}[\text{OM}_2]$ layer may be regarded as consisting of finite *I4* complexes.

L9. A type *L9* layer was first described by Keller and Langer²⁴³ in the structure of $\text{HgPb}_2\text{O}_2\text{Cl}_2$. The layer is made up of *C3* chains by the linking of the latter *via* the corners of the tetrahedra not involved in edge-linking.

L10. A $\{uB, 1_\infty^2\}[\text{OM}_2]$ layer has been noted by Bergerhoff and Paeslack¹⁹ in the crystal structure of dolerophanite $\text{Cu}_2\text{O}(\text{SO}_4)$. This layer can also be identified in the structure of francisite²⁴⁴ (Pring *et al.*²⁴⁴ did not consider the structure of the oxocentred layer).

L11. A type *L11* layer may be found in the crystal structure of pinakioleite $(\text{Mg}, \text{Mn})_2\text{Mn}^{3+}(\text{BO}_3)_2$. Together with the tetrahedrally coordinated ‘additional’ oxygen atoms, pinakioleite contains ‘additional’ oxygen atoms with the $[4 + 1]$ coordination — a ‘tetragonal pyramid’ — as well as metal atoms not involved in the oxocentred groups. On the other hand, all the ‘additional’ oxygen atoms in the structures of a series of diorthosilicates belonging to the mosandrite–rosenbuschite group^{246–251} are involved in tetrahedral coordination, while all the cations (with the exception of innelite and goetzenite) participate in the formation of the oxocentred tetrahedra. As in the case of the

structures of the cuspidine series (with a *C3* chain), the central oxygen atom in the $[\text{OM}_4]$ tetrahedra is partly substituted by fluorine, which does not disturb the overall structure of the complex.

L12. The $[\text{OM}]$ layer. The $[\text{OM}]$ layer is one of the commonest layers with edge-linking of tetrahedral complexes. For example, in the case of lead monoxide [tetragonal and one of the orthorhombic (*Cmma*) modifications], the $[\text{OPb}]$ layer is made up of $[\text{OPb}_4]$ tetrahedra.²⁵² An oxocentred layer of this type has been detected in the structures of a multiplicity of chemical compounds (see a review²⁷⁷ as well as Table 8).

L13. The layer in the orthorhombic (*Pbcm*) PbO ²⁷¹ differs structurally from *L12* by the marked ‘corrugations’ of the PbO layers. The topological structures of these layers are also different, although their constituent $[\text{OPb}_4]$ tetrahedra are topologically equivalent.

L14, L15 (Fig. 10), **L16.** These layers can be readily obtained by ‘cutting out’ different blocks of OPb_4 tetrahedra from the tetragonal PbO layer. In $\text{AgPb}_4\text{O}_4\text{Cl}$,²⁷² one tetrahedron is ‘cut out’ in each case, whereas in $\text{Pb}_5\text{O}_3(\text{GeO}_4)$ ⁶¹ blocks of six tetrahedra (three by two in size) are ‘cut out’. In the kombatite^{62,63} and sahlinite²⁷³ structures, ‘butterflies’ consisting of seven $[\text{OPb}_4]$ tetrahedra are ‘cut out’. In the layers formed after ‘cutting out’, the symmetry of the $[\text{OPb}_4]$ is distorted as a consequence of the removal of neighbouring tetrahedra.

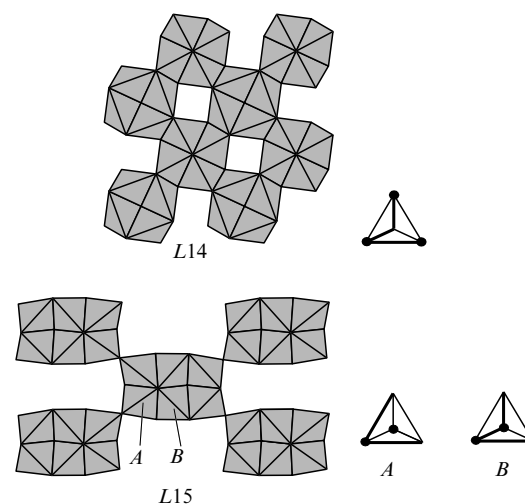


Figure 10. The oxocentred layered complexes *L14* and *L15*.

L17. The $[\text{O}_7\text{Pb}_8]$ layer of this type is a highly ‘corrugated’ version of the *L12* and *L13* layers, where individual $[\text{OPb}_4]$ tetrahedra have been ‘cut out’. The O : M ratio in such a layer is 7 : 8.

L18. The oxofluorocentred $[\text{O}_8\text{F}_3(\text{Ca}, \text{Na})_8(\text{Ti}, \text{Nb})_4]$ layer, made up of a defective (with one-tetrahedron ‘cut out’) *L12* layer to which single type *C1* chains have been added from above and from below, may be identified in the crystal structure of the mineral fersmanite.²⁷⁵ The addition takes place in such a way that the direction of the *C1* chain from the upper side of the layer is perpendicular to the direction of the same chain from the lower side. Each second tetrahedron of the chain is then located above or below the ‘cut out’ in the main layer. The $[\text{Si}_2\text{O}_7]$ diorthosilicate groups are located between the layers having this structure in fersmanite. In the original study,²⁷⁵ the oxocentred complexes were not identified.

L19. A layer of this type is made up of three-period chains with alternation: two linkages *via* the edges and one linkage *via* a corner. Such chains are loop-branched, since they are connected by two additional tetrahedra.

L20. The $[\text{O}_4\text{M}_3]$ double layer is made up of two $L12$ layers edge-linked to one another.

5. Oxocentred framework complexes

The classification of three-dimensional polyhedral structures is one of the important problems in the crystal chemistry of inorganic compounds. Tables 9 and 10 present the types of oxocentred framework complexes based on $[\text{OM}_4]$ tetrahedra and the chemical compounds containing them.

Table 9. Statistics of oxocentred framework complexes based on $[\text{OM}_4]$ tetrahedra.

Num-ber	ML	L	P	B	O:T	m	n	p	Connectedness formula
$F1$	1	1	2	uB	1:2	1	1	1	(4:1-4)
$F2$	1	1	2	uB	1:2	1	1	1	(4:1-4)
$F3$	1	1	1	uB	1:1	1	1	1	(12:1-12)
$F4$	1	1	1	lB	6:11	2	1	$A1$	(5:1-5)
								$B2$	(5:1-5)
$F5$	1, 2	1, 2	2	uB	1:1	1	1	1	(10:1-8; 2-2)
$F6$	1, 2	1, 2	4	lB	2:3	1	1	1	(6:1-5; 2-1)
$F7$	1, 2	1, 2	1	uB	1:1	1	1	1	(13:1-10; 2-3)
$F8$	1, 2	1, 2	2	uB	2:3	1	1	1	(7:1-6; 2-1)
$F9$	1, 2	1, 2	1	uB	1:1	3	2	$A1$	(8:1-4; 2-4)
								$B1$	(8:1-4; 2-4)
								$C1$	(10:1-8; 2-2)
$F10$	2	1, 2	2	uB	2:1	1	1	1	(22:1-16; 2-6)
$F11$	2	1, 2	2	lB	3:2	1	1	1	(16:1-12; 2-4)
$F12$	2	1, 2	5	lB	1;1	1	1	1	(9:1-6; 2-3)
$F13$	1, 2	1, 2	4	lB	2:3	1	1	1	(4:1-1; 2-3)
$F14$	1, 2	1, 2	4	uB	2:3	2	2	$A1$	(8:1-7; 2-1)
								$B1$	(6:1-6)
$F15$	1, 2	1, 2	2	uB	3:2	1	1	1	(16:1-12; 2-4)
$F16$	1, 2	1, 2	2	uB	2:3	1	1	1	(7:1-6; 2-1)
$F17$	1, 2	1, 2	2	hB	3:4	3	3	$A1$	(8:1-7; 2-1)
								$B1$	(10:1-9; 2-1)
								$C1$	(10:1-10)
$F18$	1, 2	1, 2	2	uB	2:3	4	2	$A1$	(9:1-8; 2-1)
								$B1$	(8:1-8)
								$C1$	(8:1-8)
								$D1$	(8:1-8)
$F19$	1, 2	1, 2	2	uB	6:7	1	1	1	(15:1-14; 2-1)
$F20$	1, 2	1, 2	2	oB	9:14	2	2	$A1$	(10:1-8; 2-2)
								$B2$	(7:1-6; 2-1)
$F21$	1, 2	1, 2	3	lB	10:13	5	5	$A1$	(4:1-2; 2-2)
								$B1$	(5:1-2; 2-3)
								$C1$	(6:1-3; 2-3)
								$D1$	(7:1-3; 2-4)
								$E1$	(8:1-4; 2-4)

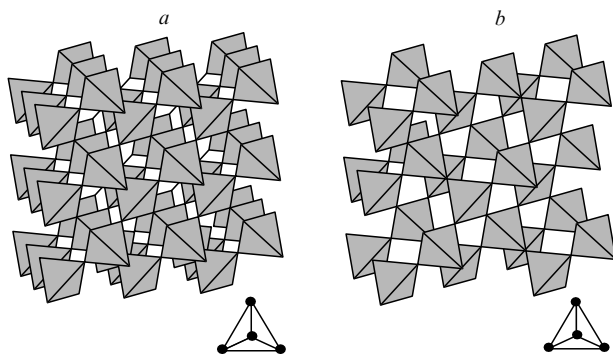


Figure 11. The crystal structure of cuprite Cu_2O and the $[\text{OCu}_2]$ double layer framework made up of $[\text{OCu}_4]$ tetrahedra (a) and the $F1$ framework (b).

Table 10. Chemical compounds containing oxocentred framework complexes based on $[\text{OM}_4]$ tetrahedra.

Num-ber	Type of complex	Chemical formula of complex	Chemical compound	Ref.
$F1$	$\{uB, \frac{3}{\infty}\}[\text{OM}_2]$	$[\text{OCu}_2]$	Cu_2O (cuprite)	278
		$[\text{OCu}_2]$	Cu_2OCl_2 (melanothallite)	279
			$\text{Cu}_2\text{O}(\text{SeO}_3)$, $P2_1/n$	51
			$\text{Cu}_2\text{O}(\text{SeO}_3)$, $P2_13$	51
		$[\text{OPb}_2]$	Pb_2O	280
			Pb_2OF_2	281
		$[\text{OPd}_2]$	Pd_2OCl_2	282
		$[\text{OFe}_2]$	$\beta\text{-Fe}_2\text{O}(\text{PO}_4)$	283, 284
		$[\text{ONiCr}]$	$\text{NiCrO}(\text{PO}_4)$	283
		$[\text{OA}_2]$ ($A = \text{Hg}, \text{Cd}, \text{Ag}, \text{Bi}, \text{Pb}$ etc.)	$\text{A}_2(\text{B}_2\text{O}_6)\text{O}$ ($B = \text{Ru}, \text{Rh}, \text{Ti}, \text{Cr}$ etc.)	285, 286, 287
$F2$	$\{uB, \frac{3}{\infty}\}[\text{OM}_2]$	$[\text{O}_2\text{MgAl}_3]$	$\text{MgAl}_3\text{O}_2(\text{SiO}_4)(\text{BO}_3)$	288
$F3$	$\{uB, \frac{3}{\infty}\}[\text{OM}]$	$[\text{OZn}]$	ZnO (zincite)	289, 290
		$[\text{OBe}]$	BeO (bromellite)	291
$F4$	$\{lB, \frac{3}{\infty}\}[\text{O}_6\text{M}_{11}]$	$[\text{O}_{12}\text{Bi}_4\text{Ag}_{18}]$	$\text{Bi}_4\text{Ag}_{18}\text{O}_{12}$	292
$F5$	$\{uB, \frac{3}{\infty}\}[\text{OM}]$	$[\text{OCu}]$	CuO (tenorite)	293
			AgO	293
$F6$	$\{lB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_2\text{Cd}_3]$	$\text{Cd}_3\text{O}_2\text{Cl}_2$	294
$F7$	$\{uB, \frac{3}{\infty}\}[\text{OM}]$	$[\text{O}_2\text{CuFe}]$	CuFeO_2 (delafossite)	295, 296
		$[\text{O}_2\text{AgFe}]$	AgFeO_2	297
		$[\text{O}_2\text{CuM}]$ ($M = \text{Al}, \text{GaSc}, \text{Y}$)	CuMO_2 ($M = \text{Al}, \text{GaSc}, \text{Y}$)	298
$F7$	$\{uB, \frac{3}{\infty}\}[\text{OM}]$		CuAlO_2	299
		$[\text{O}_2\text{CuMn}]$	CuMnO_2 (crednerite)	300
$F8$	$\{uB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_4\text{Cu}_5\text{Sn}]$	$\text{Cu}_5\text{Sn}(\text{BO}_3)_2\text{O}_4$	301
$F9$	$\{uB, \frac{3}{\infty}\}[\text{OM}]$	$[(\text{F}, \text{O})\text{Pb}]$	$\text{Pb}_{12}\text{Ta}_9\text{O}_{20}\text{F}_{29}$	302
$F10$	$\{uB, \frac{3}{\infty}\}[\text{O}_2\text{M}]$	$[\text{O}_2\text{Ce}]$	CeO_2	303
$F11$	$\{lB, \frac{3}{\infty}\}[\text{O}_3\text{M}_2]$	$[\text{O}_3\text{FeMn}]$	FeMnO_3	304
		$[\text{O}_3\text{CuTi}]$	$\text{Cu}_{1-x}\text{Ti}_{1-x}\text{Fe}_{2x}\text{O}_3$	305
$F12$	$\{lB, \frac{3}{\infty}\}[\text{OM}]$	$[\text{OIn}]$	$\text{In}_6\text{O}_6(\text{WO}_6)$	306
$F13$	$\{lB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_2\text{La}_3]$	$\text{La}_3\text{Ir}_3\text{O}_{11}$	307
		$[\text{O}_2\text{Bi}_3]$	$\text{Bi}_3\text{Ru}_3\text{O}_{11}$	308, 309
$F14$	$\{uB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_2\text{Co}_{2.1}\text{Al}_{0.9}]$	$\text{Co}_{2.1}\text{Al}_{0.9}\text{BO}_5$	310
		$[\text{O}_2\text{Ni}_2\text{Al}]$	Ni_2AlBO_5	310
		$[\text{O}_2\text{Cu}_2\text{Al}]$	Cu_2AlBO_5	310
$F15$	$\{uB, \frac{3}{\infty}\}[\text{O}_3\text{M}_2]$	$[\text{O}_3\text{Al}_2]$	Al_2O_3 (corundum)	311
$F16$	$\{uB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_2\text{Ag}_2\text{Pb}]$	Ag_2PbO_2	312, 313
		$[\text{O}_2\text{Cu}_2\text{Pb}]$	PbCu_2O_2	314
$F17$	$\{hB, \frac{3}{\infty}\}[\text{O}_3\text{M}_4]$	$[\text{O}_3\text{Ag}_3\text{Bi}]$	Ag_3BiO_3	315
$F18$	$\{uB, \frac{3}{\infty}\}[\text{O}_2\text{M}_3]$	$[\text{O}_4\text{Ag}_5\text{Bi}]$	Ag_5BiO_4	315
$F19$	$\{uB, \frac{3}{\infty}\}[\text{O}_6\text{M}_7]$	$[\text{O}_6\text{Ag}_5\text{Pb}_2]$	$\text{Ag}_5\text{Pb}_2\text{O}_6$	312
$F20$	$\{uB, \frac{3}{\infty}\}[\text{O}_9\text{M}_4]$	$[\text{O}_{18}\text{Ag}_{25}\text{Bi}_3]$	$\text{Ag}_{25}\text{Bi}_3\text{O}_{18}$	316
$F21$	$\{lB, \frac{3}{\infty}\}[\text{O}_{10}\text{M}_{13}]$	$[\text{O}_{10}\text{Pb}_{13}]$	$\text{Pb}_{13}\text{O}_{10}\text{Br}_6$	317

F1 (Fig. 11). The oxocentred type $F1$ framework is a reverse analogue of the cristobalite framework, which has been frequently noted by many investigators (see, for example, Belov⁷⁷). The crystal structure of cuprite Cu_2O ^{277, 278} consists of two interpenetrating electrically neutral anticristobalite $[\text{OCu}_2]$ frameworks (Fig. 11a). When univalent copper is replaced by divalent copper, the $[\text{OCu}_2]$ framework (Fig. 11b) acquires a 2+ charge per tetrahedron. The introduction of additional anions into this framework in order to compensate for the charge leads to the

crystal structures of melanothallite Cu₂OCl₂²⁷⁹ and Cu₂O(SeO₃)₂ (two modifications⁵¹). Similar frameworks with additional anions occur also in the Pd₂OCl₂²⁸² and Pb₂OF₂²⁸¹ structures. The latter structure was examined by Bergerhoff and Paeslack¹⁹ as an oxocentred framework. Pannetier and Lucas²⁸⁶ suggested that the A₂B₂O₆O' pyrochlore structural type, in particular, be considered as one containing the cuprite-like A₂O' (A = Sc, Y, Ln, Bi, Cd, Hg, Pb, *etc.*) framework. The following considerations were adduced in support of this model: firstly, the model makes it possible to consider the characteristic features of the disposition of the O' atom (position 8b), the orbitals of which are sp³-hybridised and the coordination is represented by a regular tetrahedron; secondly, the distortion of the cubic pyrochlore structure may be compared with the observed distortions of the polymorphic modifications of silica SiO₂; thirdly, if position A is occupied by a d¹⁰ atom of type Hg²⁺, Cd²⁺, or Ag⁺, the A–O' bond becomes stronger than the A–O bond and the O' oxygen becomes less mobile. The possibility of describing the pyrochlore structure taking into account the tetrahedral coordination of the O' oxygen has also been pointed out by Belov *et al.*²⁸⁷

F2. The oxocentred [O₂MgAl₃] framework, made up of L1 layers linked *via* corners not participating in the formation of the layer, may be identified in the crystal structure of grandierite.²⁸⁸

F3. The F3 framework is the oxocentred version of the wurtzite structure. Four [OZn₄] tetrahedra converge at each corner of this framework.

F4. The oxocentred [O₆M₁₁] framework has been found in the Bi₄Ag₁₈O₁₂ structure.²⁹² This framework consists of two types of fundamental chains — two-period C5 chain and a four-period chain formed as a result of the corner-linking of tetrahedra. In the structure of this compound, the chains are parallel to the *y* axis. This structure shows that the topological equivalence of all the tetrahedra in the polyion does not as yet ensure their configurational equivalence. In this structure, there are two configurational types of tetrahedra belonging to one topological class.

F5. The oxocentred framework of this type is made up of C7 lanarkite chains linked by the corners of the tetrahedra so that four tetrahedra converge at a single corner.

F6. The F6 framework is made up of L8 layers linked by non-shared corners of the tetrahedra.

F7. The delafossite CuFeO₂ structural type consists of a framework made up of continuous hexagonal layers of [OCuFe₃] tetrahedra linked *via* corners at which the copper atoms are located; within the layer, the linking is *via* the iron atoms.^{295, 296}

F8. The [O₂M₃] framework may be represented as consisting of single type C12 chains.

F9. The type F9 framework is made up of C1 chains linked in the following way: six C1 chains fitted together edgewise form a six-fold chain belonging to the O_nM_{n+2} family. The complex chains linked in this way are linked *via* the corners of the tetrahedra to form a framework dividing space into a series of broad parallel channels with a square cross-section. In the crystal structure of the compound Pb₁₂Ta₉O₂₀F₂₉, infinite columns of [TaO₆] octahedra are accommodated in these channels.³⁰²

F10, F11, F12. The frameworks of these types may be regarded as derivatives of the fluorite CaF₂ structure, which can be represented in its turn as one consisting of [FCa₄] tetrahedra. CeO₂,³⁰³ the structure of which is made up of [OCe₄] tetrahedra, is an analogue of fluorite. The structural type of bixbyite^{304, 305} corresponds to a defective fluorite framework, like the [OIn] framework in the crystal structure of In₆O₆(WO₆).³⁰⁶

F13 (Fig. 12a). The F13 type framework is made up of finite groups J6 linked by nonshared corners. The La₃Ir₃O₁₁ structure³⁰⁷ includes two interpenetrating [O₂La₃] frameworks.

F14 (Fig. 12b). The three-dimensional [O₂M₃] structure, characteristic of the crystal structures of aluminoborates M₂AlBO₅ (M = Co, Cu, Ni), has one-dimensional distorted hexagonal cavities in which the (BO₃) anions are accommodated.³¹⁰

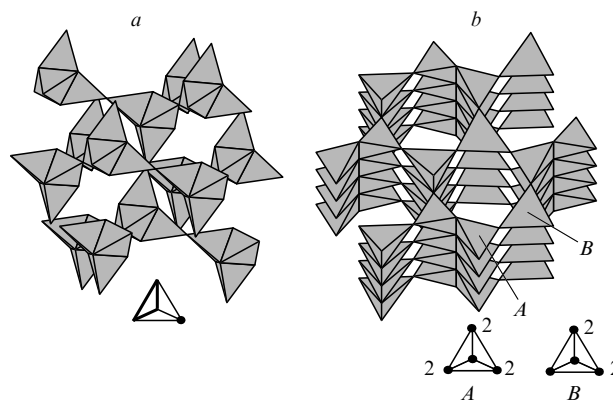


Figure 12. The oxocentred frameworks F13 (a) and F14 (b).

F15. The type F15 framework describes the crystal structure of corundum Al₂O₃ when it is considered taking into account the tetrahedral coordination of the oxygen atoms.³¹¹ It is possible to describe the structure as hexagonal close packing of the oxygen atoms in which octahedral cavities are filled by aluminium atoms. However, the latter are appreciably displaced from the centres of the octahedral cavities, which is due to the tendency of oxygen to acquire the ideal tetrahedral coordination. The structure of corundum is also remarkable because three [OAl₄] tetrahedra are linked together in it *via* a single [Al–Al] edge.

F16. The [O₂M₃] framework consists of C12 single chains linked *via* corners participating in edge-linking within the chain.

F17. Analysis of the Ag₃BiO₄ structure showed that it contains a complex oxocentred framework made up of [OAg₃Bi] tetrahedra of three configurational types.³¹⁵

F18. In the crystal structure of Ag₅BiO₄, there is a complex framework with the ratio O : M = 2 : 3.³¹⁵ This framework is formed as a result of the intertwining of C5 single chains, so that five-petal 'flowers' made up of oxocentred tetrahedra converging at one corner are produced.

F19. The C12 chains in the Ag₅Pb₂O₆ structure are joined together in threes to form columns with a trigonal symmetry and are linked into a framework *via* the corners of the tetrahedra not participating in the linking process.³¹²

F20. In the study of the crystal structure of Ag₂₅Bi₃O₁₈³¹⁶ within the framework of the approach employed, a single common edge [Bi–Ag] between three [OAg₃Bi] tetrahedra was noted. This framework consists of [OAg₃Bi] tetrahedra of two topological types. The type A tetrahedra, linked to form triple edge 'knots', consist of vertical columns with symmetry 3. The type B tetrahedra form groups made up of six tetrahedra converging at one corner. These groups link the vertical 'knotted' columns into a three-dimensional framework.

F21. The F21 framework was identified by Riebe and Keller³¹⁷ in the crystal structure of Pb₁₃O₁₀Br₆. It consists of infinite chains of corner-linked [OPb₄] tetrahedra. These complex chains, arranged crosswise in the structure, are linked *via* the corners of the tetrahedra into a three-dimensional framework.

6. Structures with different oxocentred complexes

In conclusion of the description of the topological types of oxocentred complexes, it is essential to note the existence of the structural type with two different complexes based on [OM₄] tetrahedra. In the crystal structures of the compounds Pb₁₁Si₃O₁₇¹⁵⁵ (Fig. 13), and Pb₁₁Ge₃O₁₇,¹⁵⁶ there are two oxocentred polyions of different dimensionality — the C3 chain and the L19 layer. The [OPb₂] C3 chains are arranged in the (001) plane in the form of a layer (without mutual linking), while the [O₄Pb₇] L19 layer is parallel to this plane. These layers alternate, the orthosilicate and diorthosilicate groups [SiO₄]^{4–} and [Si₂O₇]^{6–} being located in the space between them. The crystal-

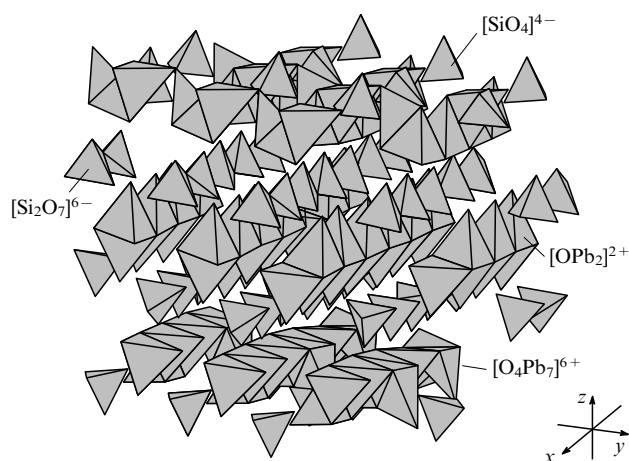
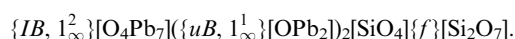


Figure 13. The crystal structure of $\text{Pb}_{11}\text{Si}_3\text{O}_{17}$.

chemical formula of the $\text{Pb}_{11}\text{Si}_3\text{O}_{17}$ structure should be written thus:



The presence in this structure of different polycations and poly-anions can be accounted for by their mutual stabilisation. The presence of silicate anions of two types and of different oxocentred structural units weakens the stresses generated.

V. Statistics of the corner and edge-linking $[\text{OM}_4]$ tetrahedra

The ability of oxocentred tetrahedra to be linked together in two different ways (*via* corners and edges) has led to the statistical analysis of different types of linking among the 63 polyions described.

We shall define the sharing index of an element of the tetrahedral group (corner, edge) as the number of tetrahedra between which the element is shared regardless of the method of sharing. The average sharing index of the corners of the tetrahedron $\bar{v}$ will be defined as the average of the sharing indices of its corners. Thus, if v_1, v_2, v_3 , and v_4 are the indices of the corners of the tetrahedron, it follows that

$$\bar{v} = \frac{\sum v_i}{4}, \quad i = 1-4.$$

By analogy with $\bar{v}$, we shall define the average sharing index of the edges of the tetrahedron $\bar{e}$:

$$\bar{e} = \frac{\sum e_i}{6}, \quad i = 1-6,$$

where e_i is the sharing index of the i th edge in the tetrahedron.

The average sharing index of an element [a corner ($\bar{v}$) or an edge ($\bar{e}$)] in the complex will be defined as the arithmetical mean of the sharing indices of the elements of topologically different tetrahedra. Account is taken of the number of tetrahedra of the given topological type in the complex. Thus, if there are two topological types of tetrahedra, A and B , in the complex in proportions of 2 : 1, then the average sharing index of the corners in the polyion is calculated by the formula

$$\bar{v} = \frac{2v_A + v_B}{3},$$

where v_A and v_B are the average sharing indices of the corners in the tetrahedra A and B .

The average sharing indices of the corners and edges in oxocentred complexes are presented in Table 11. For each dimensionality, the values have been averaged with respect to the

Table 11. The average connectedness indices of the corner ($\bar{v}$) and the edge ($\bar{e}$) in oxocentred complexes.

Num- ber	$\bar{v}$	$\bar{e}$	Num- ber	$\bar{v}$	$\bar{e}$	Num- ber	$\bar{v}$	$\bar{e}$
<i>I</i> 1	1	1	<i>L</i> 1	1.750	1	<i>F</i> 1	2	1
<i>I</i> 2	1.25	1	<i>L</i> 2	1.750	1	<i>F</i> 2	2	1
<i>I</i> 3	1.375	1	<i>L</i> 3	4	1.500	<i>F</i> 3	4	1
<i>I</i> 4	1.50	1.167	<i>L</i> 4	6	1.750	<i>F</i> 4	2.250	1
<i>I</i> 5	2	1.250	<i>L</i> 5	3.500	1.500	<i>F</i> 5	4	1.333
<i>I</i> 6	2.500	1.500	<i>L</i> 6	3.667	1.556	<i>F</i> 6	2.750	1.167
	1.604 ^a	1.153 ^a	<i>L</i> 7	3.750	1.583	<i>F</i> 7	5	1.500
<i>C</i> 1	1.500	1	<i>L</i> 8	2.500	1.167	<i>F</i> 8	3	1.167
<i>C</i> 2	1.750	1	<i>L</i> 9	2.750	1.333	<i>F</i> 9	4	1.556
<i>C</i> 3	2.500	1.333	<i>L</i> 10	2	1.167	<i>F</i> 10	8	2
<i>C</i> 4	3	1.444	<i>L</i> 11	2.750	1.167	<i>F</i> 11	6	1.667
<i>C</i> 5	1.500	1	<i>L</i> 12	4	1.667	<i>F</i> 12	4	1.500
<i>C</i> 6	2.000	1.083	<i>L</i> 13	4	1.667	<i>F</i> 13	2.750	1.500
<i>C</i> 7	2.000	1.333	<i>L</i> 14	3.250	1.500	<i>F</i> 14	2.875	1.083
<i>C</i> 8	3	1.500	<i>L</i> 15	2.667	1.389	<i>F</i> 15	6	1.667
<i>C</i> 9	3.333	1.556	<i>L</i> 16	2.875	1.444	<i>F</i> 16	3	1.167
<i>C</i> 10	4.333	1.611	<i>L</i> 17	3.571	1.619	<i>F</i> 17	3.500	1.111
<i>C</i> 11	4.333	1.611	<i>L</i> 18	4.091	1.424	<i>F</i> 18	3.125	1.042
<i>C</i> 12	1.750	1.167	<i>L</i> 19	2.450	1.267	<i>F</i> 19	5	1.167
<i>C</i> 13	2.250	1.250	<i>L</i> 20	6	1.833	<i>F</i> 20	5	1.222
<i>C</i> 14	1.750	1.167		3.376 ^a	1.427 ^a	<i>F</i> 21	3.350	1.533
<i>C</i> 15	1.667	1.111					3.886 ^a	1.328 ^a
<i>C</i> 16	2.33	1.278						
	2.437 ^a	1.278 ^a						

^a Average value.

number of polyions. It was found that the values of $\bar{v}$ naturally increase on passing from finite to framework complexes: 1.604 for *I*, 2.437 for *C*, 3.376 for *L*, and 3.886 for *F* (Fig. 14). As regards edge-linking, the values of $\bar{e}$ increase from 1.153 to 1.427 (1.278 for chains) on passing from finite layered complexes, but in the case of frameworks $\bar{e}$ diminishes to 1.328. This shows that edge-linking is most favourable for the linking of the $[\text{OM}_4]$ tetrahedra into a layer, *i.e.* into a two-dimensional structure. For framework complexes, this type of linking is less common apparently because the involvement of a large number of edges in a tetrahedral structure leads to an unduly high concentration of oxygen atoms and a decrease in the stability of the complex. The frameworks are formed preferentially by the corner-linking of the tetrahedra.

The average sharing indices of the corners and edges for oxocentred complexes as a whole, calculated from the data

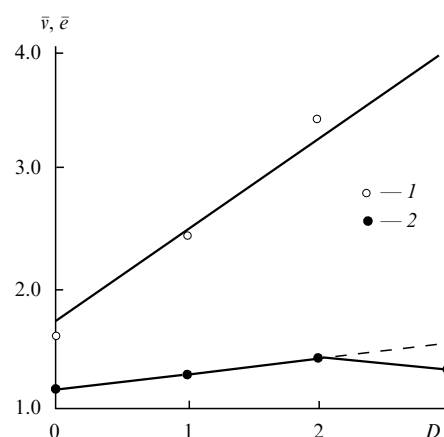


Figure 14. Dependence of the average sharing indices of the corners (1) and edges (2) on the dimensionality of the oxocentred complexes.

presented in Table 11, proved to be 3.139 and 1.330 respectively. Thus each corner in the oxocentred complexes based on the [OM₄] tetrahedra belongs on average to three tetrahedra and each edge belongs to $1\frac{1}{3}$ tetrahedra.

We may note that the edge-linking of tetrahedra inevitably increases the sharing index of their corners. Thus one (out of six) shared edge of the tetrahedra increases the average sharing index $\bar{v}$ by $1/6$ and, by creating two (out of four) common corners, it increases $\bar{v}$ by 0.5. If the fraction due to edge-linking is subtracted from $\bar{v}$, we obtain the following values of $\bar{v}$ for pure corner-linking: 1.145 for *I*, 1.603 for *C*, 2.098 for *L*, and 2.902 for *F*. This demonstrates yet again the importance of corner-linking in the organisation of oxocentred frameworks.

VI. Rules governing the linking of oxocentred [OM₄] tetrahedra

The description of the established types of cationic complexes based on oxocentred [OM₄] tetrahedra can be usefully completed by the rules according to which individual tetrahedra are linked together into a structural fragment.

1. The [OM₄] tetrahedra can be linked together *via* corners (M) and/or edges (MM).
2. One corner may be shared by more than two oxocentred tetrahedra but as a rule by not more than eight tetrahedra.
3. One edge is usually shared by not more than two oxocentred tetrahedra and in exceptional cases by three tetrahedra.
4. The corner-linking of the [OM₄] tetrahedra is characteristic of polyions of any dimensionality, while edge-linking is primarily characteristic of finite chain and layered structural units. The frameworks are formed mainly as a result of the corner-linking of tetrahedra.

The elucidation of the maximum number of tetrahedra converging at one corner constitutes an interesting problem. If the set of tetrahedra ('petals') converging at one corner is called a 'flower', then the maximum number of 'petals' (8) has been noted in topologically identical 'flowers' produced from the four-fold layer *L*4, the double layer *L*20, and the fluorite-like framework *F*10. The central atoms in these 'petals' are Bi, Ba, and Ce respectively. It was found that, among the oxocentred complexes known to us, there are eleven topologically different 'flowers' in which the number of 'petals' ranges from 5 upwards. Evidently the 'flower' with eight 'petals' constitutes the limit, the addition of yet another tetrahedron to the latter being impossible without the formation of a face-linkage.

The instance where three tetrahedra are edge-linked has not apparently been encountered in the crystal structures of anionic complexes with tetrahedral structural units, but does occur in the oxocentred corundum frameworks [O₃Al₂] and [O₁₈Ag₂₅Bi₃]. In the latter case, the steric interactions of the M corners not involved in the three-fold edge-linking of two neighbouring tetrahedra are weakened as a result of the inclination of the M–M edge relative to the horizontal. If one edge in the tetrahedral complexes may be shared by not more than three tetrahedra, then the distance *R* between nonshared M corners of neighbouring tetrahedra corresponds exactly to the length of the M–M edge. If four tetrahedra are linked *via* a single edge, (without a face-linkage), the distance *R* cannot be greater than or equal to the length of the M–M edge without complete loss of tetrahedral geometry by the linked complexes.

Sn₂O(SO₄), Pb₂O(SO₄) (lanarkite), and Cu₂O(SO₄) (dolerophanite) may serve as examples of compounds in which the chemical composition of the cations influences the topology of the oxocentred polyion. In the first compound, there are finite groups *I*6 having the composition [O₄Sn₈], in lanarkite there are *C*7 [OPb₂] chains, whilst in dolerophanite there are *L*10 [OCu₂] layers.

Analysis of the incidence of various structural units based on [OM₄] tetrahedra shows that complexes made up of configura-

tionally and topologically equivalent tetrahedra are commonest. This is fully consistent with Pauling's rule.

VII. Statistics of the M–O bond lengths and M–O–M bond angles in [OM₄] complexes

It was stated above that, as a consequence of the edge-linking of two tetrahedra, the value of the opposite bond angle diminishes. The average values of the M–O–M bond angles based on the M–M edge shared by two [OM₄] tetrahedra are listed in Table 12 for M = Cu, Sn, Pb, and La.[‡] Evidently the M–O–M angle depends on the size of the atom M. The greater the M–O bond length, the smaller the diminution of the M–O–M angle. It is of interest that the average value <M–O–M> for all the atoms M considered is close to the 'ideal' value of 109.5°. The decrease in one or several M–O–M angles, induced by the presence of a common edge in the tetrahedron, is compensated by the increase in the bond angles based on the nonshared edges.

Table 12. The average M–O–M bond angles in [OM₄] complexes.

Bond	M–O / Å	M–O–M / deg ^a		M–O–M / deg ^b	
		I	II	I	II
Cu–O	1.94	93.5 (91.4–95.9)	12	109.6	72
Sn–O	2.26	101.8 (98.1–104.4)	3	109.0	6
Pb–O	2.33	103.1 (94.4, 98.2–109.2)	83	109.5	120
La–O	2.36	104.4 (101.6–107.6) average value	32	109.4	48
				109.5	246

Note. The following designations have been adopted: I — average values of the angles, the limits of the variation of the angle in the structure being indicated in brackets; II — number of values taken into account.

^a Values for the angle based on the common edge. ^b Values for all the angles in the tetrahedron.

Another fundamental feature of [OM₄] complexes is the possibility of the linking at one atom M of several [OM₄] tetrahedra. Table 13 presents the average M–O bond lengths for M corners of different connectedness in complexes with M = Cu or Pb. The M–O bond lengths for a nonshared M corner and for a M corner linking two [OM₄] tetrahedra do not actually differ. When the M–M edge is shared and the number of tetrahedra converging at an atom M increases, the M–O bond length also increases. When a corner is shared by three tetrahedra so that one tetrahedron is edge-linked to a second tetrahedron and corner-linked to a third tetrahedron (Table 13), the M–O bond length for M = Pb increases sharply (2.35 Å). When four [OPb₄] tetrahedra are linked *via* a single edge so that a tetrahedron is edge-linked to two others and corner-linked to the fourth, the bond length also increases (2.40 Å). We may note that in the last case we did not take into account in the calculation of the M–O bond length the type *L*12 layered [OPb] complexes in which all the corners of the [OPb₄] tetrahedron are shared in this way. For these complexes, the M–O bond length is on average 2.34 Å (24 bonds were taken into account) (the limits of their variation were 2.31–2.36 Å), *i.e.* smaller by 0.06 Å than for the analogous corners in the remaining complexes. Overall, one may say that an increase in the number of [OM₄] tetrahedra converging at one M corner induces an increase in the M–O bond length.

[‡] Only data for [OM₄] complexes with a single cation M were used for the analysis.

Table 13. The M–O bond lengths for M corners with different connectedness in [OM₄] tetrahedra.

Corner of tetrahedron ^a	Number of tetrahedra converging at one M corner	Number of compounds taken into account	Number of bonds taken into account	(M–O) _{av} /Å	Limits of variation of M–O /Å
Cu–O					
	1	15	43	1.92	1.90–1.95
	2	13	38	1.92	1.86–2.00
	2	10	36	1.94	1.81–2.00
	4	2	8	1.96	1.91–2.02
Pb–O					
	1	5	11	2.26	2.18–2.32
	2	5	7	2.25	2.20–2.34
	2	11	38	2.27	2.23–2.32
	3	5	15	2.27	2.19–2.34
	3	3	19	2.35	2.34–2.37
	4	8	33	2.40	2.39–2.41

^a The filled circle designates the corner where two tetrahedra are linked and the numeral 2 at the filled circle indicates that a further two tetrahedra are attached to the given tetrahedron *via* a corner; the semibold edge signifies that yet another tetrahedron has been attached to the given tetrahedron *via* an edge.

VIII. Conclusion

The topological types of the structural units based on oxocentred [OM₄] tetrahedra have been described in the present review. In all, 63 different [OM₄] polyions have been identified; 6 finite, 16 chain, 20 layered, and 21 framework polyions. Since the aim of the present review was the discovery and systematic topological treatment of the oxocentred complexes, we have hardly touched upon the analysis of the geometrical and energetic characteristics of specific crystal structures and on their relation with the type of organisation of the [OM₄] tetrahedra to form a complex. Only the relation between the physical properties of the compounds containing [OM₄] groups and the characteristic features of the linking of these tetrahedra into a complex has been illustrated (for georgbokiite). The studies initiated will be continued by a detailed analysis of the lengths and angles in various types of oxocentred complexes, the study of the correlation of the structures of the compounds described from the standpoint of the crystal chemistry of oxocentred complexes with the properties of these compounds, the discovery of a relation between the traditional and proposed methods for the description of structures, and questions concerning the existence of oxocentred complexes in noncrystalline media, for example in gases.

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Rhenium-containing catalysts in reactions of organic compounds

M A Ryashentseva

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Abstract. The problems in the use of rhenium compounds and supported mono-, bi-, and poly-metallic rhenium-containing catalysts for carrying out reactions involving the metathesis of alkenes and unsaturated functional compounds, the hydrogenation and dehydrogenation of hydrocarbons, the conversion of hydrocarbons and their industrial mixtures, and the hydrogenation of fractions comprising carboxylic acids and the products of the hydroformylation of synthetic aliphatic acid esters are examined. The characteristic features of the behaviour of platinum–rhenium/alumina catalysts under reforming conditions are described. The specificity of the action of rhenium heptasulfide in the hydrogenation reactions of condensed N-containing aromatic compounds and in the reductive C-alkylation of indoloisoquinoline by alcohols is noted. The bibliography includes 251 references.

I. Introduction

Rhenium, discovered in 1925,^{1,2} occupies a special place in the family of rare elements. In its various compounds, rhenium can exhibit oxidation states ranging from -1 to $+7$. The commonest oxidation state of $+7$ is characteristic of compounds such as rhenic acid and its salts or rhenium heptoxide.

Supported metallic and metal oxide catalysts are of great importance in heterogeneous catalysis. One of the requirements which must be met by a supported metal is its resistance to recrystallisation during the catalytic process. It is therefore useful to introduce into a catalyst a metal with a high melting point, which promotes an increase in the resistance of the catalyst to ageing. Such a metal may be rhenium, the melting point of which is 3170°C . It is also noteworthy that the high solubility of ammonium perrhenate, rhenium heptoxide, and rhenium pentacarbonyl in water facilitates the preparation of rhenium catalysts by the impregnation method.

A series of patents, the authors of which described the ability of rhenium to catalyse a wide variety of chemical reactions,

appeared soon after the discovery of rhenium.³ The relevant data, published up to 1984, have been presented in a monograph.⁴

Reactions involving the hydrogenation of ethene to ethane and the preparation of methane from CO and hydrogen on rhenium-containing copper catalysts were investigated at the beginning of the 1930s.^{5,6} The introduction of rhenium greatly increased their activity.

It was shown in 1935 that rhenium catalysts exhibit a higher activity in the dehydrogenation of alcohols than platinum, nickel, zinc, and copper.⁷ An extensive investigation of the catalytic properties of rhenium and of its compounds with oxygen, sulfur, and selenium under the conditions of the liquid-phase hydrogenation of more than 100 organic compounds at an elevated pressure in a static system was carried out in the 1950s.^{8,9} In contrast to the usual catalysts, rhenium oxides are capable of reducing carboxylic acids to the corresponding alcohols (ranging from ethyl to undecyl alcohol) and carboxylic acid amides to amines. Rhenium sulfides have a superior activity to that of the familiar catalysts for the dehydrogenation of alcohols to aldehydes and ketones, such as platinum, nickel, zinc, or copper.

The hydrogenation of hydrocarbons on supported rhenium–carbon catalysts was achieved in 1958.^{10,11} The $\text{Re}/\text{Al}_2\text{O}_3$ catalysts showed a high activity in the conversion of C_5 – C_7 hydrocarbons in the reforming process at elevated temperatures and hydrogen pressures.¹² At the same time, at atmospheric pressure the $\text{Re}/\text{Al}_2\text{O}_3$ and $\text{Re}/\text{Al}_2\text{O}_3 \cdot \text{SiO}_2$ catalysts proved to be appreciably less active than platinum/alumina catalysts.¹³

The promoting effect of rhenium introduced into a palladium/alumina catalyst was observed in 1962.¹⁴ Bimetallic (1% Re, 1% Pd) catalyst supported on Al_2O_3 and $\text{Al}_2\text{O}_3 \cdot \text{SiO}_2$ exhibited a high activity in the reactions of C_6 hydrocarbons and in the reforming of petrol fractions,^{14,15} ensuring an increase in their octane number as a result of the increase in the content of aromatic and paraffinic isohydrocarbons.

The disproportionation reaction of alkenes (metathesis), which makes it possible to convert an individual alkene into two others, one of which has a higher and the other a smaller molecular mass than the initial hydrocarbon, was discovered in 1964.¹⁶ Thus ethene and butenes were obtained from propene on $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ at 25 – 100°C . Rhenium behaves in this reaction similarly to transition metals such as tungsten and molybdenum. Since 1966, the disproportionation reaction has begun to be used in industry (the ‘triolefin’ process). Information about the development of this process has been reported.¹⁷

A catalyst containing 0.01% – 3.0% of Pt and 0.01% – 5.0% of Re on alumina, which is active in the dehydrogenation of

M A Ryashentseva N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 137 65 18

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cyclohexane to benzene and in the reforming of the petrol fraction, was patented in the USA in 1968.¹⁸ The first factory in which an effective and stable bimetallic catalyst R-16, containing platinum and rhenium supported on an oxide, began to operate in May, 1968.¹⁹ The R-16, R-19, R-22, E-500, and E-501 bimetallic catalysts were introduced into industry by the American Companies Universal Oil Products, Chevron Research Co., and Engelhard Minerals and Chemicals Co., while the process itself came to be called 'rheniforming'.

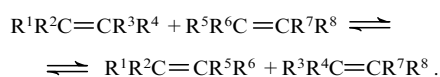
In our country, the Lenneftkhim Scientific-Industrial Conglomerate (SIC) developed polymetallic rhenium-catalysts of the KR series for the reforming process.^{20, 21} The first industrial batch of the KR-104 catalyst (containing 0.36% of Pt and 0.20% of Re) was prepared in 1976. The properties of improved compositions of the KR-108 and KR-110 catalysts were not inferior to the best world-class specimens.

About 75%–80% of the mined rhenium has been used for the production of various alloys, which are widely employed in electrical engineering and in electronics, aviation, rocket, and space technology. Petroleum-processing undertakings became major consumers of rhenium in 1969. They began to use it in combination with platinum as the catalyst for the reforming process.⁴ As early as 1978, 92% of rhenium was consumed in the USA for the production of bimetallic Pt–Re catalysts for the conversion of petrol fractions into high-octane petrols. The importance of the employment of rhenium as the reforming catalyst has been noted at the plenary session of the International Symposium on Rhenium and Rhenium Alloys in Orlando (USA),²² which was devoted to the 70th anniversary of the discovery of this element.

The development of studies on rhenium-containing catalysts used in petroleum processing and in basic and fine chemical synthesis during recent years is analysed in the present review.

II. Catalytic properties of rhenium oxide/alumina systems

The metathesis of alkenes reduces to the exchange of alkylidene fragments between alkene molecules:



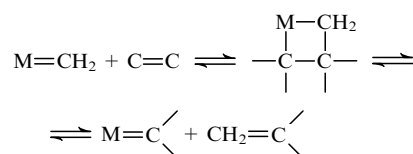
Valuable compounds, which may be used in perfumery, agriculture, and other fields, are formed in the metathesis of alkenes with functional groups.^{23–26}

Catalysts containing rhenium, molybdenum, and tungsten ($\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, $\text{MoO}_3/\text{Al}_2\text{O}_3$, and $\text{WO}_3/\text{Al}_2\text{O}_3$) are the most active in the metathesis of alkenes. The rhenium/alumina catalyst merits special attention because it exhibits a high activity and selectivity even at room temperature and atmospheric pressure. The metathesis of propene in the presence of $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ occurs at 50 °C, whereas on $\text{MoO}_3/\text{Al}_2\text{O}_3$ and $\text{WO}_3/\text{Al}_2\text{O}_3$ the corresponding temperatures are 207 and 402 °C respectively.²⁷ Catalysts containing rhenium with a lower valence, for example $\text{Re}_2(\text{CO})_{10}/\text{Al}_2\text{O}_3$, are also active in this reaction.

Nowadays investigators have concentrated attention on the improvement of rhenium/alumina catalysts. Their activity in the metathesis of functional alkenes can be increased by introducing small amounts of promoting additives, for example allyltin,^{25, 26, 28} which is known as the cocatalyst in homogeneous catalytic systems. Such additives increase the effectiveness also of heterogeneous systems, initiating the formation of a metallocarbene in accordance with the scheme



One of the stages of the widely known carbene chain mechanism of metathesis²⁹ involves the formation of a metallocyclobutane:

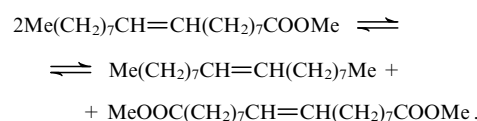


Rhenium/alumina catalysts containing < 5% of Re_2O_7 exhibit a slight activity in the metathesis of alkenes.^{30, 31} A necessary reaction stage on these catalysts is the reduction of the carbene formed. Propene and higher alkenes are capable of reducing Re_2O_7 on aluminium oxide even at room temperature.³²

1. The metathesis of olefins and unsaturated functional compounds

The properties of the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3 \cdot \text{SiO}_2$ catalyst containing 3 mass % of Re_2O_7 have been investigated at room temperature in relation to the model reaction involving the disproportionation of propene to ethene and but-2-ene in a microcatalytic flow system.³³ Its activity, exceeding that of $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, was further increased on introduction of tetramethyl- and tetraethyl-tin as a result of the participation of the Brønsted acid centres of the support in the process. The removal of surface OH groups reduced the activity of the catalyst. SnR_4 probably stabilises the active complex, which is especially important in the metathesis of functional alkenes.³⁴ SnR_4 -promoted $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, which is more active than the catalyst containing the oxides of other metals, for example MoO_3 , WO_3 , or V_2O_5 , is used as the catalyst in this process.³⁵

The new catalytic system $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3 \cdot \text{B}_2\text{O}_3$ has been tested in relation to the model reaction involving the metathesis of methyl oleate — a typical functional alkene:³⁶

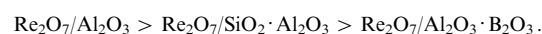


The catalysts were prepared by impregnation and partial drying at 110 °C. The amount of B_2O_3 introduced was 5%, 10%, 15%, and 20%. The catalyst containing 3 mass % of Re_2O_7 deposited on Al_2O_3 to which 15 mass % of B_2O_3 had been added exhibited the highest activity. The optimum catalyst activation temperature was 477 °C. For a reaction time longer than 1.5 h, a higher degree of conversion was achieved on this catalyst than on 18% $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$. The added B_2O_3 interacts with the acid centres of Al_2O_3 and weakens the linkages between rhenium particles and aluminium oxide. When the content of deposited B_2O_3 is in excess of the optimum value, the amount of rhenium reduced on the surface diminishes, which lowers the activity of the catalyst. The high activity and selectivity of the low-percentage $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3 \cdot \text{B}_2\text{O}_3$ catalyst at room temperature has been explained by the presence on the surface of strong Brønsted acid centres.

The catalytic activity may be altered by employing various cocatalysts. The promoting effect diminishes in the series³⁶



The most active metathesis catalysts — $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, $\text{Re}_2\text{O}_7/\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$, $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3 \cdot \text{B}_2\text{O}_3$, and $\text{M}_x\text{O}_y/\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ ($\text{M}_x\text{O}_y = \text{MoO}_3$, WO_3 , or V_2O_5) — were investigated by the temperature-programmed reduction method and thermal analysis.³⁷ The rhenium particles in the $\text{Re}_2\text{O}_7/\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$ and $\text{M}_x\text{O}_y/\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ specimens exhibit redox properties. The presence of V_2O_5 , WO_3 , or MoO_3 diminishes the thermal stability of the rhenium particles in the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalysts in the following sequence:



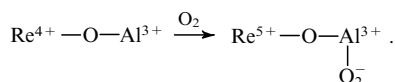
The unequal activities of these catalysts in the metathesis of alkenes and functional alkenes cannot be accounted for either by the different capacities of the rhenium particles for reduction, or

by possible steric hindrance in the formation of the rhenium–cyclobutane complex, or by a change in the thermal stability of the rhenium particles.³⁶

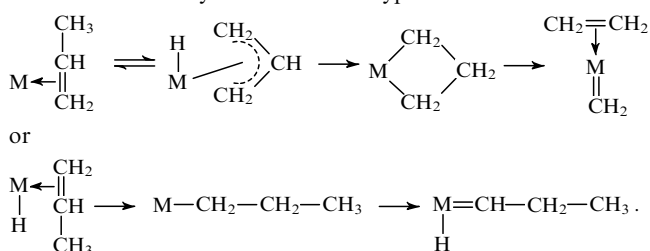
The activity of the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalysts of the metathesis of propene increases on raising the heat treatment temperature during their preparation.³⁸ The optimum heat treatment temperature depends on the Re_2O_7 content and is in the range 827–927 °C. For a low Re_2O_7 content, the maximum heat treatment temperature is required. The much higher activity of the catalyst containing 3 mass % of Re_2O_7 has been attributed to the redistribution of the ReO_4 groups on the Al_2O_3 surface, which has been confirmed by spectroscopic data. The catalyst heat-treated at a high temperature can be regenerated after deactivation by heat treatment at the usual temperature of 550 °C without appreciable loss of the initial activity.

The strength of the Brønsted and Lewis acid centres increases with increase in the amount of Re_2O_7 supported on Al_2O_3 .³⁹ The impregnation of a catalyst having a low rhenium content (6 mass % of Re_2O_7) with hydrochloric acid promotes the manifestation of Brønsted acidity. With increase in the Re_2O_7 content, the Brønsted acidity of the aluminosilicate gradually increases, while the Lewis acidity passes through a maximum. The activity of the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$, $\text{M}_x\text{O}_y/\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ ($\text{M}_x\text{O}_y = \text{V}_2\text{O}_5, \text{MoO}_3, \text{or WO}_3$), and $\text{Re}_2\text{O}_7/\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$ catalysts of the metathesis of alkenes is directly correlated with their Brønsted acidity, in contrast to the Lewis acidity. Thus, in order to increase the activity of low-percentage rhenium catalysts in the metathesis of alkenes, it is necessary to increase their Brønsted acidity by introducing various modifying agents.³⁹

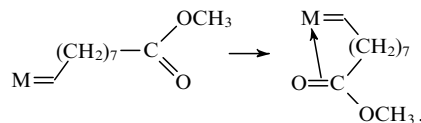
After heat treatment, a monolayer containing Re^{7+} ions is formed on the surfaces of the $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalysts.⁴⁰ For a low content of rhenium, the latter enters mainly into monomeric tetrahedrally coordinated ReO_4^+ ions, while in the presence of a high rhenium content $\text{Re}-\text{O}-\text{Re}$ linkages are formed. After interaction with the reactants, the rhenium is reduced and carbene complexes active in the metathesis are formed. The fraction of active rhenium ions is less than 1%. In the absence of cocatalysts, $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ altogether fails to exhibit an activity in the metathesis of alkenes with polar functional groups. The modification of the support, for example the introduction of SiO_2 into Al_2O_3 , increases the activity of the catalyst. The addition of a third metal oxide, for example MoO_3 , WO_3 , or V_2O_5 , increases the turnover number of the reaction for a low content of deposited rhenium. The addition of a tetraalkyltin not only increases the activity of the catalyst in the metathesis of alkenes but also makes it possible to achieve the metathesis of alkenes containing functional groups. The increase in the activity of low-percentage catalysts after their preliminary treatment with hydrogen at 500 °C and subsequent chemisorption of oxygen at 77 °C has been investigated by the temperature-programmed reduction, XPES, laser Raman spectroscopic, and EPR methods.⁴⁰ After such treatment, the signal due to adsorbed O_2^- ions was observed in the spectra. The active centres are formed in accordance with the scheme



It has been suggested that the carbene complex is formed during metathesis as a result of the generation of acid vacancies, which is followed by reactions of the type



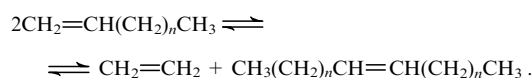
Catalysts such as $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ are highly polar and therefore react with polar compounds, for example with alkenes, as well as water, which may be present in the reactants and is a catalytic poison. Molecules with polar groups are capable of blocking the free centres necessary for metathesis, for example



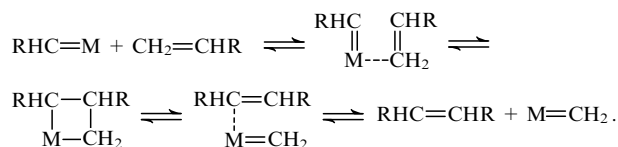
Other possible causes of deactivation have also been discussed.⁴⁰

The possibility of regenerating the 12% $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalysts, promoted by tetrabutyltin with the ratios $\text{Sn}:\text{Re} = 1:4, 2:4$, and $3:4$, and also of 3% $\text{Re}_2\text{O}_7/\text{SiO}_2 \cdot \text{Al}_2\text{O}_3$ promoted by tetraethyltin has been investigated. The metathesis of propene was carried out on these catalysts in a microcatalytic flow reactor at 20 and 80 °C and a pressure of 1.5 atm.⁴¹ The activity of the deactivated catalyst could be partially restored by increasing the content of the promoting agent and also by carrying out regeneration in a stream of oxygen with subsequent repeated addition of the promoting agent. Nevertheless, there was a partial loss of activity after each regeneration cycle. A study of the catalyst surface by scanning electron microscopy and X-ray diffraction after the temperature-programmed reduction showed that the loss of activity is associated with the formation on the surface of the oxide SnO_2 , which interacts with Re_2O_7 .

The study of the reactivity of alk-1-enes in metathesis under industrial conditions over the 12% $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalyst in the liquid phase⁴² showed that the rate of reaction diminishes with increase in the length of the hydrocarbon chain (from hex-1-ene to dec-1-ene). It has been suggested that this is associated with the fact that the rate of reaction is determined by the desorption of the product. Alkenes with a long chain and a symmetrical disposition of the inner double bond are formed in the metathesis of higher alkenes (oct-1-ene, dec-1-ene):



The reaction proceeds in accordance with the mechanism



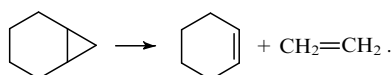
Four products — ethene, tetradec-7-ene, hexadec-7-ene, and octadec-9-ene — are formed in the joint metathesis of oct-1-ene and dec-1-ene.⁴²

The kinetic description of the metathesis of oct-1-ene on $\text{Re}_2\text{O}_7/\gamma\text{-Al}_2\text{O}_3$ in the liquid phase was based on the metallocarbene mechanism.⁴³ The rate-limiting stage is either the internal conversion of the carbene complex or the desorption of the product. It was not possible to make a final choice on the basis of the experimental data. The proposed mathematical model makes it possible to describe the deactivation of the catalyst as a function of the duration and temperature of the reaction. The apparent activation energy for metathesis is 22.5 kJ mol⁻¹ and that for the deactivation of the catalyst is 12.0 kJ mol⁻¹. The constancy of the degree of conversion under the conditions of the deactivation of the catalyst can be maintained by gradually increasing the reaction temperature. Calculation within the framework of the mathematical model showed⁴³ that the temperature-programmed regime makes it possible to convert a much larger amount of oct-1-ene in each catalytic cycle.

The $\text{Re}_2\text{O}_7/\text{Al}_2\text{O}_3$ catalyst modified by the introduction of B_2O_3 into the support has been used for the metathesis of methyl oleate.⁴⁴ The concentration of Lewis and Brønsted acid centres

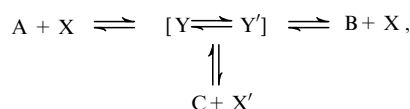
was determined spectroscopically during the reaction and also during the heat treatment of the support and the catalyst. When $\leq 5\%$ of B_2O_3 is introduced, the Al_2O_3 and B_2O_3 phases are present simultaneously in the specimen, each containing surface hydroxy-groups. For a higher B_2O_3 content, the hydroxy-groups of aluminium oxide are fully coated by boron oxide. The number of hydroxy-groups linked to boron diminishes with increase in the B_2O_3 content as a result of the formation of boron-containing linear polymers. When Re_2O_7 is supported on B_2O_3 -free Al_2O_3 , the ReO_4 groups react in the first place with the Lewis acid centres. If the B_2O_3 content exceeds 3%, then the surface hydroxy-groups are also substituted by the ReO_4 groups, which increases the catalytic activity. The ReO_4 groups which have reacted with the Lewis acid centres of the boronated support substitute the hydroxy-groups of the aluminium oxide during heat treatment. The hydroxy-groups of boron oxide are substituted only after heat treatment during ≥ 2 h at $550^\circ C$. For a B_2O_3 content greater than 10%, the reaction of the hydroxy-groups of boron with ReO_4 competes with the condensation reaction of two neighbouring hydroxy-groups. If it is supposed that the ReO_4 group substituted for the OH group of the support is a precursor of the active centre, then the increase in the activity of Re_2O_7 as a result of the introduction of B_2O_3 into Al_2O_3 can be explained either by the restoration of the linkages between the strong Lewis acid centres and ReO_4 or the formation of new surface hydroxy-groups, which serve as the acid centres.⁴⁴

The metathesis of cyclopropane hydrocarbons with different structures, namely n-butylcyclopropane, bicyclo[4.1.0]heptane (norcarane), and 1-methyl-1-phenylcyclopropane, at $20^\circ C$ has been investigated on a 20% $Re_2O_7/\gamma-Al_2O_3$ catalyst prepared by impregnating the support with a saturated NH_4ReO_4 solution containing tetrabutyltin.⁴⁵ The reactions were carried out under an argon atmosphere, using hexane or octane as the solvent. Ethene was present in the gas phase in all cases. The liquid phase contained $\sim 1\%$ of cyclohexene — the product of the elimination of carbene in the metathesis of norcarane:



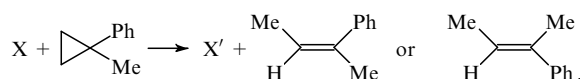
When the reaction involved bicyclo[3.1.0]hexane, ethene was also present among the gaseous products, but the liquid product did not contain cyclopentene. This has been explained by the greater tendency of cyclopentene to polymerise. C_6 – C_{12} monoalkenes, including undec-5-ene (55 mass %), dodec-6-ene (35 mass %), dec-5-ene (5 mass %), nonene, octene, heptene, and hexene (~ 1 mass % each), were formed from n-butylcyclopropane. The degree of conversion of 1-methyl-1-phenylcyclopropane into ethene was 40%.

The scheme proposed for this process⁴⁶ combines the carbene chain mechanism of metathesis and the mechanism involving the formation of cyclopropane compounds:



where A and B are alkenes, C are cyclopropane compounds, X and X' are catalytic centres, and Y and Y' are intermediate complexes.

In the reaction involving 1-methyl-1-phenylcyclopropane, X probably represents a catalytic centre for metathesis, arising in the activation of the rhenium/alumina catalyst by tetrabutyltin.⁴⁵ The interaction with a substrate molecule, accompanied by the isomerisation of the initial hydrocarbon, is necessary for the transformation of X into the X' centre:



The isomerisation products may be *cis*- and *trans*-2-phenylbut-2-enes, which apparently polymerise. Carbene may also be eliminated from the initial molecule on the centre produced, while the elimination product (α -methylstyrene) also isomerises. Thus the cyclopropane hydrocarbons isomerise on the rhenium/alumina catalyst and eliminate carbene with evolution of ethene, while the compounds formed polymerise or undergo metathesis.⁴⁵

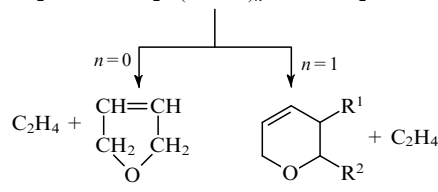
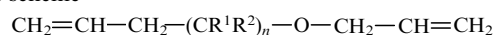
It has been established by the XPES method that the activity of the Re_2O_7/Al_2O_3 catalysts is determined by the reduction of Re^{7+} to give an intermediate oxidation state, which begins at 200 – $300^\circ C$. The reduction of rhenium in Re_2O_7/Al_2O_3 is known to be more difficult than in Re_2O_7/SiO_2 .^{47, 48} The state of rhenium in a fresh unpromoted 15% Re_2O_7/Al_2O_3 metathesis catalyst and in a specimen promoted with phenylcyclopropane has also been investigated by the XPES method.⁴⁹ The rhenium in the unpromoted catalyst exists in the form of ReO_4 tetrahedra linked to the support *via* one oxygen atom. The promotion of the catalyst with phenylcyclopropane has been explained⁴⁹ by the appearance on the surface of fragments with a rhenium–carbon bond in which the atomic ratio $Re:C = 1:1$. Such fragments may be carbene complexes containing the $Re=C$ double bond. The composition includes $> 90\%$ of the total number of rhenium atoms in the catalyst. The high concentration of these complexes on the surface of the specimen ensures its high catalytic activity in the metathesis of hex-1-ene, which has been confirmed experimentally.

2. Metathesis of functional alkenes

The metathesis of alkenes containing functional groups has been achieved on promoted and unpromoted rhenium/alumina catalysts.^{50–57} The experiments were performed at atmospheric pressure in a liquid-phase static system with stirring, ensuring that the reaction occurred in the kinetic region. The metathesis of allyl chloride, the allyl ether of allylcarbinol, allylbenzene, and diallyl ether⁵⁰ was achieved on catalysts supported on alumina and containing 0.5%–1.5% of Re with 5% or 10% of Mo or 1.5% of Re with 5% or 10% of V,⁵⁰ in which the molar ratios of the initial substances and Re_2O_7 were 560–3000 at temperatures of 22 and $55^\circ C$. Tetrabutyltin was used to promote the catalyst. The conversion of the initial substances into the corresponding bifunctional or cyclic unsaturated compounds (2,5-dihydrofuran and 2,3-dihydro- α -pyran) was 15%–20% (after 30 min) for a selectivity of 93%–95%. The catalyst containing 0.5 mass %–1.5 mass % of Re_2O_7 and 5 mass %–10 mass % of MoO_3 or V_2O_5 proved to be optimal.

The structure of the alkenyl fragment in an alkenyl allyl ether influences the selectivity and rate of its metathesis.⁵¹ The reactions of allyl-, methylallyl-, and phenylallyl-carbinols and the allyl ethers of allyl-, methyl-, dimethyl-, and phenyl-carbinols have been investigated on a rhenium/alumina catalyst promoted with tetrabutyltin (15 mass % of Re_2O_7 , 5 mass % of SnR_4 , and 80 mass % of $\gamma-Al_2O_3$) at temperatures ranging from 0 to $80^\circ C$ and for molar ratios of the initial substance and Re_2O_7 between 60 and 460. The reactivity of the ethers investigated depends on the structure of the alkenyl fragment. The presence of substituents at the carbon atom directly adjoining the oxygen atom retards the intramolecular metathesis. In the temperature range 20 – $80^\circ C$, the metathesis was characterised by a low activation energy (of the order of 10 – 13 kJ mol^{–1}).

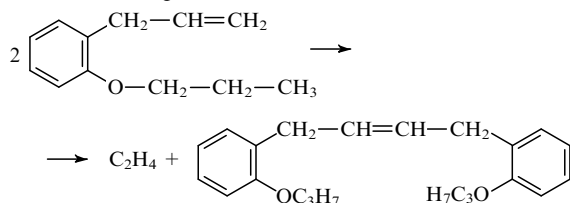
The unsaturated cyclic ethers are formed in accordance with the scheme



$R^1, R^2 = H, CH_3, C_6H_5$.

The intramolecular reaction predominates in the metathesis of ethers with two double bonds.⁵¹

If the hydroxy-group of *o*-allylphenol is converted beforehand into an ether group, it is possible to achieve a high rate of metathesis of the corresponding compound. The metathesis of *o*-(allyl)propoxybenzene with formation of 1,4-bis(*o*-propoxyphenyl)but-2-ene has been carried out on a rhenium/alumina catalyst promoted with tetrabutyltin at 22 °C in solvents (hexane or benzene).⁵² The selectivity reached 94%–96%. It is suggested that the metathesis proceeds *via* the intermolecular mechanism.

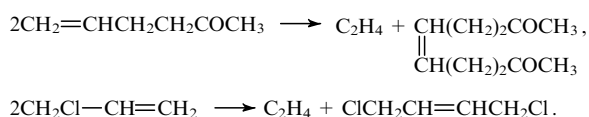


Aromatic alkenyl compounds can be arranged in the following sequence in terms of their reactivity in the above reaction: allylbenzene > *o*-(allyl)propoxybenzene > styrene.

The influence of the preliminary treatment of the support on the activity of a catalyst containing Re₂O₇ (15 mass %), (C₄H₉)₄Sn (5 mass %), and γ-Al₂O₃ (80 mass %) has been investigated in relation to the metathesis of *n*-hex-1-ene, allyl chloride, and diallyl ether.⁵³ Treatment with water and a 0.1 N aqueous solution of hydrochloric acid increased the rate of metathesis of *n*-hex-1-ene and allyl chloride. This can be explained by the increase in the number of active centres of the catalyst and the increase in the acidity of the support, since an increase in acidity, especially Brønsted acidity, promotes the metathesis of unsaturated compounds with a functional group.³⁵ On the other hand, treatment of the support with ammonium hydroxide diminished the rate of metathesis.

When the support of the Re₂O₇/γ-Al₂O₃ catalyst was treated with trialkyl borate, which decomposes to boron trioxide, the rate of metathesis of *n*-hex-1-ene and diallyl ether decreased by a factor of 2.5–3 compared with the initial untreated specimen.⁵⁴ Thus the Re₂O₇ content can be increased from 10 mass %–15 mass % to 1 mass %–2.5 mass % without diminishing the activity of the catalyst. The maximum activity is attained for 2 mass %–4 mass % of Re₂O₇ and 1 mass %–5.0 mass % of triethyl borate. The structure of the substituent in the trialkyl borate does not affect the rate of metathesis. The degree of conversion of *n*-hex-1-ene on the catalyst containing 10% of (C₂H₅O)₃B, 5% of Re₂O₇, 1.5% of (C₄H₉)₄Sn, and 83.5% of Al₂O₃ reached 86.9% after 5 min, whereas the degree of conversion on the catalyst untreated with tetrabutyltin was 32.0% after 20 min. The rhenium/alumina–boron oxide catalyst can operate in the temperature range 0–48 °C.

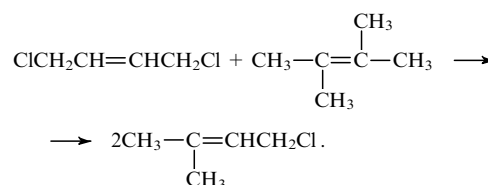
The metathesis of allyl chloride and allylacetone on a similar rhenium/alumina–boron oxide catalyst, prepared using the ratio Re₂O₇:Sn(C₄H₉)₄ = 3 proceeds *via* an intermolecular mechanism in accordance with the equation⁵⁵



The metathesis products are dec-5-ene-2,9-dione and 1,4-dichlorobut-2-ene. As in the metathesis of *n*-hex-1-ene and diallyl ether, the Re₂O₇ content in the catalyst can be reduced from 15 mass % to 2.5 mass %–7.5 mass % as a result of the treatment without diminishing the activity and selectivity. However, these active and selective catalysts of the metathesis of unsaturated compounds with functional groups are not sufficiently stable.^{54,55} One of the causes of instability is the ability of the functional group to compete with the C=C bond for the active centres of the catalyst, *i.e.* the deactivation of the catalyst by the reactant.⁴⁰ The

introduction of variable-valence metals (Mo or V) into the rhenium/alumina catalyst makes it possible to activate it and reduce the rhenium oxide content.⁵⁶ In a modification of a rhenium/alumina catalyst, both untreated and treated with SnBu₄, with constant-valence metals (Na⁺, K⁺, Mg²⁺), its activity in the metathesis of *n*-hex-1-ene falls and the degree of conversion diminishes from 10.9% to 2.6%. The addition of Pd increases the activity of the catalyst containing 5 mass % of Re₂O₇, but its selectivity decreases from 93%–98% to 68%–76%. Preliminary treatment of the rhenium/alumina catalyst with triethyl borate^{54,55} increases its activity.

The stabilising effect of aluminium oxide on rhenium apparently weakens with increase in the degree of its coverage by boron, which agrees with the data of another publication.³⁶ Treatment of the support with hydrogen chloride and triethyl borate increases the activity of rhenium/alumina catalysts in the joint metathesis of 1,4-dichlorobut-2-ene and 2,3-dimethylbut-2-ene,⁵⁶ so that the Re₂O₇ content could be reduced by a factor of two — from 15% to 7.5%. The reaction, the product of which is 4-chloro-2-methylbut-2-ene, proceeds in accordance with the equation



The activity of rhenium/alumina metathesis catalysts depend on the conditions of their activation (duration and temperature of the heat treatment, the medium, *etc.*).⁵⁷

The highest activity of the catalyst containing 5 mass % of Re₂O₇ is reached after its treatment at 620–640 °C. The productivity of the catalyst in the metathesis of allyl chloride increases by a factor of 3. After the activation of the rhenium/alumina catalyst containing 15 mass % of Re₂O₇, the degree of conversion of both *n*-hex-1-ene and allyl chloride at 580 °C increases. The activity and productivity of the catalyst can also be increased by increasing the activation time to 13 h. The rate of metathesis of *n*-hex-1-ene then increases by a factor of ~1.5, while the productivity of the catalyst in the metathesis of allyl chloride increases by a factor of 2–3. A further increase in the activation time to 20 h does not alter the activity appreciably. Yet another way of increasing the activity is the deposition of ammonium perrhenate on aluminium oxide with an intermediate heat treatment at elevated temperatures.⁵⁷

III. Catalytic properties of other rhenium compounds

Metallic rhenium is known to be in most cases inferior in its hydrogenating activity to group VIII metals,⁴ but some of its compounds exhibit a high hydrogenating capacity.

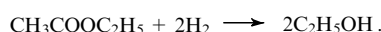
1. Hydrogenation of organic compounds

Rhenocene hydride (η⁵-C₅H₅)₂ReH manifested a high activity in the hydrogenation reactions of cyclohexene, benzene, ethyl acetate, and 36% acetic acid.^{58,59}

At a temperature of 150 °C and a hydrogen pressure P_{H₂} = 100 atm, the degree of conversion of cyclohexene on a catalyst containing 0.8% of Re relative to the mass of the hydrocarbon attained 73% after 1 h in an autoclave. An increase in temperature to 180 °C made it possible to lower the amount of catalyst and the reaction time by a factor of 2 and to obtain cyclohexane in a quantitative yield. Rhenocene hydride was much more active than Re₂S₇ and even ReO₃.⁵⁹ When rhenium trioxide was used, the amount of rhenium had to be increased by a factor of 3, the reaction time had to be prolonged by a factor of 8, and the pressure had to be raised by a factor of 2 in order to attain the same activity.

Benzene was hydrogenated fully on rhenocene hydride at 180 °C and $P_{H_2} = 100$ atm for a reaction time $\tau = 30$ min and for a rhenium content of 1.0% relative to the mass of benzene. In this reaction too, the catalyst was much more active than ReO_3 .

The degree of conversion of ethyl acetate (EA) in the hydrogenation reaction at 200 °C, $P_{H_2} = 100$ atm, and $\tau = 3$ h reached 60%. Under these conditions, ~49% of EtOH accumulated in the catalytic reaction mixture. Under comparable conditions, the overall degree of conversion of ethyl acetate into EtOH on Re_2O_7 was lower by a factor of 2. It is noteworthy that platinum and palladium sulfides did not exhibit a hydrogenating activity. A high activity of Re_2O_7 in the ethyl acetate reduction reaction has been observed:⁶⁰ the yield of EtOH reached 82% at 175 °C, $P_{H_2} = 210$ atm, and $\tau = 5$ h. However, up to 6% of AcOH was formed under these conditions. The reaction proceeds in accordance with the equation



The appreciable activity of rhenocene hydride and a fairly high selectivity of the reaction have been noted in the hydrogenation of 36% acetic acid.⁵⁹ At 230 °C, $P_{H_2} = 120$ atm and $\tau = 3$ h for a Re content of 1% and for an overall degree of conversion of ~86%, the yield of EtOH was ~52%. Ethyl acetate was formed together with EtOH. Rhenocene hydride decomposed under the conditions indicated. The metallic phase formed exhibited an increased activity, since it was more highly disperse than bulk rhenium. The following activity series has been established for the rhenocene hydride-based heterometallic catalysts in the hydrogenation of acetic acid:



Rhenium pentacarbonyl $Re_2(CO)_{10}$ also exhibits a high hydrogenating activity.^{61–63} Cyclohexene was fully hydrogenated on this catalyst after 15 min at 230 °C and $P_{H_2} = 50$ atm and for a Re content of 1% relative to the mass of the substrate. The hydrogenation of benzene required a higher hydrogen pressure (100 atm). In terms of its activity in the cyclohexene and benzene hydrogenation reactions $Re_2(CO)_{10}$ is superior to rhenium oxides⁶⁰ and is slightly inferior to rhenocene hydride.⁵⁹ However, it decomposes under the conditions indicated above with formation of a metallic phase exhibiting a higher activity than bulk rhenium. The lower activity of rhenium pentacarbonyl compared with rhenocene hydride can be explained by the fact that part of

the metal remains bound in the form of the carbonyl. IR spectroscopic study showed that, under the conditions of the hydrogenation of both cyclohexene and benzene, rhenium carbonyl reacts with the components of the reaction mixture. One cannot apparently rule out the possibility that not rhenium carbonyl itself but its unstable complex is catalytically active. The complex differs from the four known rhenium carbonyl hydrides — the monomeric $HRe(CO)_5$ and the cluster compounds $H_3Re_3(CO)_{12}$, $H_4Re_4(CO)_{12}$ and $HRe_3(CO)_{14}$. It also follows from the analysis of the IR spectra that hydrogenation of benzene entails the formation of a metal carbonyl complex different from that in the hydrogenation of cyclohexene.⁶²

Rhenium oxides with the perovskite structure and having the general formula $Ba_2Bi^{III}_{1/3}\square_{2/3}Re^{VII}O_6$, where $B^{III} = Y$ or Sm , or $Ba_3LaZnRe^{VII}\square O_{12}$ (the symbol $\square$ denotes a vacancy in the cationic lattice) also possess hydrogenating properties.⁶⁴ The catalysts were synthesised under solid-phase reaction conditions using a known method^{65,66} and were identified by X-ray phase analysis. The hydrogenation of ethyl acetate on these catalysts was carried out in a static system (in an autoclave) at 280 °C and $P_{H_2} = 100$ atm and for $\tau = 3$ h. The $Ba_2Y_{1/3}\square_{2/3}ReO_6$ catalysts showed the highest activity: the overall degree of conversion of ethyl acetate was 35% for a selectivity in the formation of ethanol of 83.4%. After the catalyst worked for 3 h, the reaction products were removed and a fresh portion of ethyl acetate was introduced. After this, the degree of conversion of ethyl acetate into ethanol in the course of 3 h of the reaction increased from 29.2% to 43.2%. Yet another repetition of the same procedure led to a further increase in the degree of conversion from 43.2% to 47.9% (selectivity 86%). The increase in activity may be associated with the activation of the specimen in the course of the experiment by virtue of the reduction of $Re(VII)$. The transition of rhenium to lower oxidation states in the course of the reaction was indicated by a change in the colour of the specimen from yellow or yellow-green to black. Ethyl acetate is reduced on Re_2O_7 even at 230 °C, whereas on the oxides described this requires 280 °C, other conditions being equal. It may be that the hydrogenating activity is determined by the presence in the catalyst not only of rhenium but also of other cations. One may postulate that the hydrogenating activity can be partly accounted for also by the formation of reduced rhenium in a highly disperse state under the experimental conditions.

The hydrogenation of benzene and ethyl acetate has also been achieved on rhenium oxides with the perovskite structure having

Table 1. Hydrogenation of benzene^a and ethyl acetate^b on rhenium oxides with the perovskite structure⁶⁷ and certain other rhenium catalysts.

Catalyst	Yield of C_6H_{12} obtained from benzene (%) ^a	Hydrogenation of ethyl acetate ^b				
		composition of catalytic reaction mixture (%)			conversion (%)	
		H ₂ O	EtOH	ethyl acetate	in EtOH	overall
$Ba_{3.6}Sr_{0.4}CoRe_2\square O_{12}$	18					
$Ba_{3.2}Sr_{0.8}CoRe_2\square O_{12}$	20					
$Ba_{2.8}Sr_{1.2}CoRe_2\square O_{12}$	20					
$Ba_{2.0}Sr_{2.0}CoRe_2\square O_{12}$	22	3.9	6.9	89.1	6.6	10.6
$Ba_{1.6}Sr_{2.4}CoRe_2\square O_{12}$	50					
$Ba_{1.2}Sr_{2.8}CoRe_2\square O_{12}$	52	5.7	13.3	81.0	12.7	19.0
$Ba_{0.4}Sr_{3.6}CoRe_2\square O_{12}$	78					
$Sr_{4.0}NiRe_2\square O_{12}$	90	8.2	10.6	81.2	10.2	18.8
$Sr_{4.0}CoRe_2\square O_{12}$	90					
$Sr_{4.0}CaRe_2\square O_{12}$	0					
Re_2S_7	3	4.0	20.9	75.1	20.0	24.9
ReO_3	100 ^c					
$Ba(ReO_4)_2$	0					
$Ba_2Y_{1/3}\square_{2/3}ReO_6$ ^d		4.5	30.5	65.0	29.2	35.0
						83.4

Reaction conditions: ^a $T = 200$ °C, $P_{H_2} = 100$ atm, $\tau = 2$ h, 1% of Re; ^b $T = 280$ °C, $P_{H_2} = 100$ atm, $\tau = 3$ h, 2% of Re; ^c $T = 240$ °C, $P_{H_2} = 100$ atm, $\tau = 4$ h, 3% of Re (data of Broadbent and Bartley⁶⁰); ^d data of Ryashentseva *et al.*⁶⁴

the general formula $A_4BRe_2O_{12}$, where $A = Ba$ or Sr and $B = Co$ or Ni .⁶⁷ The results obtained are presented in Table 1.

For a rhenium content of 1% relative to benzene, the yield of cyclohexane increases from 18% to 78% as the barium content falls.⁶⁴ Evidently the presence of the large barium ions (ionic radius 1.36 Å) in the catalyst structure hinders the hydrogenation of benzene. Among barium-containing catalysts, the $Ba_{0.4}Sr_{3.6}CoRe_2O_{12}$ specimen had the highest activity under the reaction conditions (200 °C, $P_{H_2} = 90-100$ atm, Re content 1%) and the yield of cyclohexane, amounting to 78%, remained unchanged for 6 h. In the succeeding 16 h, the yield of cyclohexane fell to 35%. The $Sr_{4.0}CoRe_2O_{12}$ and $Sr_{4.0}NiRe_2O_{12}$ catalysts proved to be the most active in the hydrogenation of benzene. Benzene was virtually fully hydrogenated on these catalysts, containing 1% of rhenium, at $T = 200-300$ °C and $P_{H_2} = 100-120$ atm and for $\tau = 2-3$ h. The catalytic activity increased with increase in the ionisation potential of the cations A ($Ba < Sr$) and B ($Ca < Ni < Co$).

The state of the surfaces of the $Sr_4CoRe_2O_{12}$ and $Ba_4CaRe_2O_{12}$ specimens before and after catalysis has been investigated by the method of thermovacuum electrical conductivity curves (TVE). The specimens exhibited semiconducting properties. After the experiment on a strontium specimen, exhibiting a high hydrogenating activity, changes were observed in the surface possibly due to its reduction. However, the specimen remained a semiconductor, *i.e.* there was no reduction to the metallic or pseudometallic state. The low specific surface of the specimen ($1.5\text{ m}^2\text{ g}^{-1}$) and the presence on the surface of $\sim 12\%$ of reduced rhenium, relative to its overall content, after catalysis (according to XPS data) made it possible to suggest that metallic rhenium is largely located not on the surface but in the bulk of the catalyst and in a highly disperse form. In order to create active hydrogenation catalysts with the perovskite structure, it is apparently necessary to reduce the rhenium on the surface. It has been demonstrated by the XPS method that Re^{4+} and Re^{6+} ions are present in the $Sr_4CoRe_2O_{12}$ and $Sr_4NiRe_2O_{12}$ catalysts and may enter into the composition of the active centres.

The perovskites $Ba_2Sr_2CoRe_2O_{12}$, $Ba_{1.2}Sr_{2.8}CoRe_2O_{12}$, containing 2% of Re, and $Sr_4NiRe_2O_{12}$ proved to be less active and selective than Re_2S_7 and $Ba_2Y_{1/3}O_{2/3}ReO_6$ in the hydrogenation of ethyl acetate ($T = 280$ °C, $P_{H_2} = 100$ atm, $\tau = 3$ h) (Table 1). Consequently, rhenium oxides with the perovskite structure exhibit different activities in the reactions involving the hydrogenation of the benzene ring and the carbonyl group. The hydrogenation of the latter requires more severe conditions and is more sensitive to the cationic environment of the rhenium oxides.⁶⁴

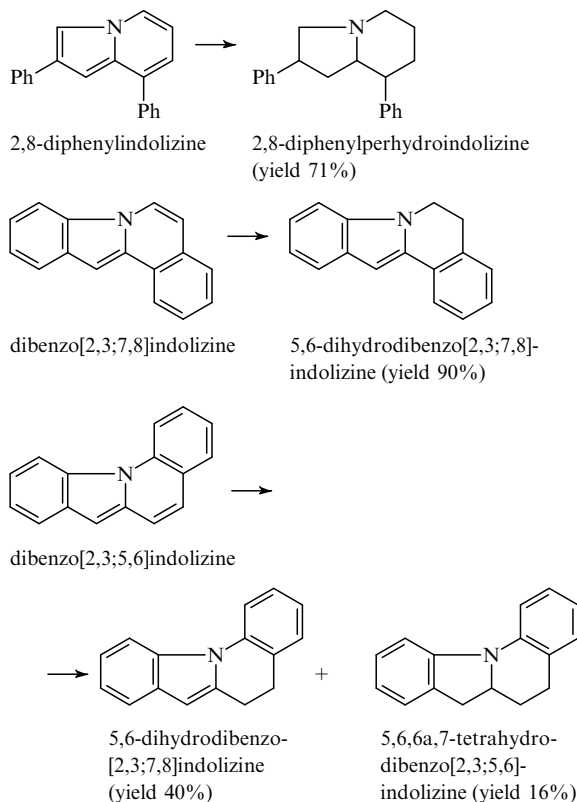
2. Selective hydrogenation of N-containing condensed aromatic compounds

Rhenium heptasulfide exhibits a specific activity in the hydrogenation and reductive *N*-alkylation by C_1-C_4 alcohols of pyridine, picoline, and lutidines.⁶⁸⁻⁷¹ It is an effective catalyst of the selective hydrogenation of aryl-substituted pyridines, isoquinolines, indeno[2,1*a*]pyridines, benzo- and dibenzo-indolizines (the reaction does not involve the benzene ring), and dihydroxyanthracenes. In the presence of alcohols, *N*-alkylation takes place on Re_2S_7 simultaneously with hydrogenation. The results have been surveyed in a review.⁷²

New compounds, which are of interest from the standpoint of their biological activity, have been obtained by the hydrogenation of compounds of the indolizine series⁷³ on Re_2S_7 ($T = 250$ °C, $P_{H_2} = 140$ atm, $\tau = 4$ h). The following compounds were obtained: 2,8-diphenylperhydroindolizine from 2,8-diphenylindolizine, 1,2,3,4-tetrahydrobenzoindolizine and 1,2,3,4,4a,5-hexahydrobenzo[2,3]indolizine from benzo[2,3]indolizine, 5,6-dihydrobenzo[2,3;5,6]indolizine and 5,6,6a,7-tetrahydrodibenzo[2,3;5,6]indolizine from dibenzo[2,3;5,6]indolizine, 5,6-dihydrodi-

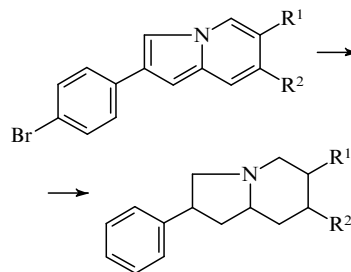
benzo[2,3;7,8]indolizine and 1-benzylidene-1,2-dihydroisoquinoline from dibenzo[2,3;7,8]indolizine, 4-(4-aminophenyl)-6-ethyl-2,3-dimethylpyridine and 4-(4-aminophenyl)-6-ethyl-2,3-dimethylpiperidine from 6-ethyl-2,3-dimethyl-4-(4-nitrophenyl)pyridine, and 1,2-dihydro-, 1,4-dihydro-, and 1,2,3,4-tetrahydroisoquinolines from 1-benzylisoquinoline.

The following reactions merit special attention:



The pyridine ring in benzoindolizines is hydrogenated more readily than the pyrrole ring. The presence of phenyl substituents in the indolizine does not prevent its complete reduction, while alkyl substituents hinder the hydrogenation reaction. The annelation of the pyrrole and pyridine rings of indolizine diminishes the degree of its hydrogenation. The nitro-group is reduced to the amino-group.

The hydrogenation of bromo-substituted 6- and 7-alkyl-2-(4'-bromophenyl)indolizines in the presence of Re_2S_7 has also been investigated.⁷⁴

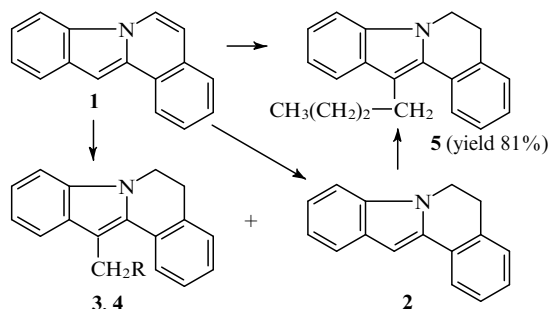


$R^1 = Et, R^2 = H; R^1 = H, R^2 = Me; R^1 = H, R^2 = Et;$
 $R^1 = H, R^2 = Pr; R^1 = H, R^2 = C_5H_{11}.$

Under the conditions selected ($T = 260$ °C, $P_{H_2} = 140$ atm, $\tau = 4$ h), a mixture of *trans*- and *cis*-isomers, with respect to the fusion between the pyrrolidine and piperidine rings, of bromine-free 6- and 7-alkyl-2-phenylindolizines is formed. The 6- and 7-alkyl-2-phenylindolizines isolated are characterised by a *trans*-fusion involving the pyridine ring in the 'chair' conformation and

the pyrrolidine ring in the 'envelope' conformation. The nitrogen atom is located outside the plane passing through the four carbon atoms of the pyrrolidine ring. The ratio of the *cis*- and *trans*-isomers of the compounds obtained is 1 : 1.4.

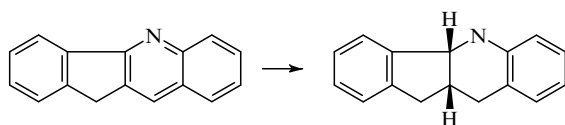
The hydrogenation of indolo[2,1-*a*]isoquinoline **1** in protic solvents (alcohols) has been achieved in the presence of Re_2S_7 ($T = 250^\circ\text{C}$, $P_{\text{H}_2} = 140\text{ atm}$, $\tau = 4\text{ h}$).⁷⁵ The *N*-alkylation of the initial compound observed previously⁷² is ruled out owing to the presence in the molecule of a bridgehead nitrogen atom. Alkylation at the C_{11} atom takes place instead:⁷⁵



$\text{R} = \text{H}$ (**3**), CH_3 (**4**).

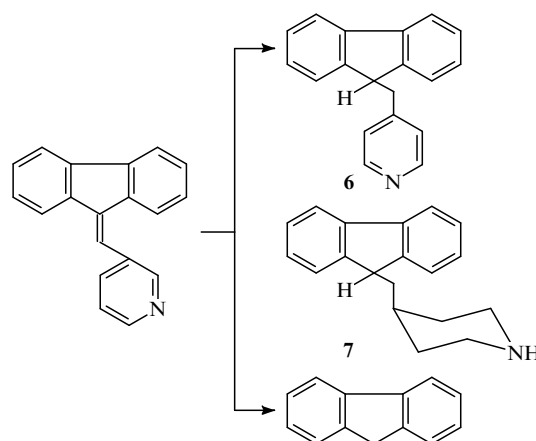
Methanol, ethanol, 1-butanol, and isopropyl alcohol were used as the alkylating agents. A mixture of compounds **2**, **3**, and **4** is formed in the first two instances in a high overall yield. The hydrogenation in 1-butanol leads to the formation of only the 11-butyl derivative **5** in 81% yield. If the dihydro-derivative **2** is subjected to reductive alkylation by 1-butanol, it is converted into 11-*n*-butyl-5,6-dihydroindoloisoquinoline **5** in a high yield. In the presence of Re_2S_7 , the isoquinoline **1** is initially hydrogenated under the conditions indicated above to dihydroisoquinoline **2**, which is subsequently alkylated with formation of the 11-alkyl derivatives of compound **5**. The alkylation proceeds *via* an electronic substitution mechanism, the yield of products increasing with decrease in the acidity of the alcohol.

5,5a,10a,11-Tetrahydro-10*H*-indeno[1,2-*b*]quinoline has been obtained by the hydrogenation of 10*H*-indeno[1,2-*b*]quinoline ($T = 250^\circ\text{C}$, $P_{\text{H}_2} = 140\text{ atm}$, $\tau = 4\text{ h}$) in benzene in the presence of Re_2S_7 . Its structure was confirmed by mass-spectrometric and IR spectroscopic data, electronic absorption spectra, and ^{13}C and ^1H NMR spectra:⁷⁶



The *cis*-fusion between the indane and tetrahydroquinoline fragments as well as the axial orientation of the proton at the C(5a) atom and the equatorial orientation of the proton at the C(10a) atom have been confirmed by molecular mechanical methods using the PC MODEL program.

The possibility of hydrogenating an exocyclic double bond of the fulvene type on Re_2S_7 has been investigated in relation to 9-(4-pyridylmethylene)fluorene, 9-(4-pyridylmethylene)-4-azafluorene, and 9-benzylidene-4-azafluorene.⁷⁷ The hydrogenation of 1-fulvene ($T = 250^\circ\text{C}$, $P_{\text{H}_2} = 130\text{ atm}$, $\tau = 4\text{ h}$) proceeds to the extent of 90%. Three compounds — 9-(4-pyridylmethyl)fluorene **6**, 9-(4-piperidylmethyl)fluorene **7**, and fluorene (the hydrogenolysis product) — were isolated from the products in 33%, 16%, and 10% yields respectively. The hydrogenation involves preferentially the exocyclic double bond of the fulvene fragment with formation of 9-azafluorenyl(pyridyl)methanes.



IV. Catalytic properties of rhenium and its compounds on supports

1. Hydrogenation of benzene and ethyl acetate

The dependence of the properties of supported rhenium-containing catalysts on the nature of the support (α -, θ -, and γ - Al_2O_3 , SiO_2 , $\text{Al}_2\text{O}_3 \cdot \text{SiO}_2$, MgO), the concentration of the metal (0.3 mass %, 0.4 mass %, 2.0 mass %, and 3.7 mass %) and the nature of the initial rhenium compounds [HReO_4 , NH_4ReO_4 , KReO_4 , and $\text{Ba}(\text{ReO}_4)_2$] has been investigated.⁷⁸ The degree of dispersion of rhenium, measured by the hydrogen thermal desorption method, was compared with the activities of the supported catalyst in the hydrogenation of benzene (flow system, $T = 200^\circ\text{C}$, $P_{\text{H}_2} = 27.3\text{ atm}$, $P_{\text{C}_6\text{H}_6} = 2.7\text{ atm}$). Before the start of the experiments, the catalysts were reduced in a stream of purified hydrogen (500°C , space velocity $\nu_{\text{vol}} = 15\,000\text{ h}^{-1}$, $\tau = 4\text{ h}$). High-temperature reversible chemisorption of H_2 was observed on the fresh samples. Its overall extent depended on the nature of the support and the concentration and nature of the initial rhenium compounds taken for the preparation of the catalysts. The reversible chemisorption occurred only after the attainment of high degrees of reduction of rhenium. On the other hand, if rhenium was not fully converted into the metallic state, hydrogen was absorbed at temperatures corresponding to the additional reduction temperature. The degree of chemisorption was independent of the specific surface of the support: the maximum chemisorption was observed on Re/MgO ($S = 94\text{ m}^2\text{ g}^{-1}$) and the minimum chemisorption was noted on $\text{Re/Al}_2\text{O}_3 \cdot \text{SiO}_2$ ($S = 370\text{ m}^2\text{ g}^{-1}$). When the support was impregnated with perrhenic acid, the maximum chemisorption of H_2 was observed on silica gel and the minimum occurred on γ - Al_2O_3 . On γ - Al_2O_3 , the maximum chemisorption of hydrogen was attained when NH_4ReO_4 was employed, whereas on SiO_2 the minimum chemisorption was observed on the sample impregnated with KReO_4 . The chemisorption on the catalyst obtained by impregnating aluminium oxide with a solution of the salt NH_4ReO_4 appreciably increased with increase in the concentration of rhenium from 0.3 mass % – 0.4 mass % to 2.0 mass % – 3.7 mass %, while its further increase to 7% was accompanied by a less significant rise in chemisorption. The activity of the reduced rhenium depended on the strength of bonding of the chemisorbed hydrogen and was not correlated with the specific surface of the metal. Two regions of the thermal desorption of hydrogen were observed: at 70 – 400°C (form I) and at 500 – 800°C (form II). In order to estimate the degree of dispersion of rhenium, it is useful to employ the quantities characterising the desorption of form I.

The activities of the $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ catalysts containing 10.4 mass % and 1.04 mass % of rhenium, subjected to a preliminary treatment with hydrogen at 550–800 °C (hydrogenation of benzene) or at 80–300 °C (hydrogenolysis of benzene) did not change or decrease with decrease in temperature.⁷⁹ A low concentration and high degree of dispersion of rhenium are unfavourable for both reactions, particularly for the hydrogenation of benzene. The activity of the low-percentage catalyst with an average rhenium particle size $l = 1.7\text{--}2.6$ nm was several times lower in both reactions than the activity of the high-percentage catalyst with $l = 3.4\text{--}4.4$ nm and rhenium powder with $l = 166$ nm.⁸⁰ The activity of the high-percentage catalysts in the hydrogenation reaction did not change when the average particle size was increased from 3.4 to 4.4 nm. The results obtained indicate a low activity of very small metallic particles and the presence of highly specific active centres for the hydrogenolysis of benzene. The negative influence of the decrease in the particle size of the metal on its activity in the hydrogenation of benzene has also been observed on palladium,⁸¹ ruthenium,⁸² rhodium,⁸³ and nickel.^{84,85} This may be associated with the enhancement of the role of the hydrogenolysis of the hydrocarbons.⁸⁶

The catalytic properties of the 5% $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ system have been investigated in relation to the model ethyl acetate hydrogenation reaction.⁸⁷ The principal reaction product is ethanol, while diethyl ether, hydrocarbons, and water are formed as side products. A change in temperature from 190 to 250 °C, in the hydrogen pressure from 5 to 60 atm, and in the H_2 :EA molar ratio from 5 to 20 in the flow system after the catalyst had worked for 40 h did not affect its stationary activity. An increase in temperature from 250 to 270 °C did not entail an increase in the degree of conversion of ethyl acetate. The maximum degree of conversion of ethyl acetate into ethanol at 250 °C reached 40.9% for a diethyl ether content of 5.3%. It was shown that hydrocarbons are the products of the hydrogenolysis and not the dehydration of ethanol. Diethyl ether is formed from ethanol at a lower rate than from ethyl acetate. Under optimum conditions ($T = 230$ °C, $P_{\text{H}_2} = 60$ atm, H_2 :EA = 5, and $v_{\text{mass}} = 0.7$ h⁻¹), the degree of conversion of ethyl acetate into ethanol is 49%, while the selectivity is 83.5%.

The nature of the support (θ -, δ -, and α - Al_2O_3 or SiO_2) and the reduction conditions (reduction by the H_2 + EA mixture at 230 °C or by hydrogen at 500 °C) influence the hydrogenating properties of the supported rhenium catalyst in the conversion of ethyl acetate into ethanol⁸⁸ at 230 °C, $P_{\text{H}_2} = 30$ atm H_2 :EA = 5, and $v_{\text{mass}} = 0.7$ h⁻¹. The following activity series was obtained: $\text{Re}/\theta\text{-Al}_2\text{O}_3 > \text{Re}/\alpha\text{-Al}_2\text{O}_3 > \text{Re}/\delta\text{-Al}_2\text{O}_3 > \text{Re}/\text{SiO}_2 \approx \text{Re}/\gamma\text{-Al}_2\text{O}_3$. The first catalyst of this series was three times more active than the last. Regardless of the reduction procedure, the maximum selectivity in the hydrogenation of ethyl acetate to ethanol is attained on the $\text{Re}/\alpha\text{-Al}_2\text{O}_3$ sample. Diethyl ether is formed in measurable amounts only on the $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ and $\text{Re}/\theta\text{-Al}_2\text{O}_3$ catalysts. Its formation is appreciably promoted by treatment with hydrogen. On $\text{Re}/\gamma\text{-Al}_2\text{O}_3$, the yield of diethyl ether is 1.5 times greater than that of ethanol. After preliminary treatment with the H_2 + EA mixture at 230 °C, $\text{C}_1\text{--C}_4$ hydrocarbons are formed on all the catalysts (the maximum and minimum yields are on $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ and $\text{Re}/\alpha\text{-Al}_2\text{O}_3$ respectively). Preliminary treatment with hydrogen at 500 °C induces a sharp decrease in the degree of conversion of ethyl acetate into hydrocarbons on the $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ and $\text{Re}/\theta\text{-Al}_2\text{O}_3$ catalysts. On the remaining samples, the yield of hydrocarbons as well as the selectivity in their formation change insignificantly. Rhenium(VII), supported on SiO_2 and $\theta\text{-Al}_2\text{O}_3$ (but not on $\gamma\text{-Al}_2\text{O}_3$), is fully reduced by hydrogen at 500 °C. The degree of dispersion of the metal diminishes in the sequence $\text{Re}/\gamma\text{-Al}_2\text{O}_3 > \text{Re}/\theta\text{-Al}_2\text{O}_3 > \text{Re}/\text{SiO}_2$. The temperature of the maximum desorption of hydrogen (200–300 °C), which can participate in the hydro-

genation process, diminishes in the same sequence.⁷⁸ The maximum activity of the $\text{Re}/\theta\text{-Al}_2\text{O}_3$ catalyst can be explained by the higher degree of dispersion of rhenium in it compared with Re/SiO_2 and the higher oxidation state of the metal compared with $\text{Re}/\gamma\text{-Al}_2\text{O}_3$. The activity of the catalyst after preliminary treatment with the reaction mixture is as a rule higher than after treatment with hydrogen. This is manifested particularly strikingly in the case of the $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ catalyst, in which rhenium interacts strongly with the support. Hence it is reduced with greater difficulty.⁴⁷ The H_2 + EA mixture probably reduces the supported Re(VII) more effectively at 230 °C than pure hydrogen at 500 °C.⁸⁷ The kinetic data obtained suggest the possibility of the formation of diethyl ether directly from ethyl acetate.

Diethyl ether is formed with participation of the acid centres on the $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ surface, on which C_2 hydrocarbons may also be formed to some extent. The absence of acid centres from the surfaces of the supports in the Re/SiO_2 and $\text{Re}/\alpha\text{-Al}_2\text{O}_3$ catalysts promotes the manifestation of a higher selectivity by the latter but a lower hydrogenating activity than in the case of $\text{Re}/\theta\text{-Al}_2\text{O}_3$.^{88,89}

In order to discover the relation between the catalytic properties and the state of rhenium in the specimens containing 0.5% of Re on γ -, θ -, and α - Al_2O_3 , the kinetic data for the hydrogenation of ethyl acetate ($T = 230$ °C, $P_{\text{H}_2} = 30$ atm, H_2 :EA = 5) were compared with the results of an IR spectroscopic study of the chemisorption of carbon monoxide.⁹⁰ Comparison of data obtained before and after the reaction made it possible to postulate the existence of metallic rhenium in two main states on the catalyst surface — Re_x^0 and Re_y^0 , differing in the degree of dispersion, the nature of the interaction with the support, and susceptibility to saturation by coke. On Re_x^0 , ethyl acetate is converted into ethanol and hydrocarbons, whilst on Re_y^0 it is converted into ethanol and diethyl ether. On the $\gamma\text{-Al}_2\text{O}_3$ -based samples, the ionic form Re^{n+} is also present and on it ethyl acetate is hydrogenated solely to diethyl ether. The ratio of the different states of rhenium determines their activity and selectivity in the ethyl acetate conversion reactions. The ideas described concerning the nature of the activity of rhenium/alumina catalysts for the hydrogenation of ethyl acetate are to some extent simplified. However, the observed features may prove useful for the development of more selective rhenium catalysts for the hydrogenation of carboxylic acid esters.

The addition of basic oxides — lithium or lanthanide oxides — affects the properties of the 2% $\text{Re}/\gamma\text{-Al}_2\text{O}_3$ catalyst in the hydrogenation of ethyl acetate.⁹¹ Such additives are known to diminish the acid functions of the support in the $\text{Pt}/\gamma\text{-Al}_2\text{O}_3$ and $\text{Pd}/\gamma\text{-Al}_2\text{O}_3$ catalysts for the dehydrogenation of alkanes and cycloalkanes.^{92,93} The addition of 1% of lithium to the rhenium/alumina catalyst suppresses the Lewis centres of the $\gamma\text{-Al}_2\text{O}_3$ support, as a result of which the selectivity in the hydrogenation of ethyl acetate increases to 78%–81% and diethyl ether is hardly formed. However, the hydrogenating activity of the catalyst and its stability diminish simultaneously (Table 2).

The introduction of between 5% and 7% of the lanthanide oxide is accompanied by an appreciable decrease in the hydrogenating activity of the rhenium/alumina catalyst, while the yield of diethyl ether falls from 10.4% to 1.7% and 0.6% respectively. The selectivity in the formation of ethanol diminishes under these conditions. The maximum hydrogenating activity and selectivity was shown by the catalyst containing 2 mass % of Re, 7 mass % of a lanthanide oxide, and 91 mass % of $\gamma\text{-Al}_2\text{O}_3$; for an overall degree of conversion of 31.2%, the activity was 81.4% in the formation of ethanol, 0.6% in the formation of diethyl ether, and 16% in the formation of hydrocarbons. The formation of hydrocarbons is apparently unrelated to the acid centres of $\gamma\text{-Al}_2\text{O}_3$.

Table 2. The influence of lithium and lanthanide oxide additives on the properties of the 2% Re/ γ -Al₂O₃ catalysts in the hydrogenation of ethyl acetate ($T = 230^\circ\text{C}$, $P_{\text{H}_2} = 30\text{ atm}$, $v_{\text{mass}} = 0.72\text{ h}^{-1}$, $\text{H}_2:\text{EA} = 5$, $\tau = 4\text{ h}$).⁹¹

Additive	Concentration of additive		Yield of product (mass %)					Selectivity (mass %)	
	mass %	mequiv. g ⁻¹	C ₂ H ₅ OH	(C ₂ H ₅) ₂ O	C ₁ –C ₄	coke + losses	total	C ₂ H ₅ OH	C ₁ –C ₄
None ^a	—	—	34.6	6.0	8.7	0.4	49.7	69.8	17.5
	—	—	29.1	10.4	6.8	0.2	46.5	62.6	14.6
Li	0.5	0.72	23.1	1.6	4.7	0.3	29.7	77.8	15.6
	1.0	1.44	21.4	traces	4.5	0.4	26.3	81.4	17.1
	2.0	2.88	15.1	"	3.3	0.8	19.1	78.6	17.2
Lanthanide oxides ^b	5.0	0.69	24.2	1.7	5.4	0.8	32.5	75.7	16.6
	7.0	0.99	25.4	0.6	5.0	0.2	31.2	81.4	16.0
	14.0	1.95	15.9	traces	2.9	—	18.8	84.6	15.4

^a Re content in catalyst 5 mass %. ^b Composition (mass %): 28 La₂O₃, 49 CeO₂, 18 Nb₂O₅, 5 Pr₂O₃.

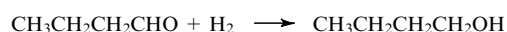
2. Hydrogenation of halogen-containing compounds

Rhenium catalysts have come to be used recently for the hydrogenation of halogen-containing compounds. A large number of various elements have been mentioned in the patent literature as catalysts for these processes: platinum group noble metals, Group VII and VIII elements, including rhenium, and certain Group II, IV, and V elements deposited on carbon. CHCl₃ and CH₂Cl₂ may be obtained from carbon tetrachloride in a flow system, the overall degree of conversion of CCl₄ amounting to 80%.^{94,95} A catalyst containing $\geq 15\%$ of Cr on TiO₂ and impregnated with $\geq 1\%$ of Pt, Pd, Rh, Ru and Os, Re, or Ir has been used for the hydrogenation of halogen-containing hydrocarbons.⁹⁶ In the presence of metallic catalysts (Re, Co, Ni, Ru, Pd, Os, Ir, or Pt on carbon), fluoro-hydrocarbons are hydrogenated.⁹⁷ In particular, CF₃CHClF and CF₃CH₂F have been obtained from CF₃CCl₂F with selectivities of 11% and 87% respectively for an overall degree of conversion of 52.9%. There are data concerning the use of rhenium for the synthesis of 4-alkyl-2-fluorocyclohexanols.⁹⁸

3. Hydrogenation of mixtures of oxygen-containing compounds

Higher alcohols are widely used in the manufacture of lubricating oils, high-quality detergents, plasticisers, etc. The direct hydrogenation of the C₁₀–C₁₆ fraction of synthetic aliphatic acids to the corresponding alcohols at $T = 325\text{--}375^\circ\text{C}$ and $P_{\text{H}_2} = 300\text{--}500\text{ atm}$ on copper–chromium and zinc–chromium catalysts is therefore of special interest. However, the rhenium sulfide/alumina catalyst containing 1.5% of rhenium has a higher hydrogenating activity than industrial oxide catalysts.⁹⁹ At 250°C , $P_{\text{H}_2} = 250\text{ atm}$, and $v = 0.13\text{ h}^{-1}$, the degree of conversion of the C₁₀–C₁₆ fraction of synthetic aliphatic acids into the corresponding higher alcohols amounted to $\sim 80\%$ even after the rhenium catalysts had been operating for 750 h. The hydrogenating capacity of oxide catalysts falls to this level already after they have been used for 60 h. Rhenium sulfide/alumina catalysts containing 5%–8% of rhenium are not only more stable but also exhibit a higher productivity than the oxide catalysts.

The results obtained using supported rhenium catalysts in the hydrogenation reactions of the products of the hydroformylation of propene,^{63,100} mainly with formation of an aldehyde, merit attention. Depending on the reaction conditions, isobutyraldehyde as well as (in amounts ranging from 10% to 20%) ethers, esters, acetals, aldols, and other oxygen-containing compounds are formed as side products. The hydrogenation of butyraldehyde is usually carried out at $T = 120\text{--}320^\circ\text{C}$ and $P_{\text{H}_2} = 250\text{--}300\text{ atm}$ in the presence of catalysts containing Co, W, Ni, Zr, Mo, Cu, and other elements in the metallic, oxide, or sulfide forms. Supported nickel and cobalt catalysts developed by various foreign companies contain at least 30%–60% of the metal. The hydrogenation of the hydroformylation products does not consist merely in the reduction of the carbonyl group to a hydroxy-group but, since the reaction



plays the main role, effective catalysts and optimum conditions are selected primarily for this reaction. When it was carried out on the hydrogen sulfide-treated 7% Re/ γ -Al₂O₃ catalyst at $T = 120^\circ\text{C}$, $P_{\text{H}_2} = 300\text{ atm}$, and $v = 4\text{ h}^{-1}$, the content of butyraldehyde in the reaction mixture gradually fell from 37% to 2.3%, while the productivity of the process was fairly high.¹⁰⁰ An increase in temperature to $140\text{--}160^\circ\text{C}$ made it possible to attain a high degree of hydrogenation (98.7%) and high space velocities, up to 8.0 h^{-1} . The highest productivity ($3219\text{ g litre}^{-1}\text{ h}^{-1}$) was achieved at 180°C and $v = 10.5\text{ h}^{-1}$. The residual content of butyraldehyde was 0.5% and there were virtually no oxygen-containing compounds in the catalyst apart from butyl alcohol. The catalyst retained its high hydrogenating activity throughout five months. At $T = 120\text{--}160^\circ\text{C}$, $P_{\text{H}_2} = 300\text{ atm}$, and $v = 4\text{--}5\text{ h}^{-1}$, the degree of conversion of butyraldehyde into butyl alcohol remained at the level of 99%–100%.

The hydrogen sulfide-treated bimetallic catalyst (5% Ni, 1% Re)/Al₂O₃ also possesses a high activity. The introduction of rhenium into the known nickel hydrogenation catalysts makes it possible to reduce its content by a factor of 6–10.

In terms of the degree of hydrogenation of the butyl esters of synthetic C₇–C₉ aliphatic acids, the (2% Re, 7% Ln)/ γ -Al₂O₃ catalyst is superior to the industrial copper–chromium catalyst GIPKh-105 (flow-type apparatus, $T = 210\text{--}218^\circ\text{C}$, $v = 0.40\text{--}0.45\text{ h}^{-1}$, $P_{\text{H}_2} = 300\text{ atm}$, rate of consumption of hydrogen 900 litre h^{-1}).⁹¹ On the rhenium catalyst, the esters are quantitatively converted into alcohols and the degree of conversion hardly changes throughout 450 h of continuous operation. This catalyst also exhibits a higher productivity ($306\text{--}427\text{ g litre}^{-1}\text{ h}^{-1}$) than the GIPKh-105 industrial hydrogenation catalyst ($210\text{--}259\text{ g litre}^{-1}\text{ h}^{-1}$).

4. Hydrogenation of other organic compounds

The hydrogenation of compounds of the type RCOO(CH₂)_nCOOH to RCOO(CH₂)_nCH₂OH (R = alkyl, $n = 8\text{--}16$)¹⁰¹ and of carboxylic acids to aromatic alcohols is carried out in an autoclave in the presence of ruthenium or Re/Al₂O₃ catalysts.¹⁰² On catalysts containing Ru, Rh, Pd, Pt, or Re deposited on cobalt, it is possible to hydrogenate carboxylic acids or esters.¹⁰³ Lactones are obtained by hydrogenating dicarboxylic acids (saturated and unsaturated) and anhydrides in the presence of a Ni catalyst, supported on zirconium oxide or carbon, to which Group VIII noble metals and rhenium have been added.^{104–106} Thus γ -butyrolactone has been obtained in 84.9% yield in the hydrogenation of succinic anhydride in the presence of tetrahydrofuran on the (10% Ni, 0.9% Pd, 0.6% Re)/ZrO₂ catalyst (specific surface $98\text{ m}^2\text{ g}^{-1}$) in an autoclave at $P_{\text{H}_2} = 50\text{ atm}$ and $T = 200^\circ\text{C}$ for $\tau = 3\text{ h}$.^{104–106}

Vinyloxirane is hydrogenated to 1,2-epoxybutane in the presence of a catalyst containing Pd and Re on BaSO₄, ZrO₂, or TiO₂.¹⁰⁷

Supported Group VIII metals and various rhenium compounds [Bu₄ReO₄, Re₂(CO)₁₀, Bu₄NReO₄, etc.] are used to obtain butane-1,4-diol by hydrogenating γ -butyrolactone, maleic or succinic anhydride, or the corresponding acids.^{108–111} For example, butane-1,4-diol has been obtained in 66.0% yield from the lactone in an autoclave in the presence of zeolites of the alkaline type or water on Pd/C and Bu₄NReO₄ at $T = 180^\circ\text{C}$ and $P_{\text{H}_2} = 50$ atm for $\tau = 16$ h.¹⁰⁸ The reaction is carried out in a solution of NEt₃ in dimethoxyethane. In the absence of NEt₃, the yield is 43.2%. An even higher yield (72.5%) is attained in the presence of Pd/C and Re₂(CO)₁₀ in ethanol at $T = 180^\circ\text{C}$ and $P_{\text{H}_2} = 100$ atm for $\tau = 16$ h.¹⁰⁹ Butane-1,4-diol is formed in 70.0% yield from succinic anhydride or succinic acid in the presence of Ru/C, Re₂(CO)₁₀, and a 3 Å zeolite or water in dimethoxyethane ($T = 160^\circ\text{C}$ and $P_{\text{H}_2} = 100$ atm, $\tau = 16$ h). The reaction does not take place in the absence of the zeolite.¹¹⁰ Butane-1,4-diol has been obtained in 88.8% yield from succinic or maleic anhydride under similar conditions on Pt/C and Bu₄NReO₄ in Me₃COH at 180°C .¹¹¹

Tetrahydrofuran has been obtained with a selectivity of 90%–92% by hydrogenating maleic anhydride ($T = 250^\circ\text{C}$, $P_{\text{H}_2} = 140$ atm) on the (Co, Pd, Re)/C catalyst.¹¹² On a catalyst containing rhenium, Group VIII metals, and acid components (inorganic or organic acids), deposited on a metal oxide or a zeolite, tetrahydrofuran may be obtained by hydrogenating not only maleic anhydride but also succinic anhydride or γ -butyrolactone.¹¹³

The synthesis of γ -butyrolactone from water and 2,3- or 2,5-dihydrofurans in the presence or absence of hydrogen on hydrogenation catalysts, including a rhenium catalyst, at an elevated temperature has been described in a patent.¹¹⁴ In the hydrogenation of 2,5-dihydrofuran in the presence of water on the 6% Re/TiO₂ catalyst ($T = 154^\circ\text{C}$, $P_{\text{H}_2} = 120$ atm), a mixture containing 85% of butane-1,4-diol, 6% of tetrahydrofuran, 3% of γ -butyrolactone, 1% of 4-hydroxybutanol, and 5% of butanol is formed in one stage with a 100% degree of conversion.¹¹⁵

The reduction of oleic acid to octadec-9-en-1-ol (*cis*- and *trans*-isomers) has been achieved with an appreciable yield in an organic solvent on a catalyst containing Re and Sn as well as Al, Si, or Ti compounds.^{116,117} The reaction was carried out in an autoclave at $T = 250^\circ\text{C}$ and $P_{\text{H}_2} = 56$ atm.

A new bimetallic rhenium–tin catalyst for the reduction of oleic acid to octadec-9-en-1-ol in a satisfactory yield under mild conditions has been proposed.¹¹⁸ The catalyst was obtained by depositing NH₄ReO₄ and SnCl₂ on Al₂O₃. Its activity and selectivity depended on the type of support, the nature of the initial compound, the molar ratio of the metals, and the conditions in the activation and the reaction itself.

The hydrogenation of neocarboxylic acids leads to the formation of neoalcohols. For example, the corresponding alcohol has been obtained¹¹⁹ from a 30% solution of pivalic acid in dioxane in a flow system on a catalyst containing 4.8% of Re and 0.5% of Pd on carbon at $T = 230^\circ\text{C}$, $P_{\text{H}_2} = 300$ atm, and $v = 0.15$ h^{–1}. The selectivity of the reaction reached 97% for a degree of conversion of 100%.

The influence of metallic promoting agents (Sn, Ge, Re) and various basic additives on the properties of Pt/SiO₂ catalysts has been investigated in relation to the alkylation of sterically hindered anilines in the vapour phase with formation of mono-*N*-alkylanilines. The reaction took place with a high selectivity and activity.¹²⁰ Doubly promoted Pt/SiO₂ catalysts accelerate the reaction of *ortho*-substituted anilines with primary and secondary alcohols. This distinguishes them from the copper–chromium catalysts, which make it possible to achieve *N*-alkylation by primary alcohols alone. The catalyst should be capable of activating three stages: the dehydrogenation of the alcohol, the condensation of the aniline with formation of carbonyl compounds,

and the hydrogenation of the resulting imine to the final product — *N*-alkylaniline. When the reaction is carried out in the vapour phase, the hydrogenation stage is the most difficult.

3,5,5-Trialkyl-3-aminomethylcyclohexylamine, used to produce urethane elastomers, may be obtained in 78.5% yield by the catalytic hydrogenation of 3,5,5-trialkyl-5-cyanocyclohexanone in methanol on the Co, Re, Mo catalyst in the liquid phase in the presence of ammonia at 120°C and 80 atm.¹²¹ Diethylenetriamine and piperazine are formed in proportions of 15:62 by weight as a result of the hydrogenation of ethylenediamine on a catalyst having the following composition (mass %): 6.2 Ni, 4.4 Re, and 1.8 B.¹²² The reaction is carried out in the liquid phase at ethylenediamine and hydrogen flow rates of 10.64 and 9.82 g mol h^{–1} kg^{–1} respectively and $P_{\text{H}_2} = 36$ atm. The reaction time at 138.2°C is 705 h and the degree of conversion of ethylenediamine is 6.60%.

The influence of rhenium on the properties of the Pd/C catalyst in the hydrogenation reactions of *o*-, *m*-, and *p*-nitrobenzoic acids in an aqueous medium at 70°C has been investigated.^{123–125} Such catalysts are resistant to poisoning by S-containing impurities in the reaction solutions.¹²³

The reactivity of nitrobenzoic acid diminishes in the sequence *para* > *ortho* > *meta* on the (Pd, Re)/Al₂O₃ catalyst.¹²⁴ The presence of rhenium as well as the texture of Al₂O₃ affect the state of palladium and the activity of bimetallic catalysts containing 4.0%–4.5% of Pd and 0.9%–1.0% of Re in the hydrogenation of *m*-nitrobenzoic acid, which reacts with much greater difficulty than *o*- and *p*-nitrobenzoic acids.¹²⁵ The texture of γ -Al₂O₃ was altered by means of a hydrothermal treatment. The hydrogenation was carried out in aqueous solutions with an acid concentration of 2.4×10^{-2} – 1.3×10^{-1} M at $T = 70$ – 90°C , $P_{\text{H}_2} = 5$ – 10 atm, and a *m*-nitrobenzoic acid: Pd molar ratio of 2000. The addition of rhenium to the palladium/alumina catalyst increases the yield of *m*-aminobenzoic acid after 30 min of the reaction from 70% to 91%, while the process selectivity rises from 88% to 93%. *m*-Azoxybenzoic acid is formed as a side product. The introduction of rhenium prevents the sintering of the palladium particles, which increases the degree of dispersion of the metal.¹²⁶ The hydrothermal treatment of Al₂O₃ alters the macrostructure of the support, makes it possible to optimise the Pt/Re ratio on the surface, and increases the content of the palladium–rhenium groups, which, like the (Pd, Re)-clusters,¹²⁷ exhibit an appreciable catalytic activity. Thus the higher activity and selectivity of the bimetallic systems compared with the catalyst to which no rhenium has been added is due to the increase in the degree of dispersion and in the thermal stability of palladium. As a result of the alteration of the macrostructure of the support during the hydrothermal treatment, the Pd/Re ratio on the catalyst surface decreases from 4:1 to 1:1.

5. Dehydrogenation of hydrocarbons

The dehydrogenation of *n*-dodecane^{128–130} and cyclohexane¹³¹ has been achieved on supported rhenium-containing catalysts. Comparison of the activities of the 0.5% Re/Al₂O₃ and 0.5% Pt/Al₂O₃ catalysts in the dehydrogenation of *n*-dodecane ($T = 480^\circ\text{C}$, $P_{\text{H}_2} = 2.5$ atm, $v_{\text{vol}} = 50$ h^{–1}, C₁₂H₂₆:H₂ = 8) showed that the yield of monoalkenes is 18.6% on the former catalyst and 12.1% on the latter. The selectivities in the formation of *n*-monoalkenes for degrees of conversion of 23.2% and 24.8% were 80% and 49% respectively. However, as a result of contact with air after the reduction of the rhenium catalyst at 900°C and its cooling in hydrogen to 20°C , the yield of monoalkenes fell from 9.8% to 4.4%. It was observed that preliminary treatment with hydrogen at 700 – 900°C influences the activity of the rhenium/alumina catalyst.^{128,129}

A similar effect, induced by the preliminary high-temperature treatment with hydrogen (900°C , 3 h), was observed also when the 0.25% Re/Al₂O₃ catalyst was employed. After treatment at 600°C , the selectivity in the formation of monoalkenes fell from 91% to 84% and their yield decreased from ~16% to ~15%. A

decrease in the concentration of rhenium to 0.1% and preliminary treatment with hydrogen at temperatures ranging from 700 to 900 °C increased the dehydrogenating activity and diminished the isomerising and cracking activities and there was an increase in selectivity. The selectivity in the formation of monoalkenes on catalysts containing 0.2% and 0.5% of rhenium also increased after the preliminary heat treatment of the support (Al_2O_3) in air at 900 °C.¹²⁷

The preliminary treatment with hydrogen of the (0.2% Re, 0.2% Pb)/ Al_2O_3 bimetallic catalyst at 700–900 °C instead of the usual temperature of 500 °C also had a positive effect.¹²⁸ The yields of n-monoalkenes formed from n-dodecane were respectively 5.4% and 12.4% after treatment with hydrogen at 500 and 700–900 °C, while the productivity of the catalyst was 2.5 and 8.3 g of n-monoalkenes per gram of the catalyst per hour. The selectivity remained at a high level (93%) in both cases.

Iron has a positive effect on the dehydrogenating activity of the rhenium/alumina catalyst.¹³⁰ The catalyst obtained by depositing NH_4ReO_4 on the $\text{Fe}(\text{NO}_3)_3/\text{Al}_2\text{O}_3$ system heat-treated beforehand in air showed the highest activity in the dehydrogenation of n-decane and n-dodecane ($T = 480$ °C, $P_{\text{H}_2} = 2\text{--}2.5$ atm, $v_{\text{vol}} = 35\text{--}80$ h⁻¹, molar ratio hydrocarbon : hydrogen = 8). The degree of conversion of n-dodecane may be increased by a factor of 2.5–3 if the catalyst is subjected to a preliminary treatment with hydrogen at 500–800 °C. The activity of the resulting catalyst is higher than that of the (Pt, Re)/ Al_2O_3 specimen prepared similarly and reduced with hydrogen at the normally employed temperature of 500 °C. The dependence of the activity of the catalyst on the temperature of its preliminary treatment with hydrogen in the range from 500 to 900 °C passes through a minimum in the region of 600–700 °C.

The promoting effect of iron on rhenium is manifested for low iron contents. At an iron concentration of 3 at. %, the degree of conversion of n-dodecane increases by a factor of 1.7–2.0 if the preliminary activation of the sample with hydrogen is carried out at 900 °C and not 500 °C. However, for an iron content of 5 at. % and a reduction temperature in excess of 700 °C, the promoting effect vanishes. The highest degree of conversion is attained if the rhenium content is 0.25 mass %.

Modification with iron makes it possible to reduce by 150–200 °C the temperature at which the same effectiveness in the conversion of n-alkanes is reached as on the monometallic Re/ Al_2O_3 specimen. It has been suggested¹²⁸ that, in order to overcome the strong interaction between the metal, activating the C–H bond in alkanes, and the support, it is necessary to reduce the metal to the zerovalent state. The formation of the Re^0 active centres on the Al_2O_3 surface is favoured by reduction at a temperature above 700 °C and, in the case of bimetallic catalysts, by the deposition of a compound of the active metal (by impregnation with NH_4ReO_4) on the modified $\text{Fe}/\text{Al}_2\text{O}_3$ supports subjected to preliminary thermal oxidation.

The state of rhenium on the 0.25% Re/ Al_2O_3 catalyst reduced with hydrogen at 500–900 °C has been studied by analysing the diffuse reflection IR spectra of adsorbed CO.¹³¹ Together with ionic forms of rhenium (+1 and +4 oxidation states), a highly disperse (possibly two-dimensional) metallic phase, the electron-donating capacity of which is reduced as a result of a strong metal–support interaction, is present on the surface. The CO adsorbed in a linear form on such a metal is removed by evacuation even at 20 °C. The amount of the highly disperse metallic phase on the support surface increases monotonically with increase in the activation temperature. The activity of the catalyst in the n-dodecane dehydrogenation reaction varies in parallel with the concentration of the electron-deficient highly disperse metallic phase. On this basis, it has been concluded that the highly disperse Re^0 formed during the high-temperature treatment in a stream of hydrogen is a precursor of the catalytically active centres for the alkane dehydrogenation reaction.

The dehydrogenation of cyclohexane to benzene ($T = 350$ °C, $v = 0.5$ h⁻¹) on a rhenium catalyst in which sibunit [a granulated

pyrocarbon, bulk density 0.6 g cm⁻³, S_{sp} (with respect to N_2) = 680 m² g⁻¹, S_{sp} (with respect to phenol) = 230 m² g⁻¹] was used as the support, proceeds at a higher rate than on the catalyst obtained by depositing rhenium on γ - and θ - Al_2O_3 .¹³² On the catalysts containing 2% of Re supported on sibunit, γ - Al_2O_3 and θ - Al_2O_3 , the overall degrees of conversion of cyclohexane into benzene were 32.4 mass %, 15.2 mass %, and 9.7 mass % respectively. The selectivity of the catalysts at 350 °C diminished in the sequence $\text{Re}/\theta\text{-Al}_2\text{O}_3 > \text{Re}/\text{sibunit} > \text{Re}/\gamma\text{-Al}_2\text{O}_3$. With increase in the reaction temperature to 400 °C, the selectivities for the formation of benzene on the same three specimens were respectively 37.9%, 42.4%, and 16.8%. Evidently, the Re/sibunit catalyst is more sensitive to an increase in temperature than the catalysts on aluminium oxide. The dehydrogenating activity of the 2% Re/sibunit catalyst prepared using HReO_4 is higher by a factor of 1.3 than in the case where NH_4ReO_4 is employed. This has been attributed to the greater ease of the reduction of the $\text{Re}(\text{VII})$ formed from perrhenic acid. In contrast to the rhenium oxide catalyst, there is no strong interaction between the metal and the support in the rhenium–carbon system. The dehydrogenating activity of the catalyst is influenced by the oxidative treatment of the support with nitric and oxalic acids. After treatment with 13% nitric acid for 1 h, the selectivity of the 2% Re/sibunit catalyst ($T = 400$ °C, $v = 0.5$ h⁻¹) increased from 35.2% to 61.7%. This may be explained by a decrease in the particle size of the reduced rhenium. Preliminary addition of oxalic acid to the support has a stronger effect on the sibunit catalyst than on the θ -aluminium oxide catalyst. The selectivity in the conversion of cyclohexane into benzene on the 2% Re/sibunit catalyst for an overall degree of 40% rose from 42.2% to 51.1%, i.e. by a factor of 1.35, whereas on the 2% Re/ θ - Al_2O_3 catalyst the increase was from 50.5% to 61.2%, i.e. by a factor of 1.2.

6. Reactions with participation of CO, CO₂, and H₂O

Supported rhenium-containing catalysts have been used also in the hydrogenation of CO_2 to methanol,¹³³ which can proceed *via* the intermediate formation of CO. The rate of hydrogenation of CO on the Re/ ZrO_2 catalyst is higher than on Re/ CeO_2 . In order to elucidate the reaction mechanism, a study was made of the conversion of formic acid and formaldehyde in the presence of hydrogen using ¹³C as a tracer. It was shown that the surface formaldehyde participates in the methanol formation stage.

In contrast to the Co/ SiO_2 and Re/ SiO_2 catalysts the combined (Co, Re)/ SiO_2 catalyst is active in the hydrogenation of CO to ethanol and hydrocarbons.¹³⁴ The introduction of strontium into the bimetallic system diminishes the yield of the hydrocarbons and increases the selectivity in the formation of the alcohol from 10% to 25%. It has been demonstrated by physical methods that strontium controls the reduction of Co^{2+} to Co^0 and that the basic active centres of the catalyst contain highly disperse metallic cobalt. Rhenium promotes the reduction of Co^{2+} to Co^0 . The (Co, Re, Sr)/ SiO_2 catalyst was prepared by employing cobalt acetate. If $\text{Co}(\text{NO}_3)_2$ or CoCl_2 is used to prepare the sample, then rhenium has no modifying effect on the hydrogenation of CO to methanol.¹³⁵ The use of CoCl_2 has a particularly negative effect on the formation of methanol. Rhenium promotes the reduction of Co^{2+} to the metal, facilitating the hydrogen spill over.

The addition of promoting agents (Re, Ru, Ir, Rh, Pt or Os) to the Co/ SiO_2 catalyst obtained from $\text{Co}_2(\text{CO})_8$ did not alter its activity in the CO hydrogenation reaction.¹³⁶

An attempt has been made to use rhenium catalysts for the partial oxidation of methane by the oxygen in synthesis gas ($T = 1000$ °C, $v = 100\,000$ h⁻¹), but they were rapidly deactivated as a result of the volatilisation of the metal in the form of oxides.¹³⁷ Together with other metals (Ru, Rh, Ir), rhenium has been used as the catalyst of the reaction of methane with CO_2 .¹³⁸ At 777 °C, the degree of conversion of methane on the Re/ γ - Al_2O_3 system reached ~85%. However, at lower temperatures the activity of the rhenium catalyst diminished sharply. Thus at 500 °C the degree of conversion of methane was < 5%. The

authors explained this effect by the catalytic oxidation of the metal surface.

The characteristic features of the reduction of CO₂ under the conditions of the thermoprogrammed reaction have been investigated on the 3% Re/Al₂O₃ catalyst.¹³⁹ The rate of reaction increases sharply after the reduction of the catalyst and also as a result of the interaction of CO₂ with carbon fragments on addition of 1%–2% of hydrogen. It has been suggested that formate is formed as an intermediate in this process and that hydrogen has an initiating effect. At high hydrogen concentrations in the CO₂ + H₂ mixture, the conversion of carbon dioxide leads to the formation of CO and CH₄. The addition of formic acid to the reaction mixture increases the rate of formation of methane. It may be that the conversion of CO₂ proceeds *via* the formation of intermediate formate fragments, bypassing the CO₂ dissociation and CO hydrogenation stages. The reduction of CO₂ includes a stage in which surface carbonates are produced.

The acceleration of the Boudouard reaction ($\text{CO}_2 + \text{C} \rightleftharpoons 2\text{CO}$) has been observed on the 3% Re/Al₂O₃ catalyst in the presence of small amounts of hydrogen,¹⁴⁰ where it was less pronounced than on the 8% Fe/Al₂O₃ system. In the presence of the previously coke-saturated (in the isobutane conversion reaction) 3% Re/Al₂O₃ catalyst, the conversion of CO₂ under the conditions of thermoprogrammed heating occurred only at temperatures above 640 °C and the rate of formation of CO was low. The addition of 1%–3% of hydrogen to the stream of CO₂ induced a sharp acceleration of the reaction. The rate of conversion of CO₂ increased by a factor of 25, while the coke oxidation temperature fell by 200 °C. The activation energy for the formation of CO also decreased. The maximum rate of formation of CO was attained at 800 °C, while a further increase in temperature led to a decrease in rate. Under the conditions of thermoprogrammed cooling, the rate of conversion of CO₂ at temperatures below 800 °C was significantly higher than at the analogous temperatures under heating conditions. The authors explained this effect by a heterogeneous-chain mechanism of the reduction of CO₂ by rhenium or iron during the occurrence of the Boudouard reaction. The reaction



takes place at similar hydrogen and CO₂ concentrations.

It has been suggested that, when a heterogeneous-chain mechanism operates, ReHCOO is formed as an intermediate complex. Thus the higher reactivity of CO₂ compared with CO in hydrogenation reactions can be accounted for by the formation of intermediate active species in which the dissociation of the C–O bond is facilitated.¹³⁹

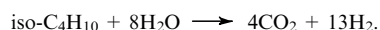
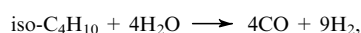
Together with other additives, rhenium improves the properties of Fischer–Tropsch catalysts containing 12%–20% of cobalt.¹⁴¹ Vada *et al.*¹⁴² added 1.0 mass % of Pt or Re to the catalyst containing 8.7% of Co and 91.3% of Al₂O₃ and carried out the hydrogenation of CO on it ($T = 200$ °C, $P_{\text{H}_2} = 5$ atm, and $\text{H}_2/\text{CO} = 2$ or $T = 220$ °C, $P_{\text{H}_2} = 1$ atm, and $\text{H}_2/\text{CO} = 7.3$). The introduction of Pt or Re appreciably increased the rate of reaction referred to unit mass of cobalt. The selectivity did not change under these conditions. The increase in the rate of reaction was induced by the fact that Pt and Re facilitate the reduction of Co atoms and increase their surface concentration.

The promoting effect of rhenium on the cobalt catalyst for the Fischer–Tropsch synthesis has been investigated by diffuse reflection IR spectroscopic methods.¹⁴³ Here it was also shown that rhenium promotes the reduction of cobalt. Rhenium is initially located in the surface layer and most probably forms the tricarbonyl.

Supported rhenium-containing catalysts are also used for the conversion of hydrocarbons by reaction with steam.

In terms of activity and selectivity in the conversion reactions of hydrocarbons with water vapour at temperatures above 600 °C, the 7% Re/ γ -Al₂O₃ catalyst is not inferior to the

industrial nickel-containing catalyst GIAP-3.¹⁴⁴ The following reactions take place under these conditions:



Later the same investigators studied the activity of the Re/ γ -Al₂O₃ catalyst containing 3% and 7.5% of rhenium in the conversion of isobutane by reaction with water vapour in the presence of the CS₂ catalytic poison.¹⁴⁵ The process was carried out in apparatus of the flow and flow-circulation types at atmospheric pressure. On the 3% Re/ γ -Al₂O₃ catalyst at $T = 700$ °C and $v_{\text{vol}} = 1500$ h^{–1} and for a steam/isobutane ratio of 12, the addition of CS₂ in amounts corresponding to sulfur contents of 4 and 30 mg per m³ of gas reduced the overall yield of the conversion product (H₂, CO, CO₂) from 95.7 vol.% (in the absence of sulfur) to 89.3 vol.% and 89.4 vol.% respectively. The introduction of 300 mg m^{–3} of sulfur not only reduced the content of H₂, CO, and CO₂ in the effluent gas but also led to the appearance of hydrocarbons with a lower molecular mass than that of the initial substance, including ethene and propene. The increase in the rhenium content from 3% to 7.5% did not improve the resistance of the catalyst to poisoning by sulfur.

The (Re, Co)/Al₂O₃ and (Re, Ni)/Al₂O₃ bimetallic catalysts have also been used for the conversion of isobutane.¹⁴⁶ The introduction of cobalt (3%) into the 1% Re/ γ -Al₂O₃ catalyst lowered and the introduction of nickel (3%) increased its activity and selectivity in the formation of H₂, CO, CO₂, and CH₄. In contrast to the 3% Ni/ γ -Al₂O₃ catalyst, the bimetallic catalysts containing 1% of Re and 3% of Ni on γ -Al₂O₃ ensured the full conversion of isobutane even at 500 °C. The gas formed had a nearly equilibrium composition, whereas in the presence of the industrial catalyst GIAP-3 as well as the nickel/alumina catalyst deviations from equilibrium towards the predominance of methane were observed. With increase in temperature, the compositions of the gas obtained on all three catalysts approached one another.

7. Oxidative dehydrogenation and acetoxylation reactions

The oxidative dehydrogenation of cyclohexane and ethylbenzene on rhenium-containing oxide systems has been investigated.¹⁴⁷ In the absence of air and water, the 2% Re₂O₇/ γ -Al₂O₃ and 2% Re₂O₇/ θ -Al₂O₃ catalysts exhibited a low activity: the degree of conversion of cyclohexane at 420 °C was only 0.5% and that of ethylbenzene was 4% at 500 °C. In the presence of oxygen, the effectiveness of the dehydrogenation of cyclohexane was higher by a factor of 10–30. In the oxidative dehydrogenation of ethylbenzene without the addition of water vapour, the activity of the catalysts increased by an order of magnitude. In the course of half an hour, the degree of conversion of ethylbenzene into styrene reached 52% for a selectivity of 90% and then remained constant.

The modification of binary magnesium-containing oxide systems by the addition of Re₂O₇ increases the activity of the catalyst. The optimum catalyst for the oxidative dehydrogenation of ethylbenzene proved to be the system incorporating V₂O₅ (11.2%), Re₂O₇ (1.2%), and MgO (87.6%). The degree of conversion of ethylbenzene into styrene on this sample was higher than on the binary system and some suppression of the extensive oxidation processes was achieved. In the presence of an excess of atmospheric oxygen (molar ratio styrene:oxygen = 1:1.5–2), the yield of styrene at 500 °C was 70% for a selectivity of 87%–88%. An increase in temperature to 540 °C led to an appreciable rise in the degree of extensive oxidation. The addition of Re₂O₇ to the V–Mg binary oxide system apparently intensifies the dehydrogenating function of the catalyst.

The gas-phase oxidative acetoxylation of propene to allyl acetate has been achieved on supported Pd and Pd, Re catalysts.^{148, 149} The reaction was carried out at atmospheric pressure, 180 °C, and a rate of supply of the acid of 2 h^{–1} using the ratios C₃H₆:AcOH:O₂ = 2:1:0.5. The high-silica zeolite TsVM

($\text{SiO}_2:\text{Al}_2\text{O}_3 = 29.6$).¹⁴⁸ $\gamma\text{-Al}_2\text{O}_3$, and $\text{Al}_2\text{O}_3\cdot\text{SiO}_2$ were used as supports.¹⁴⁹ The activities of the 1.5% Pd/TsVM and (1.5% Pd, 1.5% Re)/TsVM catalysts were 5.89×10^{-3} and $9.06 \times 10^{-3} \text{ mol g}^{-1} \text{ h}^{-1}$ for selectivities of 81% and 83% respectively. The introduction of rhenium increased the activity by a factor of 1.5. The activity of the (Pd, Re)/zeolite catalyst was influenced by the concentration of rhenium, the order in which it was introduced, and the composition of the initial perhenate [NH_4ReO_4 , KReO_4 , $\text{Ba}(\text{ReO}_4)_2$, or HReO_4]. The bimetallic catalyst with the ratio Pd:Re = 1, prepared from ammonium perhenate, had the highest activity. The introduction of 0.5%–0.7% of Re into the 0.7% Pd/ $\text{Al}_2\text{O}_3\cdot\text{SiO}_2$ catalyst increased its activity without altering the selectivity ($\sim 80\%$). A further increase in the rhenium concentration to 1%–1.5% diminished the activity and selectivity of the catalyst. The higher activity of the bimetallic catalysts, obtained as a result of the introduction of rhenium after the reduction of palladium, compared with the monometallic palladium sample, may be due to the interaction of rhenium oxides with the support surface, which depends on the degree of dehydroxylation of the surface.¹⁵⁰

V. Mixed rhenium-containing catalysts

1. Reactions of hydrocarbons

The principal reactions of the reforming process are dehydrogenation, aromatisation, isomerisation, and hydrogenolysis. The properties of many rhenium-containing catalysts have been investigated in relation to these reactions.

The (Pt, Re)/ Al_2O_3 bimetallic catalysts, prepared by precipitation, were investigated in the propane dehydrogenation reaction.¹⁵¹ The (Pt, Re)/ Al_2O_3 sample proved to be less active and selective in relation to the formation of propene than (Pt, Sn)/ Al_2O_3 . The hydrogenolysis of n-butane on Pt/ Al_2O_3 catalysts involves the formation of adsorbed carbon particles, which influence the proportions of the products obtained.¹⁵² The centres responsible for the dissociation of the central C–C bond are poisoned preferentially. Such species are not adsorbed on the (Pt, Re)/ Al_2O_3 catalysts.

The (Pt, Re)/ Al_2O_3 catalyst proved to be less active under n-heptane reforming conditions than (Pt, Ir)/ Al_2O_3 owing to cracking, which intensifies if the reduction takes place in the presence of water.¹⁵³ In order to facilitate the aromatisation of C_6 and C_7 alkanes on the Pt, Re reforming catalyst and to increase the selectivity of this reaction, it has been recommended that platinum deposited on the L-zeolite be introduced into the catalyst.¹⁵⁴ The catalyst is obtained by the mechanical mixing of the standard reforming catalyst with Pt/L-zeolite.

The aromatisation of n-hexane under reforming conditions using rhenium- and platinum-containing catalysts in proportions of 1:1 and 2:1 has been investigated.¹⁵⁵ Hydrogen has only a weak influence on the dehydrocyclisation of hexane to benzene. With increase in pressure, the selectivity of the reaction diminishes, which intensifies the isomerisation of n-hexane. However, this has little effect on the activity of the catalyst. The deposition of coke on both catalysts diminishes with increase in pressure and the $\text{H}_2:\text{C}_6\text{H}_{14}$ molar ratio. On the catalyst with Re:Pt = 2:1, the extent of the deposition of coke was much smaller than on the catalyst with the 1:1 composition.

The activity of (Pt, Re)/ Al_2O_3 catalysts depends on the method used for their preparation (joint or successive impregnation) and on the reduction procedure (direct reduction after the deposition of the metal, heat treatment with subsequent reduction).¹⁵⁶ Heat treatment appreciably diminishes the metal–metal interaction, which is indicated by the results obtained in the study of the hydrogenolysis of cyclopentane. Sulfiding of the catalysts increases their activity in the n-heptane dehydrocyclisation reaction.

The dehydrocyclising capacity of the Pt/ Al_2O_3 and (Pt, Re)/ Al_2O_3 metal cluster catalysts has been investigated in relation to the conversion of n-heptane into toluene under conditions close to

those in reforming ($T = 500^\circ\text{C}$, $P_{\text{H}_2} = 12 \text{ atm}$).¹⁵⁷ Platinum–rhenium metal cluster catalysts exhibited a higher selectivity and stability than the samples obtained by impregnating aluminium oxide with an aqueous solution of the initial platinum and rhenium compounds. The carbonyl complexes were decarbonised with formation of carbon particles and CO_2 . The increased activity of the catalyst was associated with the formation on their surface of highly disperse carbon particles. The metal cluster Pt, Re catalysts were more stable than the analogous Pt catalysts and the standard (Pt, Re)/ Al_2O_3 reforming catalysts.

The addition of boron and tin to the Pt/ Al_2O_3 and (Pt, Re)/ Al_2O_3 catalysts influences the activity of the latter in the dehydrogenation of cyclohexane, the dehydroisomerisation of methylcyclopentane, and the hydrocracking of 2,3-dimethylbutane.¹⁵⁸

In order to eliminate alkenes from the reforming products, they are subjected to selective hydrogenation on a catalyst containing (mass %) 0.05–0.15 Pt, 0.001–0.05 Cd and/or 0.01–0.1 Re, and 0.01–0.1 Sb on $\gamma\text{-Al}_2\text{O}_3$.¹⁵⁹

Group VIII metals (Pt, Rh, and Ru) supported on $\text{Al}_2\text{O}_3\cdot\text{TiO}_2$ exhibit a high activity in the benzene, naphthalene, and biphenyl hydrogenation reactions at 300°C and $P_{\text{H}_2} = 65 \text{ atm}$.^{160, 161} The activity of these catalysts increases after the addition of a second metal (Ir, Re, Pd). The bimetallic catalyst exhibits an enhanced resistance to poisoning by sulfur, the source of which may be thiophene. The activity of bimetallic catalysts on the TiO_2 support increases as a result of dispersion in combination with the addition of high-valence cations, for example W^{6+} . The bimetallic catalysts have a hydrogenating activity an order of magnitude higher than the usual hydrogenation catalyst (Co, Mo)/ Al_2O_3 .

In the study of the selective hydrogenation of *o*-xylene on metals deposited on SiO_2 (Pd, Ir, Pt, Ru, Os, Ni) in combination with rhenium, a correlation was observed between the electronic conductivity of the metal and the selectivity of the catalyst in relation to the formation of the *cis*-product.¹⁶² The influence of heat treatment on the reactivity and selectivity of the bimetallic catalysts was noted.

2. The influence of chlorine, sulfur, and coke on the properties of the bimetallic catalysts

Chlorine and sulfur are known to be active modifying agents for supported Pt, Re catalysts for the conversion of hydrocarbons and the reforming of petrol fractions. The promotion of the (0.3% Pt, 0.3% Re)/ Al_2O_3 catalyst was investigated by temperature-programmed reduction methods (TPR), analysis of the fine structure of X-ray absorption spectra (EXAFS), X-ray absorption near-edge structure spectroscopy (XANES), the oxygen adsorption method, and IR spectroscopy of adsorbed CO.^{163, 164} It was found that the presence of chlorine promotes the formation of a Re^{4+} -containing phase in the course of the preliminary treatment of the catalyst at 450°C . This phase interacts strongly with the surface layer of Al_2O_3 , which prevents the formation of the Pt–Re alloy on reduction of the species, the specific role of chlorine in the interaction of the metal with the Al_2O_3 support has also been confirmed by other results.¹⁶⁵ In the absence of chlorine, such interaction may be fairly intense, but, when a solution of chloroplatinic acid is deposited, the surface hydroxy-groups are replaced by chloride ions and a stable metal-supported complex is formed.

It has been confirmed by the TPR and XANES methods that the chloride present on the Al_2O_3 surface plays the main role in the formation of an alloy between Pt and Re during the reduction process.¹⁶⁶ The rhenium on the Al_2O_3 surface (tentatively in the form of an oxide) is mobile. In the presence of sulfur, the activity of the Pt, Re catalyst in the hydrogenation–dehydrogenation reactions falls. The irreversibly adsorbed sulfur binds the entire rhenium in the form of Re_2S and $\sim 10\%$ of platinum in the form of Pt_2S . With increase in the fraction of rhenium, the undesirable sensitivity of the catalyst to sulfur increases.

Rhenium, particularly in the form of the alloy with platinum, is a very active hydrogenolysis catalyst.¹⁶⁷ Sulfidation may decrease the activity of this catalyst to zero, since sulfur covers the rhenium surface. The sulfur compounds of rhenium themselves are incapable of accelerating the hydrogenolysis of hydrocarbons and act merely as diluents of the platinum. The addition of sulfur increases the resistance of the platinum catalyst to deactivation, but the adsorbed sulfur is rapidly lost. The introduction of rhenium influences the selectivity of the catalytic system, because it induces modification of the active centres of platinum and promotes the retention of sulfur on the surface. The probability of effecting reactions in which large ensembles of platinum atoms participate (hydrogenolysis, dehydrocyclisation, isomerisation, and cyclisation) diminishes as the latter are reduced. However, the alloying of platinum with rhenium does not influence the initial rate of hydrogenolysis.

Small ensembles of platinum atoms, formed on dilution of platinum by sulfur compounds of rhenium, are resistant to poisoning by carbon deposits, since there is no space on the catalyst surface for a large polymeric carbon structure to grow. Such a catalyst is very stable until the adjacent Pt, Re, S moieties lose their sulfur.

The reactions of cyclohexane and n-hexane have been investigated at 297–467 °C on platinum catalysts in which the support was a rhenium foil with an overall surface area of 0.5–1.0 cm².¹⁶⁸ The surface was sulfided before the reaction and under the reaction conditions by adding thiophene to the hydrocarbon. The ReS formed is catalytically inactive and only the dehydrogenation and hydrogenation reactions occur in the system, but the catalyst becomes more resistant to deactivation.

The problems of the deactivation of the (Pt, Re)/Al₂O₃ reforming catalysts by coke and sulfur have attracted the attention of investigators, since stability is one of the most important requirements which must be met by industrial catalysts. The content of residual coke, deposited on the (Pt, Re)/Al₂O₃ catalyst during the reforming of petroleum in the temperature range 350–650 °C has been determined.¹⁶⁹ The residual coke was investigated by the temperature-programmed oxidation method, X-ray diffraction, IR spectroscopy, chromatograph-linked mass spectroscopy, NMR, electronic spectroscopy, EPR, and chemical analysis. After the coke had been burnt away at 400 °C, the residual deposits were characterised by a minimal H : C ratio and a maximal concentration of C=O groups. At low temperatures, the most hydrogenated and amorphous carbon particles are the first to burn. At a high temperature, the combustion is nonselective and all the deposits burn simultaneously. In the course of combustion, coke is partly oxidised and intermediate species containing the C=O and C–OH groups are formed.

The effects of coating with rhenium and sulfidation of the surface of the platinum reforming catalyst have been investigated in relation to the reactions of n-hexane and cyclohexane on platinum without a support under the conditions of ultrahigh vacuum.¹⁷⁰ In the absence of sulfur, the degree of cyclisation of n-hexane diminished with increase in the rhenium content. The introduction of sulfur decreased the hydrogenolysis and increased the cyclising activity. The maximum cyclising activity of the sulfided catalyst was observed when the surface was coated by a monolayer of rhenium. Similar results have also been obtained under the conditions of the reactions of cyclohexane on the surface of the bimetallic Pt, Re catalyst: after sulfidation, the contribution of hydrogenolysis diminished, while that of dehydrogenation increased. The maximum rate of hydrogenation was attained on the sulfided catalyst with the platinum coated by 0.5 of a rhenium monolayer.

A multiflow reactor, which makes it possible to determine the composition of the gas phase along the catalyst bed and the coke deposition profile, has been used to investigate the deactivation of the Pt/Al₂O₃ and (Pt, Re)/Al₂O₃ catalysts in the reforming of n-heptane.¹⁷¹ At a low pressure (1.05 atm), the coke content on the Pt catalyst increased, while at a high pressure (12.25 atm) it

fell. The maximum deposition of coke was observed at an intermediate pressure. Correlations were noted between the coating of the surface by coke and the formation of C₅ naphthenes and also between the changes as a function of time in the supply of the starting material, pressure, and the location of the section on which coke is deposited. The C₅ naphthenes are apparently the main source for the formation of coke deactivating the catalyst. The addition of rhenium influences the deposition of coke and the formation of C₅ naphthenes. The form of the temperature-programmed oxidation (TPO) spectrum depends on the pressure at which the coke is deposited. An increase in the overall pressure leads to identical changes in the TPO spectra on the Pt and Pt, Re catalysts. The results confirm that rhenium increases the surface concentration of hydrogen on the Pt, Re catalyst and hence diminishes its dehydrocyclising and increases its hydrocyclising capacity. A smaller amount of dialkenes with a five-membered ring is formed on the Pt, Re catalyst than on Pt/Al₂O₃ and the (Pt, Re)/Al₂O₃ catalysts are therefore less coke-saturated and are more stable.

The sensitivity of the Pt/Al₂O₃, (Pt, Re)/Al₂O₃, (Pt, Ir)Al₂O₃, (Pt, Ge)Al₂O₃, and (Pt, Sn)/Al₂O₃ reforming catalysts to poisoning by sulfur has been investigated in relation to the model cyclohexane dehydrogenation reaction.¹⁷² The permissible sulfur content in the starting material when the reaction was carried out on the above catalyst diminished in the sequence (Pt, Ge) > (Pt, Ir) ≈ Pt ≈ (Pt, Sn) > (Pt, Re). The resistance of the catalyst to sulfur decreased in the sequence (Pt, Ge) > (Pt, Ir) ≈ (Pt, Re) > (Pt, Sn). The (Pt, Ge)Al₂O₃ bimetallic catalyst thus proved to be the most resistant to sulfur and also permitted the highest sulfur content in the starting material.

The influence of the rhenium content on the activity, stability, and the resistance to poisoning by sulfur of the (Pt, Re)/Al₂O₃ reforming catalyst has also been investigated.¹⁷³ An increase in the rhenium content in the catalysts subjected to preliminary sulfidation suppressed the dehydrocyclisation of n-heptane to toluene but facilitated the conversion of methylcyclopentane into benzene without appreciable ring opening. Another result of the increase in the rhenium content was a gradual diminution of the deactivation of the catalyst and of the accumulation of coke on the surface. However, in the presence of a high rhenium content, the catalyst became more sensitive to poisoning by sulfur. The dehydrocyclisation of n-hexane was suppressed to a greater extent compared with other hydrocarbons. The different behaviour of the catalysts with high and low rhenium contents has been explained by the synergistic activity of rhenium and sulfur.

A comparative study of the noncoke-saturated and partially coke-saturated sulfided (Pt, Re)/Al₂O₃ reforming catalysts in the isomerisation and dehydrocyclisation of hexane, heptane, and methylcyclopentane showed that sulfur promotes the removal of coke from the metal surface.¹⁷⁴ The amount of irreversibly chemisorbed sulfur increases in the series of catalysts Pt/Al₂O₃ < (Pt, Re)/Al₂O₃ < Re/Al₂O₃. The ensembles of platinum atoms in the (Pt, Re, S)/Al₂O₃ bimetallic catalysts are larger and have a less distorted structure than in (Pt, S)/Al₂O₃.

3. Hydrogenation of hydrocarbon mixtures

In the 1970s, increased attention was devoted to the questions of the selection of effective catalysts for the hydrogenation of aromatic hydrocarbons in kerosene fractions. The 'Unisar' process was effected on platinum catalysts.¹⁷⁵ The modification of platinum catalysts with rhenium makes it possible to achieve the selective hydrogenation of the most undesirable hydrocarbons present in the middle petroleum fractions, namely bicyclic aromatic hydrocarbons and polysubstituted alkylbenzenes. An advantage of the bimetallic catalyst over the platinum catalyst is also its inertness to hydrocarbons of other classes — alkanes and isoalkanes, particularly in relation to their hydrocracking.⁴

The effective hydrogen sulfide-treated (1% Pd, 1% Re)/Al₂O₃ catalyst has been developed for the two-stage hydrogenation of middle petroleum fractions.¹⁷⁶ The optimum conditions

($T = 250\text{ }^{\circ}\text{C}$, $P_{\text{H}_2} = 20\text{ atm}$, $v = 1.0\text{--}1.5\text{ h}^{-1}$, circulation of 800–1000 litres of hydrogen per litre of starting material), under which the degree of conversion of aromatic hydrocarbons is $\sim 90\%$ and the yield of the target product is $\sim 98\%$, were found. A similar degree of conversion of aromatic hydrocarbons on the platinum/alumina catalyst was not attained until $300\text{ }^{\circ}\text{C}$ and a hydrogen pressure of 40 atm.

4. Reforming

The greatest advance in the field of petroleum processing has been the achievement in 1968 of the rheniforming process using bimetallic Pt, Re catalysts on an oxide support, which are more active and stable than the platinum/alumina catalyst.¹⁹ The improvement of these catalytic systems is being continued at the present time. The application of a new method for the modification of aluminium hydroxide made it possible to deposit on the latter ultrasmall amounts of platinum (0.15%) and rhenium (0.3%).¹⁷⁷ This catalyst, with the ratio Re:Pt = 2:1 shows a satisfactory activity as well as a high selectivity, stability, and mechanical strength and is readily regenerated. Among all the known reforming catalysts, it contains the smallest amount of platinum.

The productivity of the reforming catalyst can be increased by adding a zeolite of the pentasil type.¹⁷⁸ The chlorinated (Pt, Re)/ Al_2O_3 catalyst mixed with HZSM-5 exhibits an increased activity and stability in the formation of aromatic compounds from *n*-heptane. A possible reaction mechanism involves the formation of intermediate carbonium and carbene ions.

The pressure dependence of the yield of hydrogen and of the octane number (o.n.) of the reformat has been investigated on the (Pt, Re)/ Al_2O_3 catalysts.¹⁷⁹ The yield of the processing products and hydrogen increased as the pressure increased from 12 to 25 atm. The octane numbers varied linearly with the concentration of the aromatic hydrocarbons. At a pressure of 12 atm, the hydrodealkylation of C_8 and higher aromatic hydrocarbons proceeded with formation of xylenes and higher aromatic compounds.

The conditions for the regeneration of the coke-saturated (Pt, Re)/ Al_2O_3 reforming catalyst by ozone–air and $\text{O}_2\text{--NO}_2$ mixtures were found.^{180,181} Coke was removed by ozone at low temperatures (since ozone decomposes at high temperatures) and then by oxygen. However, ozone removes coke nonselectively, whereas oxygen removes it selectively. In the first place, it was possible to eliminate coke deposited on metallic centres of the catalyst.

A special procedure for the ‘minimisation of the sulfided support’ is used in the regeneration of reforming catalysts containing chloride and sulfate ions.¹⁸² In the presence of an amount of sulfate to which a sulfur concentration in excess of 0.08%–0.1% corresponds, the rate of deactivation as a consequence of the formation of coke increases. The intensification of the coke formation process is a result, firstly, of the blocking of the Lewis acid centres of aluminium oxide by sulfate ions and, secondly, of the excessive sulfidation of the metal particles by the hydrogen sulfide formed on reduction of the sulfided catalyst by hydrogen.

The Pt, Re bimetallic reforming catalyst of type IIP-IPCL (India), exhibited a high activity, selectivity, stability, and capacity for regeneration in tests on a pilot apparatus designed to generate motor fuel.¹⁸³ The first cycle of tests was interrupted after 13 experiments owing to the deposition of sulfur. In the second cycle, the catalytic activity was lower while the deactivation was very rapid owing to the sulfurisation of the catalyst in the course of the first regeneration. A special technology, involving the removal of sulfates by hydrogen at $490\text{--}510\text{ }^{\circ}\text{C}$ and a pressure of 5–7 atm in the presence of ethylene chloride, was therefore used for the second regeneration. After such regeneration, the catalyst recovered its initial activity and stability and retained them in the course of three cycles.

The influence of temperature and of oxygen content, steam, and hydrocarbons in the gas phase on the initial characteristics of the CB-6 and CB-8 reforming catalysts (China) with a low platinum and rhenium content has been investigated.^{184,185} A deficiency of oxygen in the liquid phase leads to the formation of coke in the partial drying and regeneration stages, which induces a decrease in catalytic activity or complete deactivation.

The study of the influence of process parameters on the hydrocracking and isomerisation of petrol fractions on (Pt, Re)/ Al_2O_3 catalysts (R-62 and R-16G)¹⁸⁶ in a flow system has been investigated at $T = 505\text{--}525\text{ }^{\circ}\text{C}$ and $v = 2.7\text{--}5.4\text{ h}^{-1}$. It was established that the yield of liquid products increases with increase in the space velocity. The R-16G catalyst exhibits a high activity in the formation of gaseous products, *i.e.* in the hydrocracking reaction. This is associated with the influence of the acid centres of aluminium oxide and the use in this case of a higher pressure (27 atm) than in the process on the R-62 catalyst (12 atm). On the other hand, the R-62 catalyst exhibits a higher activity than R-16G in the dehydrogenation of naphthenes to aromatic hydrocarbons. The reforming of mixed hydrorefined petroleum has been achieved on an industrial pilot apparatus on the same catalysts [$T = 490\text{--}525\text{ }^{\circ}\text{C}$, $v = 2.7\text{--}5.4\text{ h}^{-1}$, hydrogen:hydrocarbon starting material = (5–7):1, $P_{\text{H}_2} = 27\text{ atm}$ on the R-16G catalyst and 12 atm on the R-62 catalyst].^{187,188} An increase in temperature promotes an increase in the octane number of the processing product and the formation of high-quality petrol. The greater activity of the R-62 catalyst in the dehydrogenation of naphthenes to aromatic hydrocarbons noted above can be explained by the fact that the occurrence of this structure-insensitive reaction is promoted by a lower pressure. The catalyst was not deactivated by coke, since its residence in the reactor was brief ($\sim 23\text{ h}$). The dehydroisomerisation and dehydrocyclisation of alkenes to aromatic hydrocarbons occurred to a lesser extent. An increase in temperature and a decrease in space velocity from 0.8 to 0.37 h^{-1} intensified the deposition of coke. The repeated regeneration of the catalyst led to an increase in the pore volume and in the overall porosity.¹⁸⁹

The influence of the chlorine content on the properties of fresh, coke-saturated, and regenerated samples of the (0.3% Pt, 0.3% Re)/ Al_2O_3 reforming catalyst has been investigated.¹⁹⁰ The equilibrium chlorine content was attained by treating the catalyst with the vapour of the $\text{H}_2\text{O--HCl}$ mixture in a stream of air or hydrogen and was determined by the $\text{H}_2\text{O}:\text{HCl}$ molar ratio and also by the temperature of the treatment. The equilibrium chlorine content in the fresh sample was independent of the nature of the chlorine compound introduced. The amount of chlorine retained by the support, calculated per unit surface area, was the same on the fresh and regenerated specimens. The presence of coke did not alter the amount of chlorine on the surface.

(Pt, Re)/ Al_2O_3 catalysts have been tested on a pilot apparatus under the conditions of hydrocracking and isomerisation of *n*-heptane and also under the conditions of the reforming of the petrol fraction with $T_b = 77\text{--}155\text{ }^{\circ}\text{C}$.¹⁹¹ Problems arising in the use of chlorinated (Pt, Re)/ Al_2O_3 catalysts under industrial conditions, problems of the recovery of the $\text{H}_2\text{O}:\text{HCl}$ balance, problems in the monitoring of sulfur, *etc.* have been examined.¹⁹² (Pt, Re)/ Al_2O_3 catalysts prepared by the joint impregnation method and containing chlorine exhibit a high activity because of the decrease in the deposition of coke on their metallic centres.¹⁹³ The stronger interaction of the metals in such a catalyst, the smaller the degree of its deactivation by coke.

The presence of fluorine on the Al_2O_3 surface prevents the formation of the strongly bound hexachloroplatinic acid complex PtO_xCl_y .¹⁹⁴ Heating in an inert gas leads to the removal of chlorine and the formation of metallic platinum. Treatment with hydrogen limits the possibility of the formation of a homogeneous Pt–Re solid solution. An increase in the amount of free rhenium in the catalyst promotes the intensification of its hydrogenolysing and the weakening of its aromatising capacities.

The properties of the CB-6 catalyst (China) reduced by electrolytic hydrogen and hydrogen obtained in the reforming process have been compared.¹⁹⁵ Reduction by electrolytic hydrogen led to an increase in the octane number of the petrol formed as a result of reforming by a factor of 2.2 and to a slight increase in the yield. The catalyst reduced by electrolytic hydrogen also possessed a greater stability. However, reduction of (Pt, Re)/Al₂O₃ catalyst by the hydrogen, evolved in the course of the reforming of petroleum, is more economical than the reduction by electrolytic hydrogen.¹⁹⁶

Sixteen kinetic models were proposed,¹⁹⁷ which make it possible to describe the parameters of petroleum reforming processes in the presence of the (Pt, Sn)/Al₂O₃ and (Pt, Re)/Al₂O₃ catalysts.

Analysis of the patent literature of recent years^{198–228} shows that the selection of effective regenerable rhenium-containing catalysts for the reforming processes is being continued. Pt, Re, Ir catalysts deposited on Al₂O₃, SiO₂, Al₂O₃·SiO₂, or a zeolite have been proposed.^{198–200} Tin, cadmium, germanium,^{201–205} as well as titanium²⁰⁵ are used as promoting agents instead of iridium. Effective bimetallic platinum–rhenium supported catalysts, activated by chlorine or fluorine, have been developed.^{206–211} Low-octane petrol fractions are subjected to reforming (220–260 °C, atmospheric pressure) in the presence of 0.1 mass %–0.3 mass % of Ni, Re, Os, Rh, Ir, Ru, Co, and/or Fe deposited on an oxide support.²¹² W, V, Mo, Re, Ni, Co, Cr, Mn, and noble metals (Pt or Pd) can also serve as hydrogenating and dehydrogenating components.²¹³ The introduction of lanthanide oxides, for example Nd₂O₃, into an aluminosilicate support containing more than 50% of SiO₂ increases the activity of the platinum–rhenium catalyst in reforming and isomerisation processes.²¹⁴

The combination of processes makes it possible to increase the octane numbers of the reforming products. For example, the product of the conversion of the starting material on the (Pt, Re)/Al₂O₃ catalyst is passed for this purpose over the (Pt, Sn)/Al₂O₃ catalyst.^{215,216} Studies associated with the regeneration of the catalysts,^{217,218} an increase in their useful lifetime, the reforming technology, *etc.*^{219–228} are being continued.

Much attention has been devoted to the preparation and physicochemical methods for the analysis of monometallic Pt/Al₂O₃ catalysts^{229,230} and also the commonest bimetallic reforming catalysts based on Pt and Re, Pt and Sn, Pt and Ir, and Pt and Ge.²²⁹

The interaction of the metals in (Pt, Re)/ γ -Al₂O₃ bimetallic catalysts has been investigated by the EXAFS and other spectroscopic methods.²³¹ The likely usefulness of the employment of various Pt, Re clusters with a definite structure in heterogeneous catalysis has been demonstrated by comparing their properties with those of the usual (Pt, Re)/Al₂O₃ bimetallic reforming catalysts.²³²

The properties of the 0.3% Pt/Al₂O₃ (EUROPT-3) and (0.3% Pt, 0.3% Re)/Al₂O₃ (EUROPT-4) catalysts have been investigated in relation to the structure-sensitive hydrogenolysis reactions of alkanes (ethane, propane, n-butane, n-hexane, 2- and 3-methylpentanes, n-octane).²³³ The rate and selectivity of the hydrogenolysis depend on the conditions in the preliminary treatment of the catalyst and the residual coke content on the surface. The bimetallic catalyst is more sensitive to the preliminary treatment than Pt/Al₂O₃, since rhenium-enriched phases or pure rhenium may be formed on its surface, which entails a change in the surface ratio Pt : Re. Under the conditions of vigorous hydrogenolysis of alkenes (ethene, butadiene) at 0 and 127 °C in a flow system, the (Pt, Re)/Al₂O₃ catalyst is rapidly deactivated, in contrast to Pt/Al₂O₃.

The methods for the preparation of bimetallic reforming catalysts, the conditions in their heat treatment, the role of the support, the impregnation methods, the selection of the initial solutions, the stability of the catalysts, and other problems have been discussed.²³⁴ Methods for the extraction of rhenium and

platinum from spent reforming catalysts have been examined.^{235,236}

Polymetallic (Pt, Re, Cd)/Al₂O₃ catalysts of type K-104 have been tested under the conditions of reforming of petrol fractions.²³⁷ During the initial period, coke is formed on the metallic centres of the RG-482 catalyst.²³⁸ On regeneration, it is removed initially from the metallic and then from the acid centres.²³⁹

A new trimetallic reforming catalyst, which makes it possible to increase the yield of C₅ hydrocarbons and hydrogen compared with the usual (Pt, Re)/Al₂O₃ bimetallic catalyst, has been proposed in a patent.²⁴⁰ Its stability is not inferior to that of the standard industrial catalyst.

Pt/Al₂O₃ and (Pt, Re)/Al₂O₃ mono- and bi-metallic catalysts, prepared by the methods used for the synthesis of industrial reforming catalysts, have been investigated by the EXAFS method.^{241–243} Under the conditions in the reforming of n-heptane, the formation of Pt–C bonds was observed in both mono- and bi-metallic systems. The deposition of carbon was investigated.^{242,243} The Pt–C bond is formed at 460 °C on the monometallic catalyst, whereas on (Pt, Re)/Al₂O₃ it is formed only at low temperatures, the process being accompanied by an appreciable change in the structure of the metallic particles. Modification of platinum with rhenium increases the stability of the catalyst and prevents the deposition of well structured carbon residues.

The results indicate also the presence of a long Re–O bond (2.20 Å) in the reduced (Pt, Re)/Al₂O₃ catalysts, which does not conflict with the idea that a structure formed as a result of the insertion of Re into Al₂O₃ exists. Such a structure emerges partly onto the surface and is reduced by the carbon–hydrogen mixture.

(Pt, Re)/Al₂O₃ catalysts have also been investigated by transmission electron microscopy combined with energy dispersive X-ray analysis.^{244–246} Rhenium–platinum alloy is not formed in this catalyst and there is a wide size distribution of the rhenium crystals on the support surface.²⁴⁴ Two types of platinum particles have been observed: three-dimensional metallic particles and small formations containing a few atoms. Some aggregation of the platinum particles in the course of the process has been observed under the conditions of the reforming of n-octane. The interaction of rhenium with Al₂O₃ and preliminary modification of platinum influence significantly the stability and selectivity of the catalyst in reactions involving cycloalkanes and in aromatisation processes. The distribution of active elements in (Pt, Re)/Al₂O₃ catalysts has been examined.^{245,246}

The TAP method (Temporal Analysis of Products — analysis of reaction products as a function of time) has been used to investigate the conversion paths of C₆ hydrocarbons on the Pt/Mg(Al)O, Pt/KL (K is an ion-exchange zeolite), and Pd/Mg(Al)O catalysts, as well as (0.3% Pt, 0.3% Re)/Al₂O₃ industrial catalysts (sulfided and nonsulfided).²⁴⁷ The reactions were carried out under pulsed conditions at 477 and 510 °C, a pressure of 1 atm, and a H₂ flow rate of 0.25 ml min^{–1}. The reforming products were analysed mass-spectrometrically. It was found that only benzene is formed from cyclohexane, while hex-1-ene is either dehydrocyclised or is hydrogenated to n-hexane with subsequent dehydrogenation and ring closure. The possible dehydrogenation of hexane to hexadiene with subsequent cyclisation takes place at approximately the same rate as that of the dehydrogenation of cyclohexane to benzene. Under the chosen conditions, the sulfidation of the catalyst does not exert an appreciable influence on the course of the reaction.

Under industrial conditions at high pressures, the formation of benzene from alkanes on the (Pt, Re)/Al₂O₃ catalyst proceeds via a two-stage mechanism.²⁴⁸

The application of the oxygen–hydrogen titration method²⁴⁹ made it possible to determine the degree of dispersion of platinum with a reproducibility of $\pm 3\%$ and of rhenium with a reproducibility of $\pm 5\%$. Previously, the reproducibility was $\pm 5\%$ for platinum and $\pm 10\%$ for rhenium.⁴

IR spectroscopic study of the adsorption of NO and CO molecules showed that a Pt–Re alloy or metallic clusters are not formed on the surfaces of reduced (Pt, Re)/Al₂O₃ catalysts with a low concentration of the metal (0.22% of Pt and 0.43% of Re).²⁵⁰

The TPR and XANES methods have been used to estimate the influence of the content of the metal and of the Re : Pt ratio on the susceptibility of rhenium in (Pt, Re)/Al₂O₃ catalysts to reduction.²⁵¹ It was found that the final oxidation state of metallic rhenium depends on both these parameters. The catalysts were investigated with laboratory bench and pilot apparatus. The degree of reduction of rhenium determines the catalytic properties of bimetallic Pt–Re systems. With increase in the Re : Pt ratio, the lifetime of the catalyst increases and this trend is maintained so long as rhenium continues to be reduced. A second rhenium phase, the appearance of which increases the reduction temperature, arises when the Re : Pt ratio exceeds 2 : 1. In the presence of a controlled sulfur content in the starting material, the catalyst with the ratio Re : Pt = 2 : 1 works twice as long as the catalyst with the ratio Re : Pt = 1 : 1.

VI. Conclusion

The behaviour of rhenium-containing catalysts in a series of organic reactions is distinguished by specificity compared with the behaviour of other transition metals. The possibility of the modification, activation, and reduction of the concentration of rhenium in the Re₂O₇/γ-Al₂O₃ catalysts used for the metathesis of unsaturated compounds and functional alkenes has been demonstrated in recent years. Unsaturated organic compounds which are difficult to obtain, including chlorine- and oxygen-containing ones, may be synthesised by reactions involving higher alkenes. The use of rhenium-containing catalysts permits metathesis or joint metathesis under milder conditions than on other catalytic systems.

Rhenocene hydride, rhenium pentacarbonyl, rhenium oxides with the perovskite structure, and rhenium heptasulfide are effective catalysts of the hydrogenation of a series of organic compounds and condensed nitrogen-containing aromatic ones. Supported rhenium catalysts exhibit a higher activity than the known industrial oxide catalysts in the hydrogenation reactions of oxygen-containing compounds (carboxylic acids, aldehydes, synthetic aliphatic acid esters, etc.).

The studies on rhenium-containing catalysts, especially bi- and poly-metallic ones, in which rhenium is used in combination with noble and Group VIII transition metals for hydrogenation, dehydrogenation, isomerisation, disproportionation, etc. reactions are being continued: the methods for the preparation, activation, regeneration, modification, and analysis of the catalysts are being improved and the mechanism of their action is being investigated. The range of physicochemical research methods is being constantly expanded. However, many questions concerning the unique role of rhenium, for example in bimetallic platinum–rhenium supported catalysts, remain unelucidated or controversial.

Rhenium-containing catalysts are widely used in two industrial processes — metathesis and reforming. Nowadays more than 30% of the total number of reforming catalysts employed throughout the world consist of Pt, Re catalysts.²³⁶

The most promising fields of application of rhenium and its compounds as catalysts still comprise diverse organic reactions as well as reactions with participation of CO, CO₂, O₂, H₂O, and chlorine-containing compounds.

The catalytic properties of rhenium have been discovered not long ago, so the possibilities for its employment in catalysis are still far from being exhausted.

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Geminal oxygen – nitrogen – halogen systems. *N*-Halohydroxylamine derivatives

V F Rudchenko, R G Kostyanovskii

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Abstract. Published data on the synthesis and properties of *N*-halohydroxylamine derivatives are described systematically and analysed. The bibliography includes 123 references.

I. Introduction

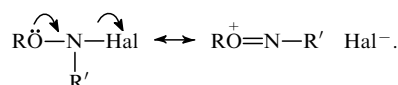
The development of the chemistry of *N*-halohydroxylamine derivatives started relatively recently, although the first representative of this class, *N*-chloro-*N*-methoxy-*p*-toluenesulfonamide, was described as early as 1953.¹ *N*-Halo-*N*,*O*-dialkylhydroxylamines are the nitrogen analogues of α -halo ethers, which are widely used in organic synthesis as highly reactive alkylating reagents.² It is this formal analogy that attracted our attention about 20 years ago. This analogy has worked perfectly, and this permitted the synthesis of new classes of organic compounds by simple nucleophilic substitution of chlorine in *N*-chlorohydroxylamine derivatives. In particular, *N*-alkoxy-*N*-*tert*-alkyl-*O*-alkylhydroxylamines (nitrosoacetals),^{3,4} *N*,*N*-dialkoxy-*O*-alkylhydroxylamines (trialkoxamines, orthonitrites),⁵ and *N*-alkoxy-*O*-alkylhydroxylamines (NH-dialkoxamines, orthoethers of nitrosyl hydride)⁶ have been synthesised in this way, and oxidation of the latter compounds gave stable dialkoxyaminyl radicals⁷ and their dimers (tetraalkoxyhydrazines).^{7,8} The vast synthetic potential of *N*-halohydroxylamine derivatives is also due to the possibility of converting them into highly reactive intermediates such as *N*-alkoxynitrenes,⁹ *N*-substituted *N*-alkoxyaminyl radicals,^{7,10} and *N*-alkoxynitrenium ions.^{5,11} Thus intramolecular cyclisation of *N*-chloro-*O*-alkylhydroxamates involving an aromatic substituent present in the acyl or alkoxyl fragment of their molecules, which occurs *via* intermediate *N*-acyl-*N*-alkoxynitrenium ions, is a general method for the synthesis of a large number of nitrogen-containing heterocycles.^{12–18}

N-Halohydroxylamine derivatives are also of interest from the stereochemical viewpoint, since the two σ -electron-withdrawing

substituents attached to the nitrogen atom markedly increase its configurational stability.^{4,19–26} This made it possible to prepare optically active derivatives of 2-chloro-1,2-oxazolidine^{19,20} and 2-chloroxaziridine^{24,25} with an asymmetric nitrogen atom. The non-symmetrically substituted *N*-alkoxy-*N*-*tert*-alkyl-*O*-alkylhydroxylamines synthesised from *N*-chloro-*N*-*tert*-alkyl-*O*-alkylhydroxylamines were partially resolved into optical antipodes, which were the first chiral compounds with asymmetric nitrogen atoms in an open chain.⁴

Some aspects of the chemical behaviour of O–N–Cl systems have been considered in a number of reviews.^{12,27–29} In the present review, we have attempted to survey all the currently available data on the synthesis, properties, and stereochemistry of *N*-halohydroxylamine derivatives.

The stereochemistry and chemical properties of geminal oxygen – nitrogen – halogen systems are mostly determined by the stabilising interaction between the non-bonding (n) orbital of the oxygen atom and the antibonding σ^* orbital of the N–Hal bond, which is described in terms of the concept of valence bonds as hyperconjugation.



According to the theory of molecular orbital perturbation, the energy of $n-\sigma^*$ stabilisation is approximately proportional to the overlap of the interacting orbitals and is inversely proportional to the difference between their energies.^{30,31} The $n-\sigma^*$ interaction results in kinetic destabilisation of the N–Hal bond, *i.e.* in an increase in its tendency to dissociate (kinetic anomeric effect³²)† yielding a nitrenium ion stabilised due to the π -overlap between the vacant $2p_z$ orbital of the N atom and the occupied $2p_z$ orbital of the neighbouring O atom (Fig. 1).^{4,13–15,33,34}

N-Alkoxynitrenium (nitrenium-oxonium ions) are ambident cations. They react with nucleophiles according to two competing pathways.^{5,10,35,36}

V F Rudchenko, R G Kostyanovskii N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117977 Moscow, Russian Federation. Fax (7-095) 938 21 56

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† The structural consequences of the $n-\sigma^*$ interaction are considered in Section VII.

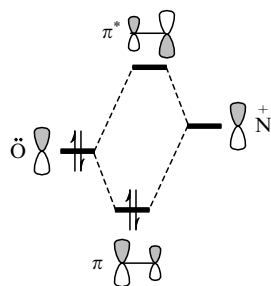
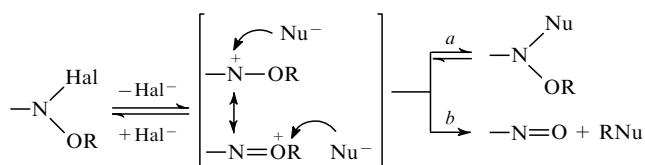


Figure 1. Interaction of the $2p_z$ orbitals of nitrogen and oxygen in alkoxyxynitrenium ions.

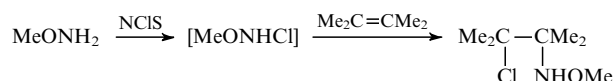


The addition of nucleophiles to the nitrenium centre [pathway (a)] is a reversible orbitally controlled reaction, which occurs in the case of 'soft' nucleophiles with high-lying highest occupied molecular orbitals (HOMO). Conversely, dealkylation of the oxonium site [pathway (b)] is an irreversible charge-controlled reaction occurring in the case of 'hard' nucleophiles having low-lying HOMO.

The thermal stability and the reactivity of *N*-halohydroxylamine derivatives depend appreciably on the type of the halogen. The former decreases,^{13,37} whereas the latter increases with an increase in the electron-withdrawing ability of the N–Hal bond. The above-mentioned properties of *N*-halohydroxylamine derivatives also depend substantially on the type of the third substituent at the nitrogen atom. Electron-releasing substituents, which favour ionisation of the N–Hal bond to even a greater extent, diminish the thermal stability and increase the reactivity of these compounds. For instance, whereas *N*-chloro-*N*-*tert*-alkyl-*O*-alkylhydroxylamines⁴ are stable distillable liquids, *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines⁵ cannot be detected by ¹H NMR spectroscopy even at -30°C . Conversely, electron-withdrawing substituents decrease the polarisation of the N–Hal bond, and in some cases, they even change the direction of polarisation; this, for example, occurs in the case of *N*-halo-*N*-alkoxy-substituted sulfonamides^{1,38} and phosphamides.³⁸

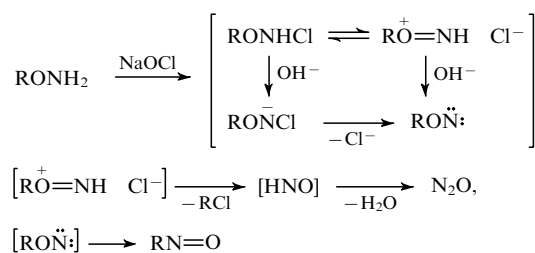
II. *N*-Halo-*O*-alkylhydroxylamines

N-Halo-*O*-alkylhydroxylamines are unstable and have not been isolated in a pure state. Nevertheless, *N*-chloro-*O*-methylhydroxylamine, generated by treatment of *O*-methylhydroxylamine with *N*-chlorosuccinimide, has been involved *in situ* in the addition to tetramethylethylene.³⁹



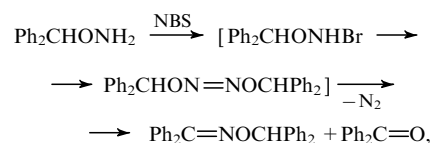
NCS is *N*-chlorosuccinimide.

Two routes of transformation of *N*-chloro-*O*-*tert*-alkylhydroxylamines have been discovered; in weakly alkaline solutions, they form N_2O , while in strongly alkaline media (6 N or 8 N NaOH), they are converted into nitrosoalkanes.⁴⁰ Dinitrogen monoxide was assumed to result from decomposition of nitrosyl hydride formed upon dealkylation of the intermediate nitrenium-oxonium ions. Nitroso-derivatives result from 1,2-rearrangement of the alkoxyxynitrenes,^{41,42} which can be generated from *N*-chloro-*O*-alkylhydroxylamines *via* 1,1-elimination⁴⁰ or deprotonation of *N*-alkoxyxynitrenium ions.³⁵



R = Bu^t, Me₂EtC.

It has been assumed that the products of monohalogenation of *O*-diphenylmethylhydroxylamine⁴³ and 1,2-bis(aminoxyl)-ethane⁴⁴ are mostly formed *via* decomposition of intermediate hyponitrites yielding N_2 and alkoxy radicals, which, in turn, disproportionate to give an aldehyde (or ketone) and an alcohol.



NBS is *N*-bromosuccinimide;

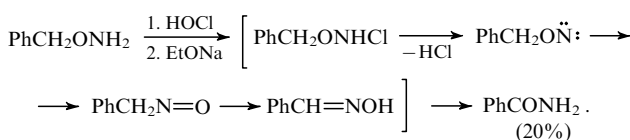


In some cases, hyponitrites are the final products of monohalogenation of *O*-alkylhydroxylamines.^{45,46}

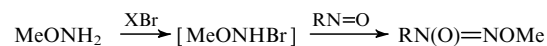


R = Et, Bu^t; XHal = Br₂, NaOCl, chloramine T.

One of the possible pathways to hyponitrites in this reaction includes decomposition of *N*-halo-*O*-alkylhydroxylamines to alkoxyxynitrenes and their subsequent dimerisation.⁴³ The intermediate formation of benzyloxyxynitrene has also been assumed⁴ for the chlorination of *O*-benzylhydroxylamine.⁴⁷

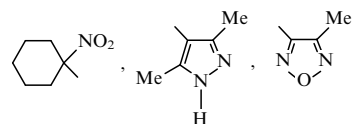


The bromination of *O*-methylhydroxylamine in the presence of *C*-nitroso-derivatives affords diazene oxides in 5%–20% yields.⁹



XBr = Br₂, NBS;

R = Me₂(NO₂)C, MeO₂CCMe₂, Ph, 2,4-(NO₂)₂C₆H₃,

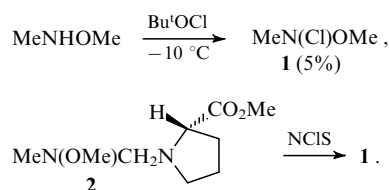


III. *N*-Halo-*N*,*O*-dialkylhydroxylamines

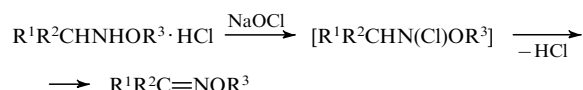
This type of compound has been studied most comprehensively. Methods for synthesis of acyclic and cyclic *N*-chloro-, *N*-bromo-, and *N*-fluoro-derivatives have been developed; chemical properties of these derivatives have been studied.

1. Synthesis

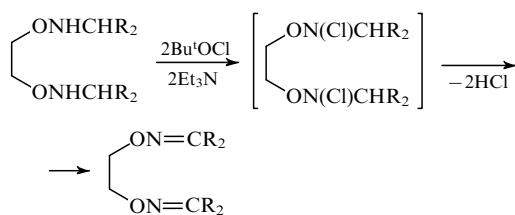
The simplest representative of acyclic *N*-chloro-*N,O*-dialkylhydroxylamines, namely *N*-chloro-*N,O*-dimethylhydroxylamine **1**, has been prepared by chlorination of *N,O*-dimethylhydroxylamine⁴⁸ and by cleavage of amina **2** upon treatment with *N*-chlorosuccinimide.⁴



Compound **1** withstands vacuum distillation (b.p. 35 °C at 200 mm Hg). It was characterised by spectroscopic methods.^{4, 48, 49} However, the attempts to synthesise other *N*-chloro-*N,O*-dialkylhydroxylamines containing an α -hydrogen atom in the *N*-substituent failed.^{50, 51} These compounds are thermally unstable and are readily dehydrochlorinated to *O*-ethers of oximes.

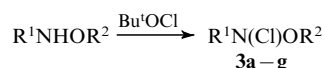


$\text{R}^1 = \text{Me, Et; R}^2 = \text{H, Et; R}^3 = \text{Et, Me}.$



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

Conversely, *N*-chloro-*O*-alkyl-*N-tert*-alkylhydroxylamines **3a–g** for which this dehydrochlorination is impossible are thermally stable under ambient conditions. They have been prepared by chlorination of the corresponding hydroxylamines^{4, 48, 52–57} and by cleavage of *N-tert*-alkyl-*N*-methoxy-*O*-methylhydroxylamine **4** upon treatment with acyl chlorides or chlorotrimethylsilane.^{58, 59}

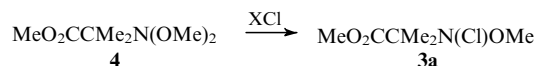


$\text{R}^1 = \text{MeO}_2\text{CCMe}_2; \text{R}^2 = \text{Me} \text{ (a)}, \text{Pr}^i \text{ (b)};$

$\text{R}^1 = \text{MeO}_2\text{CCH}_2\text{CMe}_2; \text{R}^2 = \text{Me} \text{ (c)}, \text{Pr}^i \text{ (d)}, \text{PhCH}_2 \text{ (e)};$

$\text{R}^1 = \text{MeO}_2\text{CC}(\text{CF}_3)\text{Me}; \text{R}^2 = \text{Me} \text{ (f)};$

$\text{R}^1 = (\text{EtO}_2\text{C})_2\text{CHCMe}_2; \text{R}^2 = \text{Me} \text{ (g)}.$



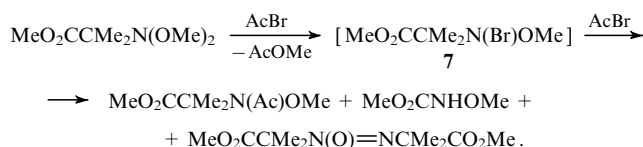
$\text{XCl} = \text{AcCl, CF}_3\text{COCl, SOCl}_2, \text{Me}_3\text{SiCl}.$

The compound **3a** in a pure state decomposes over a period of 12 h at 20 °C,⁴ whereas **3c** can be distilled *in vacuo* and remains unchanged in solution (CCl_4) for at least a month.⁴

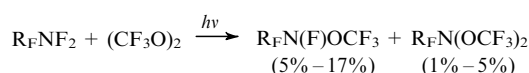
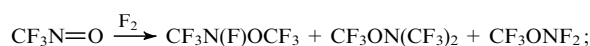
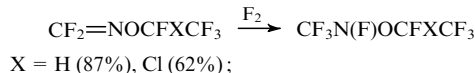
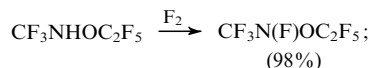
The only known acyclic *N*-bromo-*N,O*-dialkylhydroxylamine **6** was synthesised by bromination of the oxime *O*-ether **5** in the presence of CsF .⁶⁰



The attempt to prepare *N*-bromo-*N-tert*-alkyl-*O*-methylhydroxylamine **7** was unsuccessful; this compound is unstable and undergoes further transformations under the reaction conditions.⁵⁹

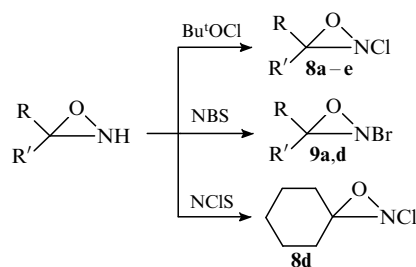


Acyclic fluorinated *N*-fluoro-*N,O*-dialkylhydroxylamines have been reported. These derivatives have been synthesised by fluorination of the corresponding NH-hydroxylamines,⁶¹ oxime *O*-ethers,⁶⁰ and trifluoronitrosomethane⁶² and by photochemical reaction of *N,N*-difluoroamines with trifluoromethyl peroxide.⁶³



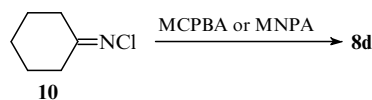
$\text{R}_\text{F} = \text{CF}_3, \text{C}_3\text{F}_7.$

Apart from the acyclic *N*-halo-*N,O*-dialkylhydroxylamines described above, a number of cyclic analogues have also been described. 2-Haloxaziridines **8a–e** and **9a,d** have been obtained in two ways: by halogenation of the corresponding NH-oxaziridines and by oxidation of *N*-chlorimine **10**.^{24, 25, 64, 65}



$\text{R} = \text{R}' = \text{Me} \text{ (a)}; \text{R} = \text{Me, R}' = \text{Et} \text{ (b)}; \text{R} = \text{R}' = \text{Bu}^t \text{ (c)};$

$\text{R, R}' = (\text{CH}_2)_5 \text{ (d)}; \text{R, R}' = \text{CH}_2\text{CH}(\text{Me})(\text{CH}_2)_3 \text{ (e)};$

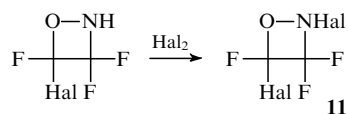


MCPBA is *m*-chloroperbenzoic acid;

MNPA is monoperphthalic acid.

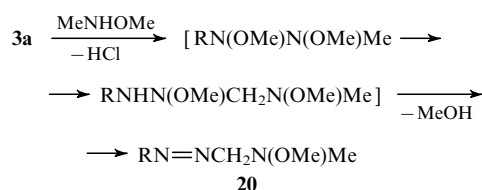
The chloroxaziridines **8a–e** can be distilled *in vacuo* without decomposition; in a pure state, they can be kept unchanged for 1 month at 0 °C, while as solutions in CDCl_3 , they are stable for 1 h at 100 °C in sealed tubes. The 2-bromoxaziridines **9a,d** are stable for 1 week at 0 °C in inert solvents; neat compounds can be stored at –78 °C but vigorously decompose to give the corresponding ketone at temperatures above 0 °C.⁶⁵

Thermally stable 2-chloro- and 2-fluoro-perhalo-1,2-oxazetines **11** have been prepared by halogenation of the corresponding 1,2-oxazetines.^{23, 66}



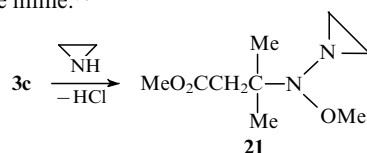
$\text{Hal} = \text{Cl, F}.$

Dimethyl 2-chloro-1,2-oxazolidine-3,3-dicarboxylate **12** has been synthesised by the chlorination of 1,2-oxazolidine **13**²⁰ and by the reaction of the methoxy-derivative **14** with SOCl_2 .^{20, 58}



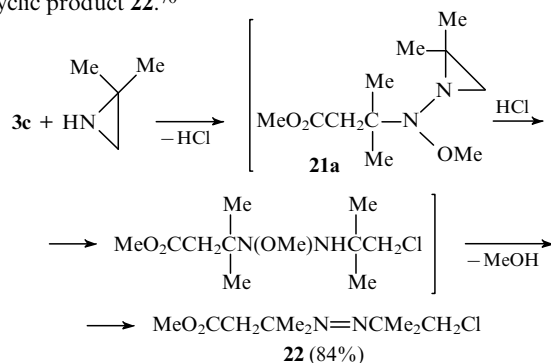
R = MeO₂CCMe₂.

Stable aziridine derivative **21** containing an *N*-methoxyhydrazine moiety was synthesised in 70% yield as the product of nucleophilic substitution of chlorine by reaction of **3c** with ethylene imine.⁷⁰



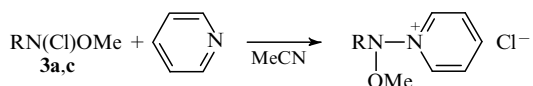
The instability of *N*-methoxyhydrazine derivatives⁷⁰ is due to the easy rupture of the N–O bond, caused by the vicinal $n_{\text{N}(1)}-\sigma^*_{\text{N}-\text{O}}$ orbital interaction. In the aziridine **21**, this interaction is weak, because the positive mesomeric effect of the ethylene imine nitrogen atom is low. This accounts for the stability of this compound.

Nevertheless, the reaction of the compound **3c** with 2,2-dimethylethylene imine under the same conditions affords the acyclic product **22**.⁷⁰



It was assumed that, due the fact that 2,2-dimethylethylene imine is more basic than ethylene imine, the aziridine ring in the chlorine substitution product **21a** formed initially is cleaved under the action of HCl according to an S_N2 mechanism.

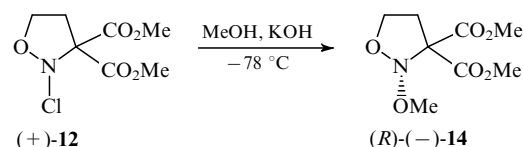
The reactions of **3a,c** with pyridine also occur as nucleophilic substitution of chlorine.⁷⁰



R = MeO₂CCMe₂, MeO₂CCH₂CMe₂.

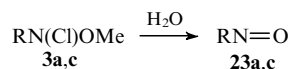
Based on kinetic studies, it was concluded that this reaction occurs by the S_N2 mechanism.²⁰

It was shown that methanolysis of optically active *N*-chloro-1,2-oxazolidine (+)-**12** (its synthesis is described in Section VIII) occurs with retention of the optical activity and affords *N*-methoxy-1,2-oxazolidine *R*-(–)-**14** with an optical purity of about 3%.^{19,20} However, since the optical purity and the absolute configuration of the starting (+)-**12** are unknown, no reliable conclusions about the mechanism of this reaction can be drawn.



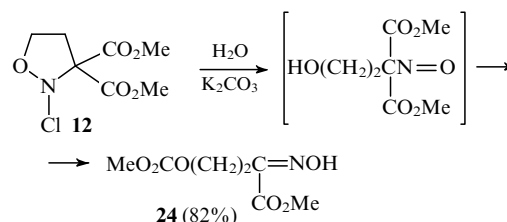
b. Formation of *C*-nitroso-derivatives

C-Nitroso-derivatives **23a,b** have been prepared by hydrolysis of *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamines **3a,c** in the presence of K₂CO₃^{10,71} or SbCl₅.⁷¹

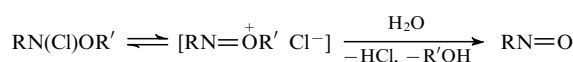


R = MeO₂CCMe₂ [**23a** (88%)], MeO₂CCH₂CMe₂ [**23c** (91%)].

Hydrolysis of *N*-chloro-1,2-oxazolidine **12** also gives rise to a nitrosoalkane. However, this product is unstable and rearranges to oxime **24** as a result of migration of the methoxycarbonyl group from the C atom to the O atom.⁵⁷

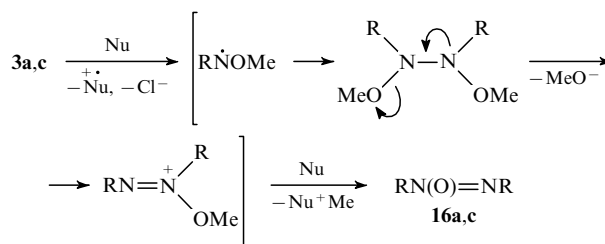


These reactions proceed presumably *via* intermediate nitrenium-oxonium ions. Water is a hard nucleophile; therefore, in conformity with the general principles outlined in Section I, it reacts with these ions with dealkylation of the oxonium centre.¹⁰



c. Redox reactions

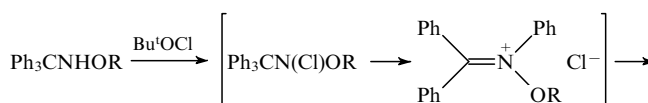
When *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamines **3a,c** react with sterically hindered alcohols in the presence of Et₃N,⁴ sterically hindered amines (Et₃N, Et₂NH),¹⁰ Grignard reagents,¹⁰ triphenylphosphine,¹⁰ or sodium ethanethiolate,¹⁰ nucleophilic substitution of chlorine is suppressed completely or partially by the competing redox reaction. This reaction affords *N*-substituted-*N*-methoxyaminyl radicals, dimerisation of which results in the formation of unstable 1,2-dimethoxyhydrazine derivatives. Decomposition of these compounds yields the final products, diazene oxides **16a,c**.

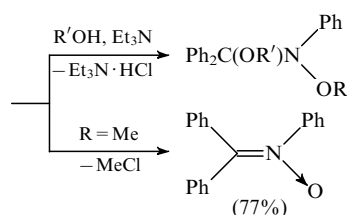


R = MeO₂CCMe₂ (**a**), MeO₂CCH₂CMe₂ (**c**).

d. 1,2-Rearrangements

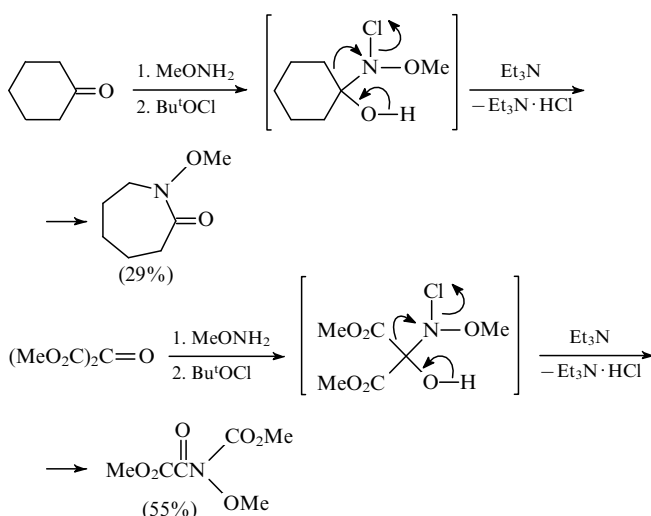
1,2-Rearrangement with migration of the phenyl group to the electron-deficient nitrogen atom is the predominant route of transformation of *N*-chloro-*O*-alkyl-*N*-triphenylmethylhydroxylamines under conditions of alcoholysis. This rearrangement occurs spontaneously even in the absence of an external nucleophile.¹¹





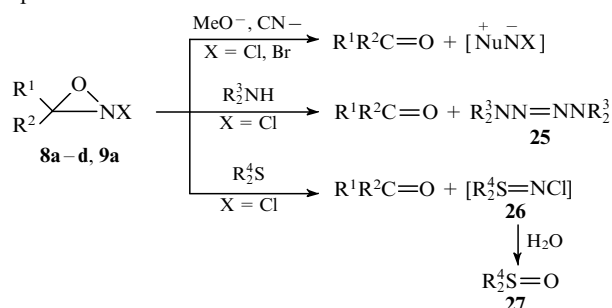
R = Me, MeO₂CCMe₂; R' = Me, Et.

A 1,2-rearrangement with migration of the alkyl or methoxycarbonyl group from the carbon atom to the nitrogen atom was found in the chlorination of the adducts of MeONH₂ with cyclohexanone or dimethyl mesoxalate. The rearrangement products were isolated after treatment with Et₃N.¹¹

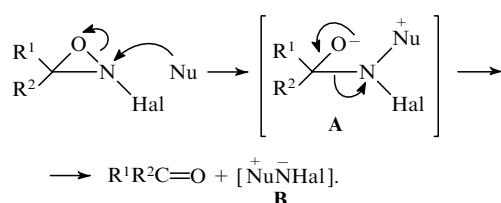


The mechanism of these rearrangements has not been studied; however, they are believed to involve the formation of intermediate nitrenium ions.

2-Haloxaziridines **8** and **9**, unlike *N*-chloro-*N,O*-dialkylhydroxylamines, possess relatively low reactivity with respect to nucleophiles. In addition, the reactions of these compounds with some nucleophiles, for example, MeO[−], Me₂NH, morpholine, dimethyl sulfide, and diisopropyl sulfide, occur as substitution of oxygen rather than chlorine, *i.e.* when the nucleophile attacks the nitrogen atom, an oxygen-containing anion becomes the leaving group.⁶⁵



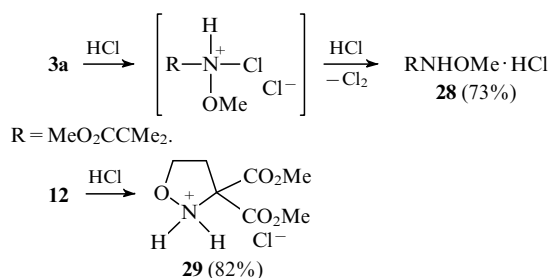
R¹ = R² = Me (**a**); R¹ = Me, R² = Et (**b**); R¹ = R² = Bu^t (**c**); R¹, R² = (CH₂)₅ (**d**); R₂³ = Me₂, (CH₂)₂O(CH₂)₂; R⁴ = Me, Prⁱ.



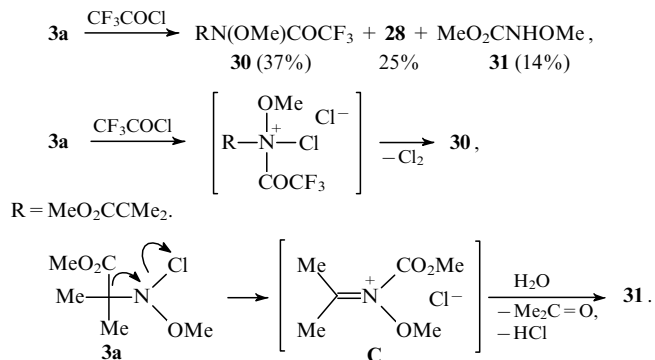
The intermediate **A** thus formed decomposes yielding the corresponding ketone and a substituted *N*-haloamine **B**. The latter reacts with amines giving rise to tetrazene **25** (apparently, *via* diazenium salt and *N*-aminonitrene) or reacts with dialkyl sulfides with formation of *N*-chlorosulfinimines **26**. The formation of sulfoxides **27** in the reactions of **8a,d** with dialkyl sulfides was explained by hydrolysis of *N*-chlorosulfinimines **26**.

3. Other reactions

N-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamine **3a**⁵⁹ and oxazolidine **12**²⁰ react with gaseous HCl to give the corresponding hydrochlorides **28** and **29**.



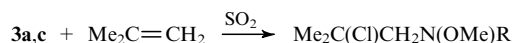
The reaction of the compound **3a** with CF₃COCl affords *N*-methoxytrifluoroacetamide **30**, the hydrochloride **28**, and methyl *N*-methoxycarbamate **31**.⁵⁹



Presumably, the trifluoroacetamide **30** is formed upon decomposition of the *N*-chloro-*N*-methoxy-*N*-trifluoroacetylammium salt formed intermediately. *N*-Methoxycarbamate **31** results from 1,2-rearrangement of the compound **3a**, accompanied by migration of the methoxycarbonyl group, and subsequent hydrolysis of the resulting intermediate **C** by traces of water. The HCl evolved during this process reacts with the initial compound **3a** according to the scheme described above to give the hydrochloride **28**.

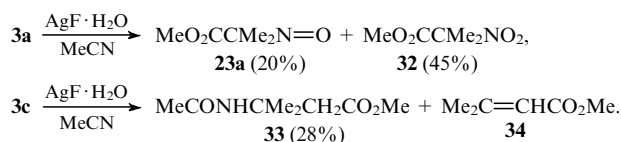
Treatment of **3a** with reagents facilitating ionisation or heterolytic rupture of the N–Cl bond, for example, SO₂ or BF₃·Et₂O, also results in 1,2-rearrangement.⁵⁹

This is why SO₂ initiates the addition of *N*-chloro-*N,O*-dialkylhydroxylamines **3a,c** to isobutene.⁵⁵

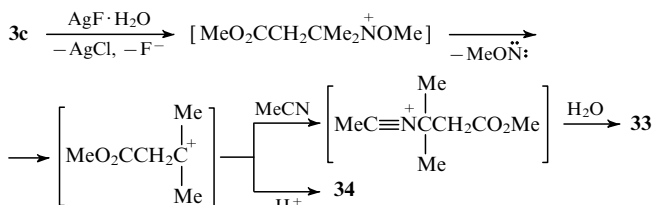


R = MeO₂CCMe₂, MeO₂CCH₂CCMe₂.

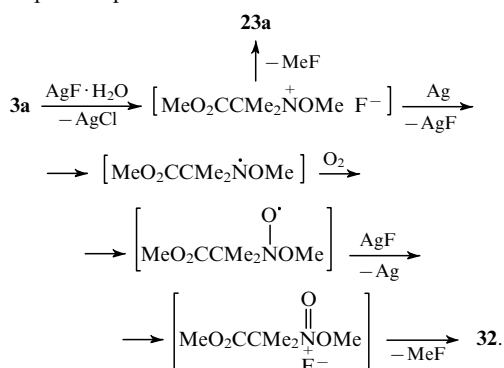
The reactions of **3a** and **3c** with AgF·H₂O in MeCN can follow different pathways depending on the nature of the alkyl substituent at the nitrogen atom.¹⁰



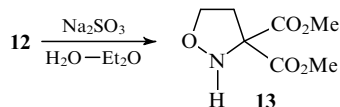
In the case of **3c**, this reaction was assumed to occur *via* elimination of methoxynitrene from the intermediate nitrenium ion to give a *tert*-alkyl cation, which is stabilised through the Ritter reaction with acetonitrile or deprotonation.¹⁰



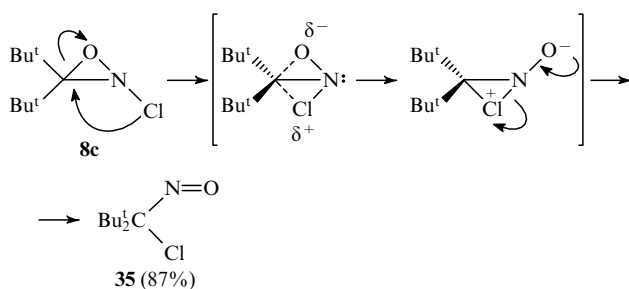
The same transformation of **3a** does not occur, because the corresponding *tert*-alkyl cation is less stable; therefore in this case, redox process predominates.¹⁰



N-Chloroxazolidine **12** is reduced by Na₂SO₃ to give 1,2-oxazolidine **13** in 67% yield.²⁰



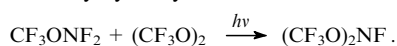
It was found that the sterically hindered 2-chloroxaziridine **8c**, unlike non-hindered **8a,b,d**, rearranges to α -chloronitrosoalkane **35**. The rearrangement of pure **8c** at 0 °C proceeds slowly, whereas that in CDCl₃ at 60 °C occurs over 15–20 min.^{64, 65} It was assumed⁶⁵ that this rearrangement occurs as intramolecular attack by chlorine on the carbon atom of the oxaziridine ring.



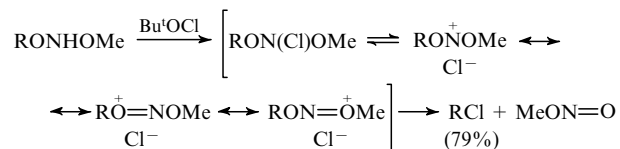
During photolysis of 2-chloroxaziridine **8c**, the corresponding oxaziridinyl radical was detected by EPR spectroscopy.⁷²

IV. *N*-Halo-*N*-alkoxy-*O*-alkylhydroxylamines

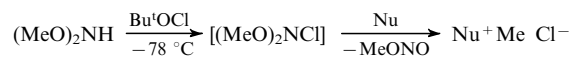
The only fluorine-containing compound of this type was prepared in 3% yield by photochemical reaction of *N,N*-difluoro-*O*-trifluoromethylhydroxylamine with trifluoromethyl peroxide.⁶³



N-Bromo- and *N*-iodo-derivatives of *N*-alkoxy-*O*-hydroxylamines are unknown. *N*-chloro-derivatives are thermally unstable, due to the easy heterolysis of the N—Cl bond yielding dialkoxynitrenium ions stabilised by resonance; these ions undergo irreversible dealkylation through the action of the internal nucleophile, *i.e.* the chlorine atom. For instance, chlorination of *N*-benzyloxy-*O*-methylhydroxylamine by Bu^tOCl gives benzyl chloride and methyl nitrite resulting from decomposition of the intermediate *N*-chloro-*N*-benzyloxy-*O*-methylhydroxylamine, which could not be detected by ¹H NMR spectroscopy even at −30 °C.⁵


$$R = \text{PhCH}_2.$$

Nevertheless, *N*-chloro-*N*-methoxy-*O*-methylhydroxylamine was *in situ* involved in several reactions. It was found that in reactions with Me₃N and pyridine, this compound, unlike *N*-chloro-*N*,*O*-dialkylhydroxylamines (Section III), acts as a methylating rather than an aminating reagent.⁵



Nu = Me₃N, Py.

This difference between the behaviour of *N*-chloro-*N,O*-dialkylhydroxylamines and *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines in the above reactions was explained⁵ by the fact that the nitrogen electrophilic centre in the latter is 'harder' and, hence, the orbitally controlled addition of nucleophiles to the nitrenium centre becomes possible only for very 'soft' nucleophiles containing high-lying HOMO. A similar difference in the properties has also been noted for monoalkoxy- and dialkoxycarbenium cations.⁷³

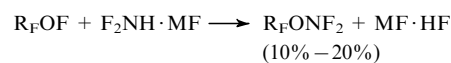
In accordance with the foregoing, nucleophilic substitution of chlorine in *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines occurs under the action of sodium methoxide and yields trialkoxyamines **36a,b**.^{5, 74}



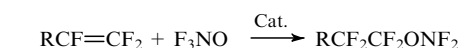
R = Me [**36a** (64%)], Et [**36b** (50%)]; DME is dimethoxyethane.

V. Derivatives of *N,N*-dihalohydroxylamines

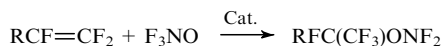
The only known compounds of this type are *N,N*-difluorohydroxylamine derivatives. The data on the synthesis and properties of compounds of the general formula XONF_2 , where $\text{X} = \text{CF}_3$, C_2F_5 , $\text{Cl}(\text{CF}_2)_2$, FOCH_2 , F_2NOCH_2 , $(\text{CF}_3)_2\text{N}$, FCO_2 , FSO_2 , SF_5 , published before 1976 have been surveyed in reviews.^{27,28} Later, a method for the synthesis of *N,N*-difluoro-*O*-perfluoroalkylhydroxylamines by reaction of perfluoroalkyl hypofluorites with difluoroamine–alkali metal fluoride complexes has been developed.⁷⁵


$$R_F = CF_3, \text{ iso-}C_3F_7, FOCF_2; MF = KF, RbF, KF-NaF.$$

N,N-Difluorohydroxylamine derivatives have also been synthesised by reactions of trifluoroamine oxide with fluoroalkenes in the presence of Lewis acids (BF_3 , AsF_5 , SbF_5).^{76, 77}

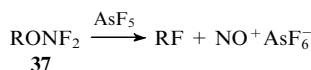


R = F, Cl, Br, C₂F₅O, C₃F₇OCF(CF₃)CF₂O;



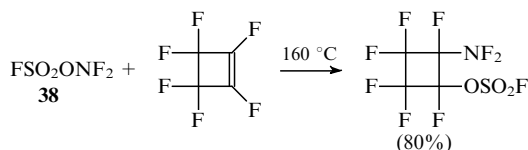
R = CF₃, C₅F₁₁, SF₅, FCO.

N,N-Difluorohydroxylamines **37** are cleaved by AsF₅ to give FNO, which is formed as a nitrosonium salt.⁷⁸

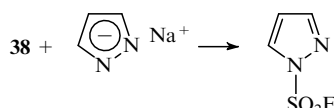


R = CF₃, SF₅.

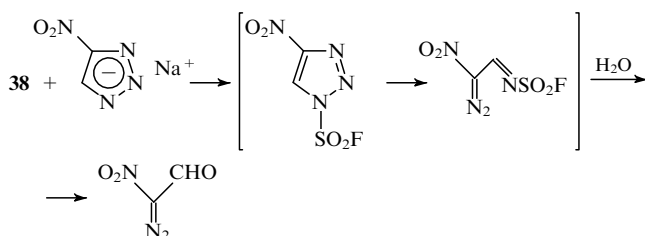
In reaction with perfluorocyclobutene, *O*-fluorosulfonyl-*N,N*-difluorohydroxylamine **38** acts as a pseudohalogen.⁷⁹



The reactions of **38** with ethylnitramine, ethylenedinitramine, and salts of azoles (imidazoles, pyrazoles, triazoles) lead to *N*-fluorosulfonylation products.⁸⁰ The reaction of **38** with the sodium salt of pyrazole was reported to be an example.⁸⁰



The reaction of the sodium salt of 4-nitrotriazole with the compound **38** is accompanied by ring opening. Subsequent hydrolysis affords formylnitrodiazomethane in 36% yield.⁸⁰

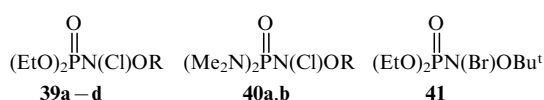


VI. *N*-Halo-*N*-alkoxyamides

As noted above, a typical feature of systems containing the O–N–Hal triad is polarisation of the N–Hal bond towards the halogen, which accounts for its anionic mobility. When the nitrogen atom carries an electron-withdrawing substituent, polarisation of the N–Hal bond decreases or even changes its direction, which has a substantial influence on the properties of these systems.

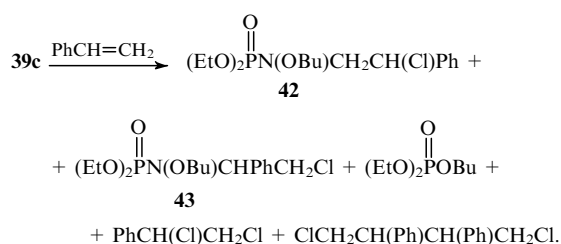
1. *N*-Halo-*N*-alkoxyphosphamides

N-Halo-*N*-alkoxyphosphamides **39**,⁸¹ **40**,³⁸ and **41**⁸² have been prepared by halogenation of the corresponding NH amides.

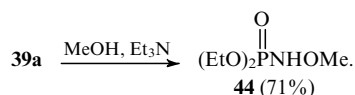


R = Me (a), PhCH₂ (b), Bu (c), Et (d).

The compounds **39a–d** are stable in a benzene solution (withstand refluxing for several hours); however, in a pure state they decompose over a period of 2 days at 0–5 °C. They give the typical 'positive chlorine' reaction.⁸¹ The addition of **39c** to styrene occurs by a radical mechanism and is not regiospecific yielding adducts **42** and **43** and some other products.⁸¹



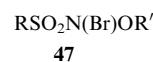
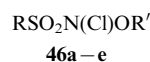
The attempts to carry out nucleophilic substitution of the chlorine atom in *N*-chloro-*N*-alkoxyphosphamides **39a** and **40a** failed. The reaction with MeONa in MeOH involves the phosphoryl group and is accompanied by elimination of the pseudo-halogen fragment N(Cl)OMe.³⁸ The compound **39a** reacts with MeOH in the presence of Et₃N giving rise to amide **44**.³⁸



Photolysis of a solution of *N*-bromo-*N*-tert-butoxyphosphamide **41** in cyclopropane at –100 °C gave radical **45**, which was detected by EPR spectroscopy.⁸²

2. *N*-Halo-*N*-alkoxysulfonamides

N-Halo-*N*-alkoxysulfonamides **46a–e**^{1,38,83} and **47**^{84,85} have been described.



R = Me, R' = Me (a), MeSO₂ (b);

R = 4-MeC₆H₄, R' = Me (c);

R = Me₂N, R' = PhCH₂ (d);

R = 2,6-Me₂-4-Bu^tC₆H₂, R' = Bu^t (e).

R = Me, Me₂N, 4-O₂NC₆H₄,

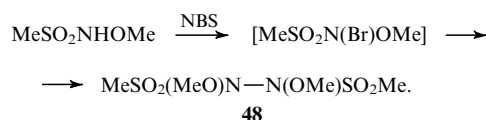
R' = Bu^t; R = 4-MeC₆H₄,

R' = Me, Et, Prⁱ, Bu^t, PhCH₂;

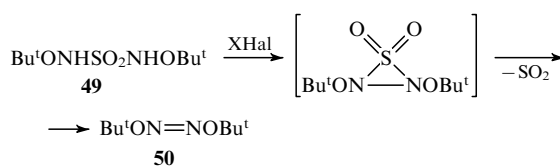
R = 2,6-Me₂-4-Bu^tC₆H₂,

R' = Me, Bu^t, PhCH₂.

The attempt to prepare the *N*-Br analogue of the compound **46a** resulted in the formation of 1,2-dimethoxyhydrazine derivative **48**.⁸³

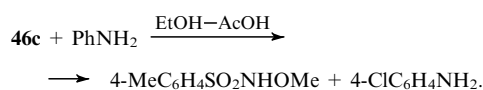


Halogenation of compound **49** yields hyponitrite **50**, apparently *via* the intermediate thiadiaziridine dioxide.^{46,86}



XHal = NaOCl, NaOBr, chloramine T.

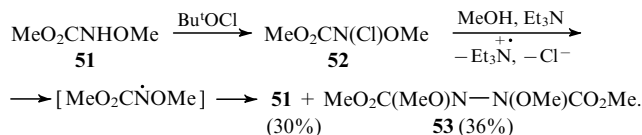
N-Halo-*N*-alkoxysulfonamides **46a,b,d** act as chlorinating reagents with respect to H₂O and MeOH, being thus converted into the corresponding NH amides.^{38,83} Thus compound **46c** chlorinates aniline into the aromatic ring.¹



Photolysis of solutions of *N*-bromo-*N*-alkoxysulfonamides **47** in CFCl₃ or in a mixture of CFCl₃ with CH₂Cl₂ at –30 to –60 °C is accompanied by the generation of the corresponding *N*-alkoxysulfonamidyl radicals, which have been detected by EPR spectroscopy.^{84,85}

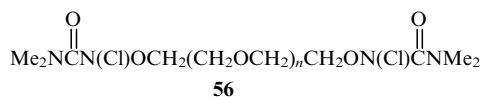
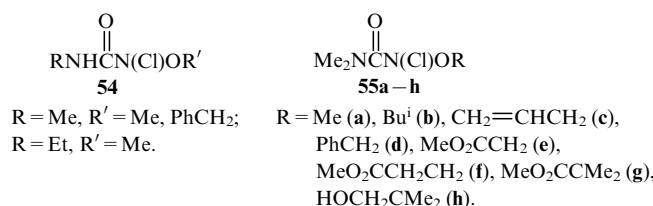
3. *N*-Halo-*N*-alkoxycarbamates

The only known compound of this type, methyl *N*-chloro-*N*-methoxycarbamate **52**, was synthesised by chlorination of the *N*-methoxycarbamate **51**. It can be distilled *in vacuo* without decomposition; upon treatment with MeOH and Et₃N it is converted into the initial *N*-methoxycarbamate **51** and hydrazine derivative **53**.^{87, 88}

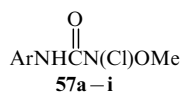


4. *N*-Chloro-*N*-alkoxyureas

N-Chloro-*N*-alkoxyureas **54**,^{89, 90} **55a–h**,^{38, 91, 92} **56**,^{8, 93, 94} and **57a–i**⁹⁵ have been prepared by chlorination of the corresponding NH ureas with Bu^tOCl.

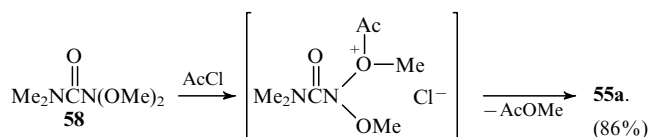


n = 0, 2, 3.

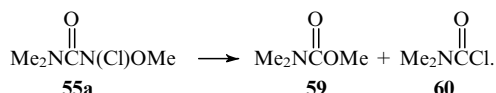


Ar = Ph (a), 4-ClC₆H₄ (b), 4-O₂NC₆H₄ (c), 4-MeC₆H₄ (d), 4-CNC₆H₄ (e), 4-MeSO₂C₆H₄ (f), 3-F₃CC₆H₄ (g), 3,4-Cl₂C₆H₃ (h), 2,6-Me₂C₆H₃ (i).

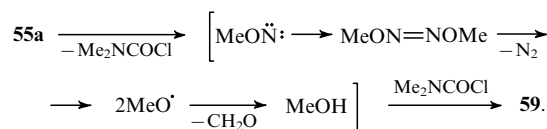
The compound **55a** was also obtained by cleavage of *N,N*-dimethoxyurea **58** upon treatment with acetyl chloride.⁹⁶



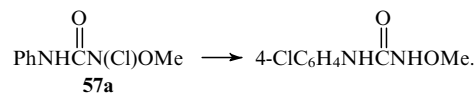
N-Chloro-*N*-alkoxyureas **54**, **55a–h**, **56**, and **57a–i** are non-distillable liquids or crystalline solids stable under ambient conditions. At room temperature in a CCl₄ solution, **55a** completely decomposes over a period of 25 days to give methyl *N,N*-dimethylcarbamate **59** and *N,N*-dimethylcarbamoyl chloride **60** in 1 : 1 ratio.³⁸



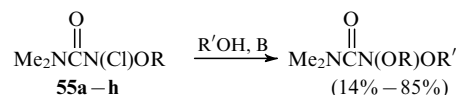
The carbamoyl chloride **60** results presumably from a concerted rearrangement with migration of chlorine to the carbonyl group and ejection of methoxynitrene (HERON rearrangement).⁹⁷ The driving force of this migration is the orbital *n*_O–σ*_{N–Cl} interaction in the O–N–Cl structural fragment. The *N,N*-dimethylcarbamate **59** is formed in this process upon interaction of *N,N*-dimethylcarbamoyl chloride with the MeOH produced among the products of decomposition of the intermediate methoxynitrene;³⁸ this process is shown below:



Among *N*-chloro-*N*-methoxyureas **57a–i**, only those which contain electron-withdrawing substituents in the aryl group are thermally stable under ambient conditions. The compound **57a** isomerises at room temperature giving *N*-(4-chlorophenyl)-*N'*-methoxyurea.⁹⁵



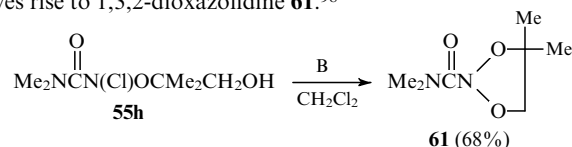
N-Chloro-*N*-alkoxyureas readily undergo nucleophilic substitution of chlorine atoms, because the carbamoyl group does not have any significant effect on the polarisation of the N–Cl bond. This also accounts for the similarity of chemical properties of *N*-chloro-*N*-alkoxyureas and *N*-chloro-*N,O*-dialkylhydroxylamines (see Section III). Thus *N*-chloro-*N*-alkoxyureas **54–56** react with alcohols and glycols in the presence of bases affording *N,N*-dialkoxyureas.^{8, 38, 89–94} For instance, these reactions have been described for **55a–h**.³⁸



B = R'ONa, collidine, NaOAc;

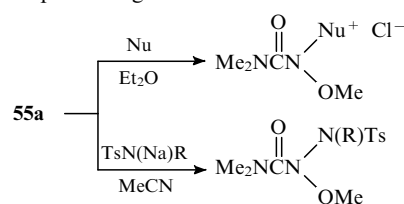
R' = Me, Et, Bu^t, CH₂=CHCH₂, CF₃CH₂, HO(CH₂)₂.

Intramolecular cyclisation of *N*-chloro-*N*-alkoxyurea **55h** gives rise to 1,3,2-dioxazolidine **61**.⁹⁸

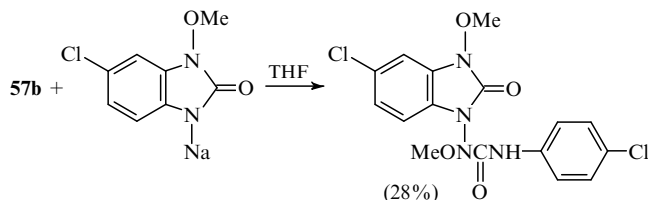


B is collidine.

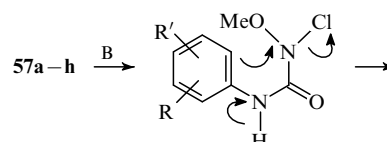
Products of nucleophilic substitution of chlorine in *N*-chloro-*N*-methoxyureas **55a** and **57b** were also obtained with other nucleophilic reagents.^{95, 99}

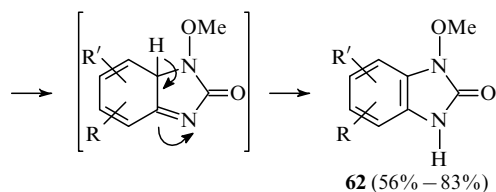


Nu = Me₃N, Py; R = Me, Ph.



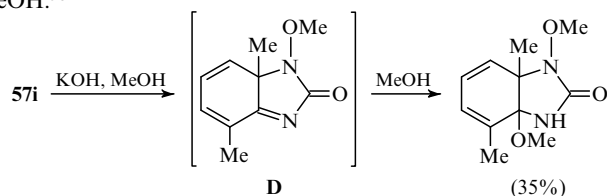
On treatment with bases, *N*-chloro-*N*-methoxyureas **57a–h** cyclise to give 1-methoxy-2-benzimidazolinones **62**.⁹⁵



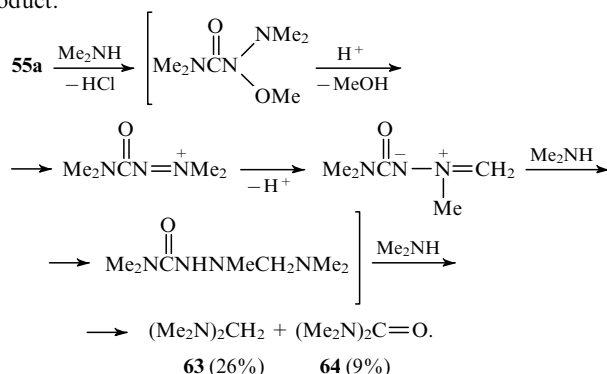


B = Bu^tOK, NaH.

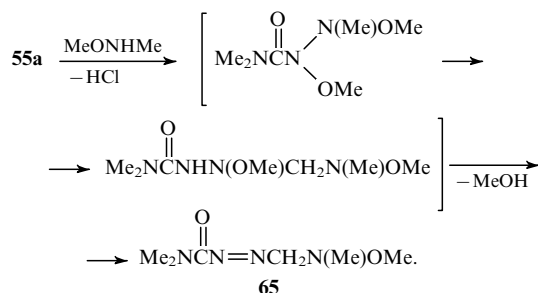
The formation of non-aromatic intermediate **D** during the cyclisation of **57i** was proved by isolation of its adduct with MeOH.⁹⁵



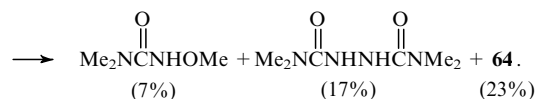
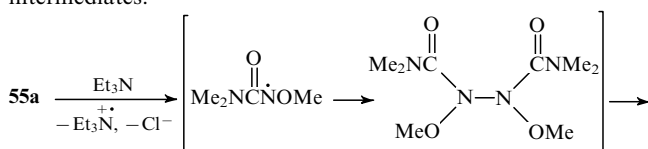
The reaction of *N*-chloro-*N*-methoxyurea **55a** with Me₂NH affords bis(dimethylamino)methane **63** and the urea **64**,⁹⁹ these products are formed *via* a scheme similar to that considered in Section III for the reaction of *N*-chloro-*N*-*tert*-alkyl-*O*-methylhydroxylamine **3c** with Me₂NH. Dimethylurea **64** results apparently from carbamoylation of Me₂NH by an intermediate product.



The reaction of *N*-chloro-*N*-methoxyurea **55a** with *N,O*-dimethylhydroxylamine affords diazene **65** in 38% yield.⁹⁹ This reaction proceeds presumably according to a similar scheme except that the intermediate aminal does not disproportionate, but instead, it eliminates MeOH yielding the product **65**.

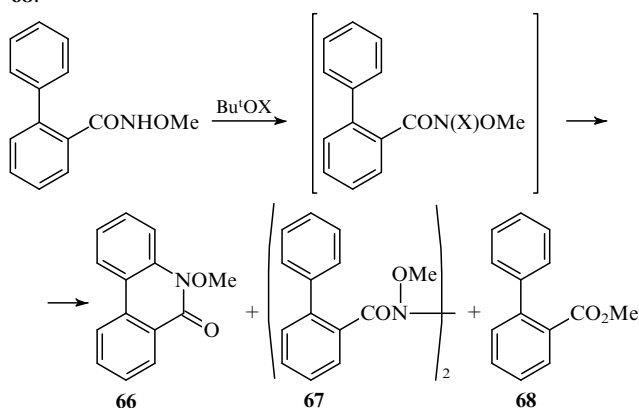


In the reaction of *N*-chloro-*N*-methoxyurea **55a** with Et₃N, nucleophilic substitution of chlorine is hampered for steric reasons. Therefore, a redox reaction occurs, the final products of which are formed upon transformations of the *N*-methoxycarbamidyl radical and substituted 1,2-dimethoxyhydrazine formed as intermediates.⁹⁹



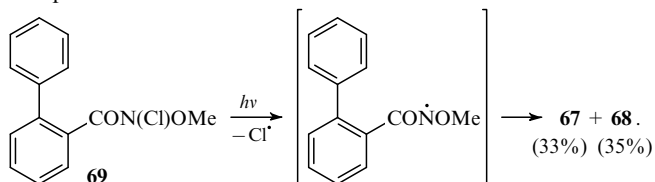
5. *N*-Halo-*O*-alkylhydroxamates

Among compounds of this type, only *N*-chloro-derivatives are known; they are synthesised by the chlorination of the corresponding NH hydroxamates with Bu^tOCl. The attempts to iodinate and brominate *N*-methoxyamide of biphenyl-2-carboxylic acid resulted in the formation of *N*-methoxy-phenanthridone **66**, hydrazine derivative **67**, and the product of its decomposition **68**.^{13, 37}

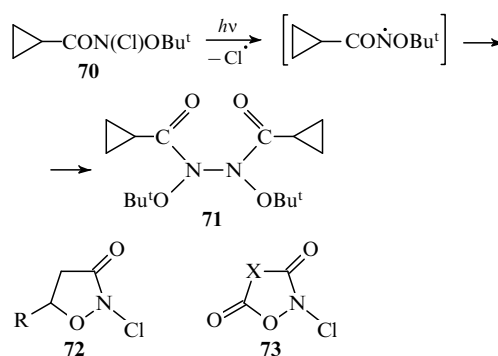


X = Br, I.

Conversely, *N*-chloro-*N*-methoxyamide **69** is stable under ordinary conditions; its photolysis is accompanied by rupture of the N–Cl bond and gives the hydrazine **67**, resulting from dimerisation of the intermediate *N*-methoxyamidyl radical, and compound **68**.^{13, 37}

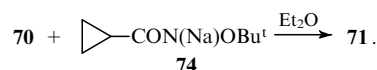


N-Alkoxyamidyl radicals have been detected by EPR spectroscopy during the photolysis of *N*-chloro-*O*-alkylhydroxamates **70**,¹⁰⁰ **72**, and **73**.¹⁰¹

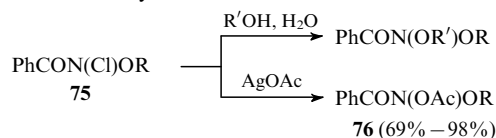


R = H, Ph; X = Et₂C, PhN, MeN.

Similarly to *N*-chloro-*N*-alkoxyureas, *N*-chloro-*O*-alkylhydroxamates are able to undergo nucleophilic substitution of chlorine. Thus reaction of the compound **70** with sodium salt **74** gives hydrazine derivative **71** in a quantitative yield.¹⁰⁰

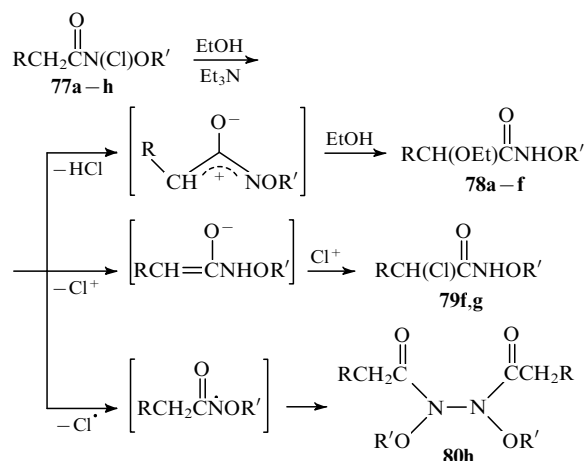


Two other reactions of *N*-chloro-*N*-alkoxybenzamides **75** — alcoholysis^{102, 103} and transformation into *N*-acetoxy-*N*-alkoxybenzamides **76** on treatment with silver acetate in ether — also proceed smoothly.^{102, 104}



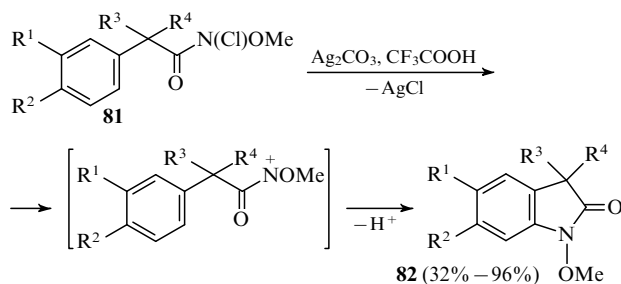
R = Et, Bu, C₈H₁₇, PhCH₂.

However, alcoholysis of *N*-chloro-*N*-alkoxyarylamides **77a–h** does not result in nucleophilic substitution of chlorine.¹⁰⁵ Depending on the nature of the substituent R, these reactions give mostly compounds **78–80**.



R = Ph, R' = Me (**a**), PhCH₂ (**b**), Bu¹ (**c**); R = 4-MeOC₆H₄, R' = Me (**d**); R = 2-naphthyl, R' = Me (**e**); R = 4-O₂NC₆H₄, R' = Me (**f**); R = PhCO, R' = PhCH₂ (**g**); R = PhCH₂, R' = Me (**h**).

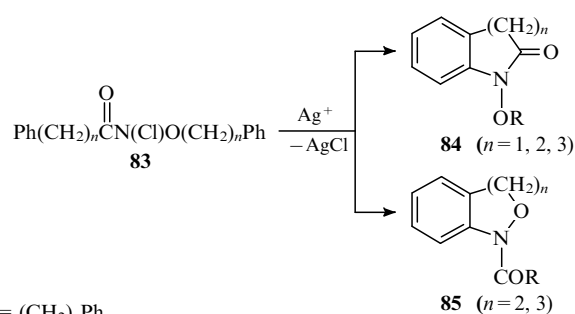
An important characteristic feature of *N*-chloro-*O*-alkylhydroxamates is their ability to be converted on treatment with Lewis acids into highly reactive intermediates, *N*-acyl-*N*-alkoxy-nitrenium ions,^{12–18, 33} which tend to undergo inter- and intramolecular electrophilic aromatic substitution. As a rule, these reactions occur at room temperature in the presence of metal ions (Ag⁺, Zn²⁺, Pd²⁺, Fe²⁺, Hg²⁺). The best results were achieved by using AgBF₄–THF, Ag₂CO₃–CF₃COOH, and Zn(OAc)₂–MeNO₂ systems. For instance, cyclisation of *N*-chloro-*N*-methoxyarylamides **81** is an efficient method for the synthesis of 2-hydroxy-1-methoxyindoles **82**.^{12, 14, 16–18}



R¹ = R³ = R⁴ = H, R² = Cl, Br, Me, MeCONH, NO₂; R¹ = R² = MeO, R³ = R⁴ = H; R¹ = R³ = R⁴ = H, R² = NO₂; R¹ = R⁴ = H, R² = MeO, R³ = Me; R¹ = H, R² = MeO, R³ = R⁴ = Me.

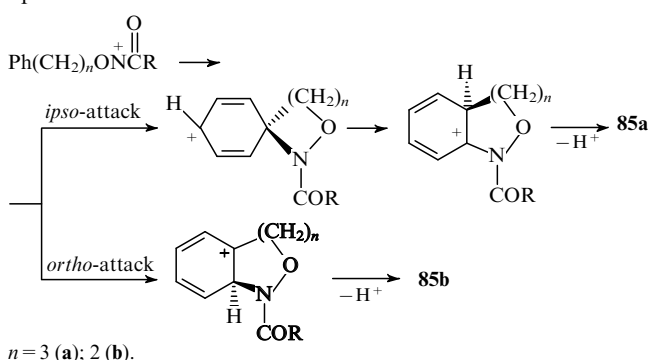
In principle, the electrophilic attack by the intermediate nitrenium ion is directed at one of three positions in the aromatic ring, C(1), C(2), or C(6).¹⁸ When the aromatic ring contains an *ortho*-substituent, the nitrenium ions attack C(2) and C(6).

Cyclisation of *N*-chloro-*O*-alkylhydroxamates **83** can involve the aromatic ring of both arylacyl and arylalkoxyl substituents.

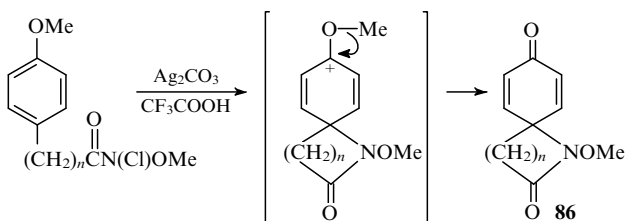


R = (CH₂)_nPh.

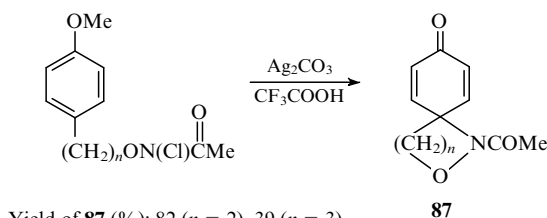
In the former case, the reaction yields γ, δ, and ε-*N*-alkoxy-lactams **84**, while in the latter case, it gives 2,1-benzoxazepines and 2,1-benzoxazines but not benzoxazoles. It was shown experimentally¹⁵ that benzoxazepines result from the *ipso*-attack of the intermediate nitrenium ion on the aromatic nucleus followed by 1,2-migration of the alkyl group, while benzoxazines are formed upon the *ortho*-attack.



The cyclisation of *N*-chloro-*O*-alkylhydroxamates containing an *ortho*- or *para*-methoxy-substituted aryl group occurs through the *ipso*-attack of the intermediate nitrenium ion on the aromatic ring and affords spirodienones.^{14, 18} For example, compounds **86** and **87** have been prepared in this way.¹⁸

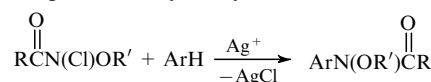


Yield of **86** (%): 71 (*n* = 1), 83 (*n* = 2), 83 (*n* = 3);



Yield of **87** (%): 82 (*n* = 2), 39 (*n* = 3).

N-Chloro-*O*-alkylhydroxamates are able to accomplish electrophilic amination of aromatic compounds in the presence of silver salts to give *N*-alkoxy-*N*-arylamides in 20%–93% yields.^{12–14, 16, 18}



ArH = C₆H₆, PhMe, *p*-MeC₆H₄, PhOMe, C₁₀H₈, PhCOOMe.

VII. Structure and stereochemistry

The stereoisomerism of molecules with a tricoordinated nitrogen atom is due to its pyramidal configuration. However, usual

N-alkylamines possess low configuration stabilities; the barriers to their pyramidal inversion ($\Delta G^\ddagger$) amount to 20–30 kJ mol⁻¹.^{106–108} An electronegative substituent at the nitrogen atom increases the inversion barriers by inducing rehybridisation of the bonding orbitals of the N atom accompanied by an increase in the *p*-character of the N–X σ -bond and, correspondingly, by an increase in the *s*-character of the nitrogen lone pair orbital.^{106–108} In addition, the planar transition state of the inversion is destabilised by the four-electron interaction between the lone pairs of the two linked heteroatoms. Both effects act in the same direction increasing the pyramidal stability. Indeed, the barriers to inversion in *N,N,O*-trialkylhydroxylamines¹⁰⁹ and in *N*-chloro-^{110,111} and *N*-fluoroamines¹¹¹ are as high as 40–50, 38, and 63 kJ mol⁻¹, respectively. The presence of two heteroatoms at the nitrogen atom in the O–N–Hal system accounts for the substantially increased configurational stability of the corresponding derivatives. In this case, the orbital $n_O-\sigma^*_{N-Hal}$ interaction also contributes to the stabilisation of the pyramidal configuration of the N atom.^{29,34,112,113} The inversion barriers in the *N*-chloro-*N,O*-dialkylhydroxylamines **3a,c,g** are 79–83 kJ mol⁻¹.⁴ The inversion barrier predicted⁴ for *N*-fluoro-*N,O*-dialkylhydroxylamines is 113 kJ mol⁻¹.

When the N atom is incorporated in a ring, its pyramidal stability further increases, because in this situation, the change of the nitrogen hybridisation to *sp*² in the planar transition state to inversion increases ring strain. Naturally, this effect is more pronounced in rigid bicyclic systems and in small rings. For instance, the inversion barrier in 2-chloro-1,2-oxazolidine **12** ($\Delta G^\ddagger = 87$ kJ mol⁻¹)^{19,20} is, on the average, 7 kJ mol⁻¹ higher than that in its acyclic analogues **3**.⁴ The nitrogen inversion in 2-chloro- and 2-fluoro-substituted perhalo-1,2-oxazetidines **11** is also hindered under normal conditions,²² and the corresponding 4-monochloro-derivatives have been obtained as stable invertomers.²³ The record-holding height of the barrier to the pyramidal inversion of nitrogen *via* a planar transition state ($\Delta H^\ddagger = 184.8$ kJ mol⁻¹) was predicted for non-substituted 2-chloroxaziridine by *ab initio* calculations in the 3–21G basis set.²⁶ However, the barrier for 2-chloroxaziridine found experimentally based on the kinetics of racemisation was almost three times lower ($\Delta H^\ddagger = 63.9$ kJ mol⁻¹, $\Delta S^\ddagger = 43.5$ e.u., and $\Delta G^\ddagger = 132$ kJ mol⁻¹ at 100 °C in *n*-heptane), and, besides, the rate of inversion increased by an order of magnitude on going to a polar solvent (*n*-butanol).²⁶ This was explained by assuming that in this case, inversion occurs by a dissociative mechanism, because inversion *via* a planar transition state is characterised by low $\Delta S^\ddagger$ values and slows down in polar solvents due to the more efficient solvation of the ground state, which is more polar (the calculation for 2-chloroxaziridine in the same basis set predicts the values $\mu = 2.7$ and 3.6 D for the transition and ground states, respectively). The transition state to the dissociative inversion is represented by a contact ion pair, because ionic mobility of chlorine is not manifested in reactions of 2-chloroxaziridines **8a–d** and **9a**.⁶⁵ The driving force of ionisation is the orbital $n_O-\sigma^*_{N-Cl}$ interaction, which results, according to the 2-chloroxaziridine structure optimised in the 6–31G* basis set, in a substantially lengthened N–Cl bond.²⁵

The introduction of a π -electron-withdrawing substituent to the nitrogen atom sharply decreases the barrier to its inversion, because π -conjugation is most efficient in the planar transition state.^{106,107} In fact, the calculated inversion barrier for *N*-chloro-*N*-formyl-*O*-methylhydroxylamine is only 10.5 kJ mol⁻¹.³⁴ For this compound, two other hindered processes can be expected, namely, amide rotation and rotation around the N–O bond with the maximum barriers of 47 and 55 kJ mol⁻¹, respectively.³⁴ The latter is ~ 10 kJ mol⁻¹ higher than the barriers to rotation around the N–O bond in *N,N,O*-trialkylhydroxylamines.¹⁰⁹ This increase in the barrier to the rotation around the N–O bond in *N*-chloro-*N*-formyl-*O*-methylhydroxylamine is due to the orbital $n_O-\sigma^*_{N-Cl}$ interaction, which makes the N–O bond ‘more double’.³⁴ The height of this barrier is in good agreement with the experimental $\Delta G^\ddagger_{N-O}$ value, equal to 58 kJ mol⁻¹, which was

determined for *N*-chloro-*N*-alkoxyurea **55g** by dynamic NMR.¹¹⁴ In *N*-chloro-*N*-alkoxyureas **55a,e,g**, hindered rotation around the Me₂N–C amide bond is also observed, the corresponding barriers being 60–67 kJ mol⁻¹.¹¹⁴

There are no experimental data about the structures of *N*-halohydroxylamines. The results of semiempirical and non-empirical calculations for 2-chloroxaziridine,^{25,65,115} *N*-chlorohydroxylamine,³³ *N*-chloro-*N*-methylhydroxylamine,⁶⁵ *N*-chloro-*N*-formylhydroxylamine,³³ *N*-chloro-*N*-formyl-*O*-methylhydroxylamine,³⁴ *N*-fluorohydroxylamine,^{116–121} *N,N*-difluorohydroxylamine,^{119,121} *N,O*-difluorohydroxylamine,^{119–121} trifluorohydroxylamine,^{119,121} and *N,N*-difluoro-*O*-fluorosulfonylhydroxylamine¹²² demonstrate that their geometry is affected by the anomeric $n_O-\sigma^*_{N-Hal}$ interaction, which is manifested as elongation of the N–Hal bonds and shortening of the N–O bonds in these compounds. In addition, it was shown that the energetically preferred conformation for *N*-chloro-³³ and *N*-fluorohydroxylamines^{116–121} as well as for *N*-chloro-*N*-formylhydroxylamine³³ and *N*-chloro-*N*-formyl-*O*-methylhydroxylamine³⁴ is that in which the H–O (or C–O) and N–Hal bonds are nearly perpendicular to each other and, hence, the anomeric $n_O-\sigma^*_{N-Hal}$ interaction is the maximum (Fig. 2, conformation A).

In the case of di- and trifluorohydroxylamines, conformation

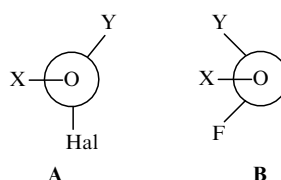
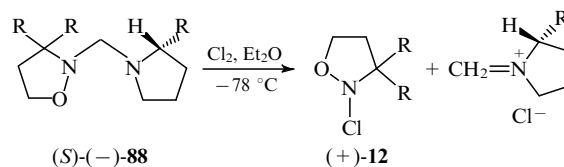


Figure 2. Newman projections along the O–N bond for *N*-halohydroxylamine derivatives XON(Y)Hal. **A:** X = Y = H, Hal = Cl, F; X = H, Y = HCO, Hal = Cl; X = Me, Y = HCO, Hal = Cl; **B:** X = H, Y = F; X = F, Y = H; X = Y = F.

B (Fig. 2) has been predicted to be more stable; this conformation is stabilised by the $n_N-\sigma^*_{O-F}$ interaction, which is the most efficient in *O*-fluorohydroxylamine.

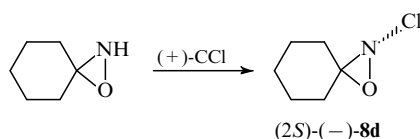
VIII. Optically active cyclic *N*-chlorohydroxylamines

The first optically active compound of this type, (+)-2-chloro-1,2-oxazolidine (+)-**12**, in which only the nitrogen atom was chiral, was prepared in a quantitative yield by cleavage of amination (*S*)-(-)-**88** by chlorine at –78 °C.^{19,20}

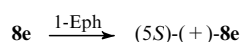
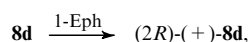


R = MeO₂C.

However, the time needed for its half-racemisation at 13 °C is only 8 min. The high configurational stability of 2-chloroxaziridines, the half-racemisation time of which at 20 °C is 833 years, made it possible to synthesise them in optically active forms by asymmetric chlorination and kinetic resolution.^{24,25}



CCl is *N*-chlorocamphorimide;



1-Eph is 1-ephedrine.

The absolute configurations of **8d** and **8e** were determined by NMR and CD methods.²⁵ The compound (5*S*)-(+)-**8e** was prepared as a mixture of two diastereoisomers in a ratio of 1.5:1, the absolute configuration of the predominant isomer being (2*R*,3*S*,5*S*). The sign of the Cotton effect of the long-wave band in the CD spectrum of optically active 2-chloroxaziridines was shown to be mostly determined by the absolute configuration of the N atom and to depend only slightly on the configurations of the carbon chiral centres.²⁵

IX. Conclusion

Analysis of the published data demonstrates that during the four decades of studies on the chemistry of *N*-halohydroxylamine derivatives, substantial progress has been achieved in this field. All main types of these compounds have been synthesised, namely, acyclic and cyclic *N*-halo-*N*,*O*-dialkylhydroxylamines, *N*-fluoro-*N*-alkoxy-*O*-alkylhydroxylamines, derivatives of *N*,*N*-difluorohydroxylamine, and *N*-halo-*N*-alkoxyamides. It was found that *N*-halo-*O*-alkylhydroxylamines and *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines are thermally unstable under ambient conditions; nevertheless, they can be involved *in situ* in various chemical reactions.

The halogen atom in most of the systems containing the O–N–Hal triad can be easily removed as the anion, which is due to the hyperconjugation $n_{\text{O}}-\sigma^*_{\text{N-Hal}}$. Hence, *N*-chloro-*N*-tert-alkyl- and *N*-chloro-*N*-alkoxy-*O*-alkylhydroxylamines are powerful alkoxyaminating reagents.

A fundamentally important result obtained along this line is the discovered possibility of nucleophilic substitution of chlorine in '*N*-chloramides': *N*-chloro-*N*-alkoxyureas and *N*-chloro-*O*-alkylhydroxamates the chlorine atom of which, unlike that in their *N*-alkyl analogues, possesses anionic mobility. Under the action of Lewis acids, *N*-chloro-*O*-alkylhydroxamates form highly reactive intermediates, *N*-acyl-*N*-alkoxynitrenium ions, capable of reacting with aromatic compounds in intermolecular and intramolecular processes of electrophilic aromatic substitution.

Compounds containing O–N–Hal fragments belong to one of the few types of derivatives characterised by high pyramidal stability of the nitrogen atom. As a result, 2-chloroxaziridines and 2-chloro-1,2-oxazolidine derivatives have been partially resolved into optical antipodes with an asymmetric N atom.

The orbital $n_{\text{O}}-\sigma^*_{\text{N-Hal}}$ interaction in O–N–Hal systems accounts for the predominant existence of the conformation with nearly *anti*-periplanar *p*-orbital of the oxygen atom in relation to the N–Hal bond.

N-Amino-substituted derivatives of *N*-halo-*O*-alkylhydroxylamines remained beyond the scope of this review, because, similarly to *N*-halohydrazines, they exist entirely as alkoxydiazonium salts $\text{R}_2\text{N}^+=\text{NOR Hal}^-$.¹²³ These compounds act as aminoaminating reagents and undergo *O*-dealkylation upon treatment with nucleophiles [see Scheme 1, pathways (a) and (b)].

The vicinal orbital interaction considered for the O–N–Hal system and related anomeric effects are typical properties of many other geminal systems, for example, N–E–Hal and O–E–Hal, where E = C, N, O, P, S.

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

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

^c — *Chem. Heterocycl. Compd. (Engl. Transl.)*

Organic derivatives of monocoordinated tellurium

I D Sadekov, A A Maksimenko, V L Nivorozhkin

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Abstract. Data on the methods of synthesis, structures, and reactivity of organic derivatives of monocoordinated tellurium, namely, compounds with C=Te bonds and phosphine tellurides $R_3P=Te$, are described systematically and generalised. The use of the latter compounds as synthetic equivalents of elemental tellurium for the preparation of metal tellurides is considered. The bibliography includes 139 references.

I. Introduction

Organic derivatives of monocoordinated tellurium, namely, compounds with C=Te bonds and phosphine tellurides $R_3P=Te$, constitute a relatively little studied class of organotellurium compounds. In fact, the first phosphine telluride, tributylphosphine telluride, was synthesised in 1963,¹ while the first and still the only one known stable telluroketone, 1,1,3,3-tetramethylindanetellone, which is stable only in solution, was synthesised only in 1993.² The synthesis, structure, and chemical properties of tellurocarbonyl compounds and phosphine tellurides have been considered most comprehensively in a monograph devoted to the chemistry of organic derivatives of selenium and tellurium.^{3,4} However, during more than a decade, which has passed after the publication of this monograph, the number of studies dealing with the derivatives of monocoordinated tellurium has approximately doubled. New fields of application of tellurocarbonyl compounds have been discovered, for example, as dienophiles in the syntheses of six- and seven-membered tellurium-containing heterocycles. Of special interest is the use of phosphine tellurides as synthetic analogues of elemental tellurium for the synthesis of some organotellurium compounds, which undergo thermal decomposition under relatively mild conditions to give metal tellurides⁵ possessing semiconductor and other valuable properties.

II. Synthesis and reactions of compounds containing C=Te bonds

Up to now, four types of tellurocarbonyl compounds have been described in the literature: telluroketones (telluroaldehydes) $R_2C=Te$ ($R = H, \text{Alk}, \text{or Ar}$), tellurocarboxylic acids

$RC(=Te)OH$, *O*-alkyl tellurocarboxylates $RC(=Te)OR^1$, and telluroamides $RC(=Te)NR^1R^2$ and their analogues (tellurohydrazides and telluroureas). These compounds sharply differ in stability. Only representatives of the two latter types have been isolated in a pure state. The formation of telluroketones (telluroaldehydes) and tellurocarboxylic acids is judged either from the NMR spectra of reaction mixtures or from the products of their chemical transformations. However, the stability of tellurocarbonyl compounds of all these types is substantially enhanced when the tellurocarbonyl carbon atom carries bulky organic substituents or relatively strong π -electron-donating groups ($OR, NR_2, NR^1NR_2^2$) or upon coordination to transition metal compounds. It should be noted that one of the most efficient methods used to increase the stability of other classes of organotellurium derivatives, such as tellurenyl halides, azides, acetates, and isothiocyanates, diorganyl tritellurides, *etc.*, has not been used so far in the chemistry of tellurocarbonyl compounds. This method consists in the introduction, into appropriate positions of aryl or alkenyl substituents of functional groups ($CHO, COR, CO_2R, NO_2, N=N, CH=N, CH_2NMe_2$, *etc.*) containing sp^2 (or, more rarely, sp^3) hybridised O or N atoms, which form strong intramolecular coordination bonds with Te atoms.⁶

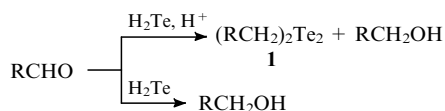
1. Telluroaldehydes and telluroketones

Despite the apparent similarity of chalcogens (S, Se, Te),⁷ their properties are appreciably different; therefore, in some cases, methods that are used successfully for the synthesis of organic derivatives of sulfur and selenium cannot be used to prepare their tellurium analogues. For example, 'dialkyl telluroketones' have been described in a study,¹⁰ which is cited in monographs dealing with the chemistry of organotellurium compounds.^{8,9} They were synthesised by a method similar to a method used to prepare thioketones, namely, by the reaction of the corresponding ketones with H_2Te in a strongly acidic medium. However, in reality, the reactions of H_2Te , generated *in situ* from aluminium telluride and water, with aldehydes and ketones afford alcohols¹¹ or mixtures of dialkyl ditellurides with alcohols.¹² Alcohols are formed in 50%–100% yields when H_2Te is passed through solutions of carbonyl compounds in THF.¹¹ When solutions of aldehydes contain strong acids ($CF_3COOH, PhSO_3H, H_2SO_4$), dialkyl ditellurides **1** are formed as the main reaction products (yields 34%–56%); in this case, only traces of primary aliphatic alcohols are formed.¹² Ketones react in a similar way, but the yields of the corresponding dialkyl and di(cycloalkyl) ditellurides are lower.¹²

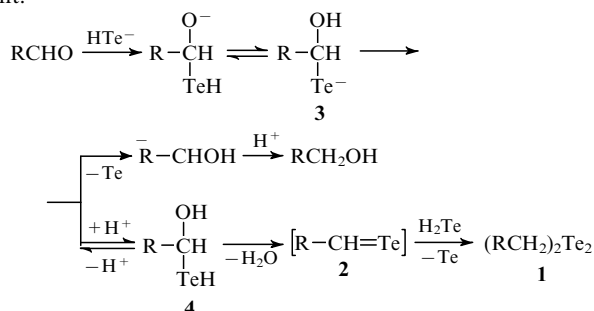
I D Sadekov, A A Maksimenko, V L Nivorozhkin Research Institute of Physical and Organic Chemistry of the Rostov State University, prosp. Stachki 194/2, 344090 Rostov-on-Don, Russian Federation. Fax (7-863) 228 56 67. Tel. (7-863) 228 08 94 (I D Sadekov)

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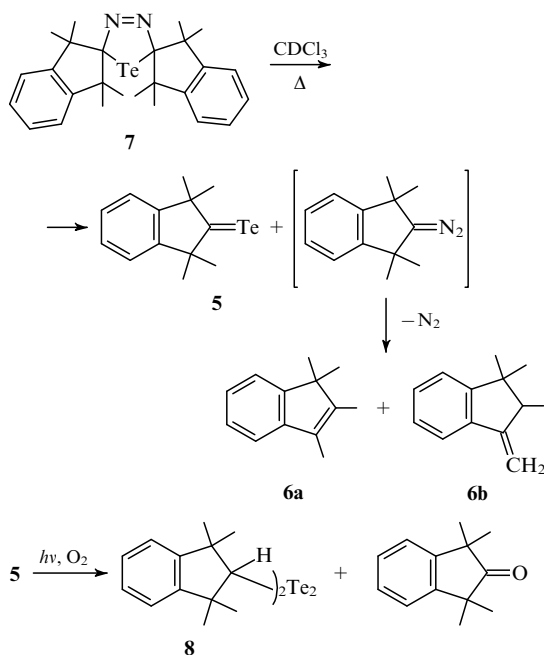


According to the scheme proposed by the researchers cited,¹² the ditellurides **1** result from the reduction of telluroaldehydes **2** with hydrogen telluride. The influence of pH on the outcome of these reactions is due to the fact that in strongly acidic media the acid–base equilibrium $3 \rightleftharpoons 4$ is almost entirely shifted to the right:



a. Stable telluroketones

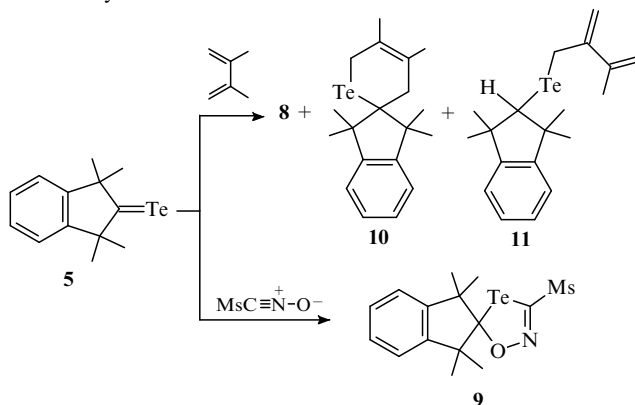
As noted above, 1,1,3,3-tetramethylindanetellone **5** is the only stable, although only in solution, telluroketone that has been characterised by various spectroscopic methods.² This compound was obtained in an almost quantitative yield, together with alkenes **6a** and **6b**, upon thermolysis of 1,3,4-tellurodiazoline **7**; the compound **7** was synthesised in 26% yield by treating the hydrazone of 1,1,3,3-tetramethylindanone with tellurium dichloride in the presence of Et₃N.¹³



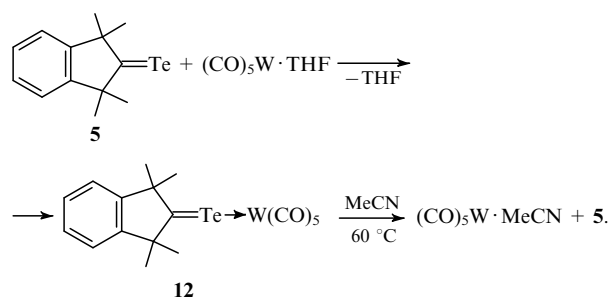
The telluroketone **5** is very sensitive to oxygen and light; on exposure to UV radiation, it is converted into a mixture of ditelluride **8** and 1,1,3,3-tetramethylindanone.² The ¹³C NMR signal for the C=Te-group carbon atom (δ 301 ppm) is substantially shifted downfield with respect to the signals for other C=X groups (C=O, δ 226.0 ppm; C=S, δ 282.1 ppm; C=Se, δ 294.0 ppm). The same is true for the ¹²⁵Te signal (δ 2858.3 ppm in relation to Me₂Te), which is the lowest-field signal in the series of organotellurium compounds known. The long-wave absorption band (λ = 825 nm) in the UV spectrum of the ketone **5** undergoes substantial bathochromic shift with

respect to the bands of the corresponding selenium (λ = 667 nm) and sulfur (λ = 527 nm) derivatives.

The compound **5** enters into 1,3-dipolar cycloaddition with mesitylnitrile oxide yielding a derivative of a new heterocyclic system, oxatellurazole **9**. Like other tellurocarbonyl compounds (see below), the ketone **5** enters into the Diels–Alder reaction with 2,3-dimethylbutadiene² to give compounds **11** and **8** in addition to 1-telluracyclohex-3-ene derivative **10**.



The complex **12** was synthesised in a yield of more than 70% by the reaction of the telluroketone **5** with the complex (CO)₅W·THF.¹⁴ Earlier, complexes of this type had been obtained only by insertion of a Te atom into C=M bonds in transition metal complexes.

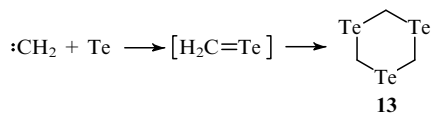


The compound **12** was isolated as dark-violet crystals. Unlike the initial telluroketone, it is resistant to heating and exposure to light. The signals for the C=Te-group atoms in the ¹³C and ¹²⁵Te NMR spectra are shifted upfield with respect to the corresponding signals in the spectra of **5**; they are manifested at δ 285 and 1783 ppm, respectively. The C=Te bond length in the complex **12** found by X-ray diffraction analysis¹⁴ amounts to 1.987 Å, which is close to the length of the similar bond in S=C=Te (1.904 Å);¹⁵ this indicates that the order of the C=Te bond in **12** is closer to two. The telluroketone **5** is a relatively weak donor; in fact, when the complex **12** is heated in MeCN at 60 °C, the tellurium-containing ligand is quantitatively replaced by MeCN.

b. Methods for the generation of unstable telluroaldehydes and telluroketones. Dimerisation and the Diels–Alder reaction

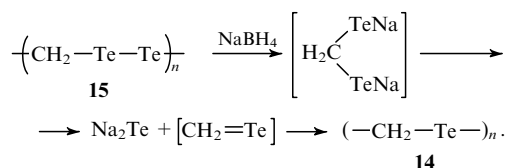
All the telluroaldehydes and telluroketones, except for the ketone **5**, are unstable. Conclusions about the formation of these compounds are based on the structures of products of their subsequent chemical transformations, first of all, dimerisation (or trimerisation in the case of telluroformaldehyde) and the Diels–Alder reaction.

Telluroformaldehyde was the first telluroaldehyde reported in the literature. It was obtained by treatment of tellurium mirrors with the carbene generated by thermal decomposition of diazomethane^{16–18} or by photodissociation of ketene.¹⁷ On cooling, the gaseous monomeric telluroformaldehyde trimerises to yield 1,3,5-tritelluracyclohexane **13**.



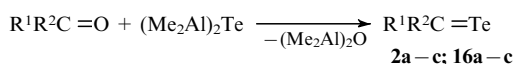
The structure of the heterocyclic compound **13** was confirmed by IR spectroscopy and mass spectrometry.¹⁸ The reactions of the compound **13** with bromine or iodine give the corresponding dihalomethanes.¹⁷

Apart from the trimer **13**, telluroformaldehyde can also exist as a polymeric form, poly(methylene telluride) **14**. Disodium methaneditelluroate resulting from reduction of poly(methylene ditelluride) **15**¹⁹ with sodium tetrahydridoborate in ethanol disproportionates into sodium telluride and telluroformaldehyde, which then polymerises to give the polytelluride **14**.²⁰



It has been suggested²¹ that the synthesis of poly(methylene telluride) occurs according to a scheme which includes reduction of the polyditelluride **15** with sodium tetrahydridoborate in methanol and alkylation of sodium methyleneditelluroate with dibromo(or diiodo)methane. In our opinion, this mechanism is erroneous. We believe that the polymer **14** results from disproportionation of the dianion as described above rather than from the alkylation.

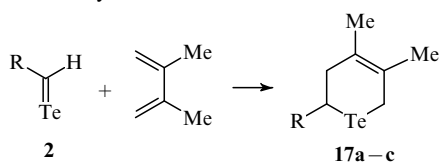
Although in recent years several methods for the generation of telluroaldehydes and telluroketones have been developed, it is fairly difficult to judge their synthetic potential, because their chemical properties have not been extensively studied. The most efficient method for the preparation of telluroaldehydes **2** and telluroketones **16** is the reaction of bis(dimethylaluminium) telluride with aldehydes or ketones in boiling dioxane.^{22,23} The driving force of these reactions is the formation of thermodynamically favourable Al–O bonds.



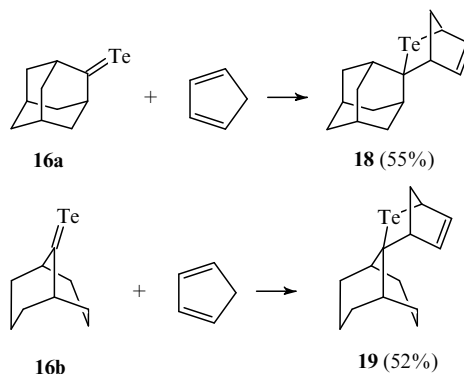
$\text{R}^1 = \text{H}; \text{R}^2 = \text{Ph}$ (**2a**), Pr (**2b**), Bu^t (**2c**);²²

$\text{R}^1, \text{R}^2 =$  (**16a**),  (**16b**);²² $\text{R}^1 = \text{R}^2 = \text{C}_5\text{H}_5\text{FeC}_5\text{H}_4$ (**16c**).²³

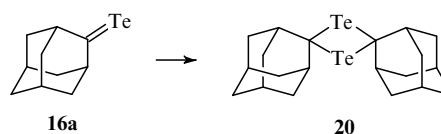
The tellurocarbonyl compounds **2** and **16** formed initially can be trapped by 2,3-dimethylbutadiene or cyclopentadiene; this gives Diels–Alder adducts **17–19** in 44%–62% yields.²² These reactions are the only methods known to date for the synthesis of 1-telluracyclohex-3-enes²⁴ and 2-tellurabicyclo[2.2.1]hept-5-enes. The formation of the telluroketone **16c** is indicated by the blue colouration of the solution. Owing to the low stability of this compound, it was impossible to determine its spectral characteristics. Unlike the sulfur and selenium analogues which form complexes with pentacarbonylchromium and -tungsten, the reaction of the ketone **16c** with $(\text{CO})_5\text{M} \cdot \text{THF}$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) occurs as detelluration and affords tetraferrocenylethylene in a quantitative yield.²³



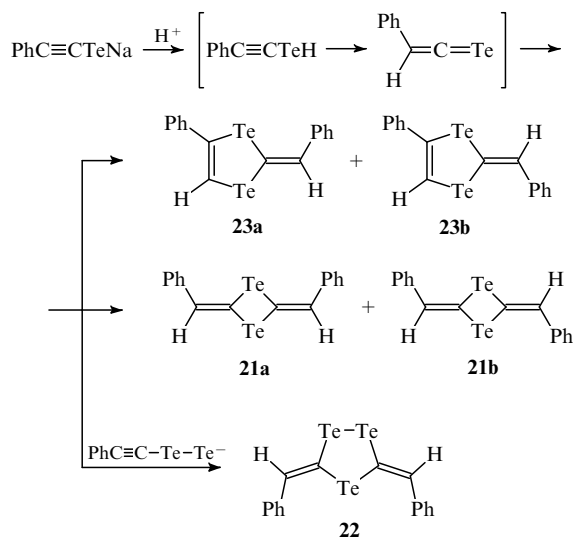
$\text{R} = \text{Ph}$ [**17a**, (49%)]; Pr [**17b**, (44%)]; Bu^t [**17c**, (62%)].



In the absence of dienes, the ketone **16a** dimerises to give 1,3-ditellurethane derivative **20** (yield 28%);²² reactions of this type for other ketones have not been reported.

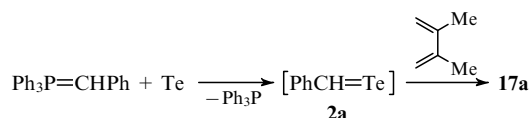


It is noteworthy that the first ditelluretanes, *cis*- (**21a**) and *trans*- (**21b**) 2,4-dibenzylidene-1,3-ditelluretanes (the structure of the *trans*-isomer was confirmed by X-ray diffraction analysis²⁵), were obtained in low yields upon protonation of sodium phenylethynyltelluroate with a solution of HCl in ether.^{25,26} It has been reported²⁷ that ditellurethane **21a** and *cis*-3,5-dibenzylidene-1,2,4-tritellurole **22** are the main products of this reaction; the structure of the latter was determined by X-ray diffraction analysis.²⁷ The protonation of sodium phenylethynyltelluroate with CF_3COOH affords a mixture consisting of **21a** and *cis*- and *trans*-2,6-diphenyl-1,4-ditellurafulvalene, **23a** and **23b**, respectively.²⁸ Apparently, these reactions involve intermediate formation of a telluroketone, which either dimerises yielding the compounds **21** or **23**, or reacts with phenylethynyltelluroate anion being thus converted into the tritellurole **22**.²⁷



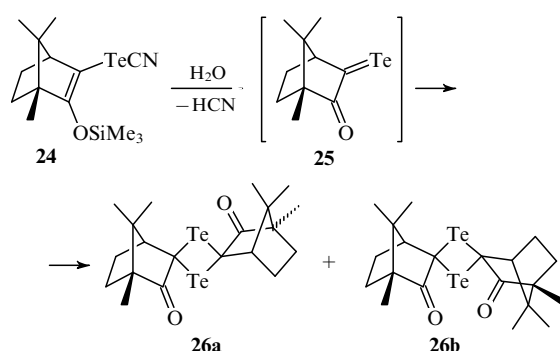
Tellurium-containing heterocycles have also been synthesised from tellurocarbonyl compounds generated by other methods. One of these methods, which has been used previously in the chemistry of selenoaldehydes,²⁹ is based on the reaction of benzylidenetriphenylphosphorane with powdered tellurium in boiling toluene.³⁰ The resulting tellurobenzaldehyde **2a** is trapped by 2,3-dimethylbutadiene to give the heterocyclic derivative **17a** in a yield of only 11%. This way of generation of telluroaldehydes is much less efficient than the method described above in which bis(dimethylaluminium) telluride acts as the tellurating reagent.

In view of the fact that phosphine tellurides (see below) are efficient synthetic analogues of elemental Te, it would be of interest to check whether these compounds could be used in this reaction instead of elemental Te.

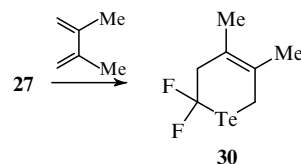
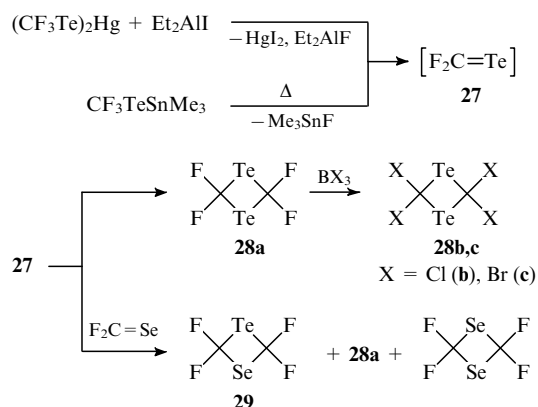


The reaction of the phosphorane with an equimolar or catalytic amount of tellurium in the absence of a diene affords only *trans*-stilbene in a yield of more than 60%.³⁰

Yet another way of generating telluroketones, which has also been borrowed from the chemistry of organoselenium derivatives,³¹ consists in the elimination of HCN from tellurocyanate **24**.³² Hydrolysis of this compound under anaerobic conditions gives rise to a mixture of the *anti*- and *syn*-isomers of 1,3-ditelluretane **26a** and **26b** (yields 45% and 6%, respectively) resulting from dimerisation of the intermediate telluroketone **25**.

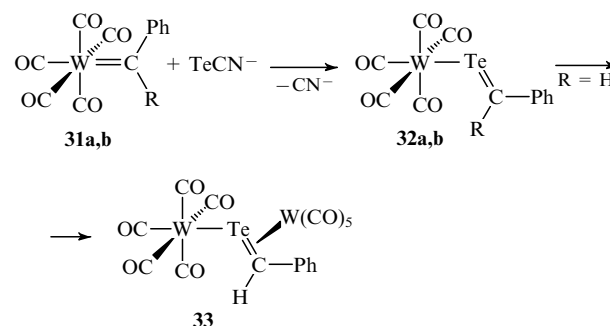


One more approach to the generation of tellurocarbonyl compounds reported in the literature, which is not associated with their formation from transition metal complexes, has been studied in relation to tellurocarbonyl difluoride **27**.^{33,34} This compound is formed in a fairly low yield upon treatment of bis(trifluoromethyltelluro)mercury with diethylaluminium iodide and rapidly dimerises to give 2,2,4,4-tetrafluoro-1,3-ditelluretane **28a**.^{33,34} The telluretane **28a** was obtained in higher yields (50%–60%) by pyrolysis of trifluoromethyltellurotrimethylstannane.³⁴ Co-condensation of the compound **27** with selenocarbonyl difluoride results in the formation of 2,2,4,4-tetrafluoro-1-selena-3-telluretane **29**.³⁴ The reaction of the compound **27** with 2,3-dimethylbutadiene gives 6,6-difluoro-3,4-dimethyl-1-telluracyclohex-3-ene **30**. This heterocyclic derivative was prepared in 48% yield by heating trifluoromethyltellurotrimethylstannane with 2,3-dimethylbutadiene in a sealed tube. The synthesis of dichloro- and dibromotelluretanes **28b,c** by treatment of the tetrafluoride **28a** with boron halides also deserves attention.³⁴



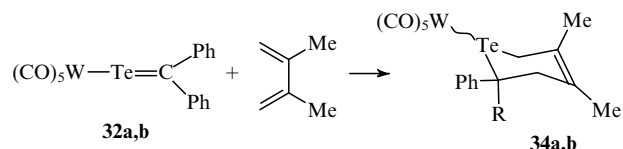
c. Telluration of transition metal complexes

Yet another method for stabilisation of telluroaldehydes and telluroketones is the formation of complexes with transition metal compounds. These complexes, unlike the complex of telluroketone with pentacarbonyltungsten (**12**) described above,¹⁴ are formed upon interaction of metal complexes of various structures with tellurium-containing nucleophiles or elemental tellurium, TeCN[−] and HTe[−] being usually employed as the tellurium-containing nucleophiles. For example, complexes **32a**³⁵ and **32b**³⁶ have been obtained in 18% and 12% yields, respectively, by the reaction of complexes **31** with TeCN[−]. The complex **32a** is thermally fairly unstable and is readily converted into binuclear complex **33** (the yield given above refers to **33**).



R = H (**a**), Ph (**b**).

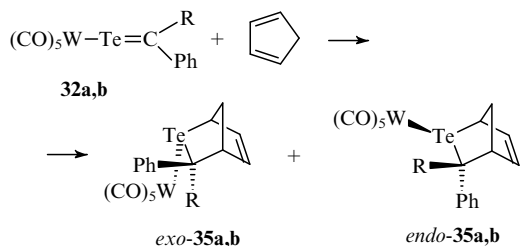
The complexes **32** enter into reactions typical of tellurocarbonyl derivatives, in particular, into the Diels–Alder reaction, *i.e.* they behave similarly to ‘free’ tellurocarbonyl compounds. Their reaction with 2,3-dimethylbutadiene leads to pentacarbonyltungsten complexes of 1-tellura-3,4-dimethylcyclohex-3-enes **34a,b** in 12%³⁷ and 8%³⁶ yields, respectively. It has been reported³⁷ that the reactivity of complexes of the (CO)₅W–X=CPh₂ type, where X = S, Se, and Te, sharply increases in the series S < Se < Te. In fact, whereas the reaction of **32b** with 2,3-dimethylbutadiene at −25 °C is completed over a period of 45 min, the reaction of the selenium analogue with the same diene requires 10 hours at room temperature. Finally, pentacarbonyl(diphenylthione)tungsten does not react with this diene at all under these conditions.



R = H (**a**), Ph (**b**).

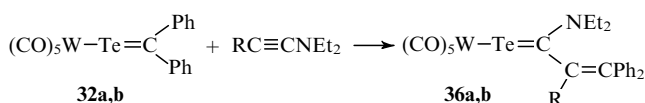
The complex **34a** exists in solution as an equilibrium mixture of two conformers in which the Ph group occupies an equatorial position.³⁶

The reactions of the complexes **32** with cyclopentadiene occur faster than with 2,3-dimethylbutadiene and afford tungsten complexes of 2-tellurabicyclo[2.2.1]hept-5-enes **35a,b**^{36,37} in 31% and 24% yields, respectively. The formation of the complex **35a** is highly stereoselective: the ratio of the *exo*- and *endo*-isomers is 11:1.³⁶ The structure of the major isomer, *exo*-**35a**, was established by X-ray diffraction analysis.³⁶



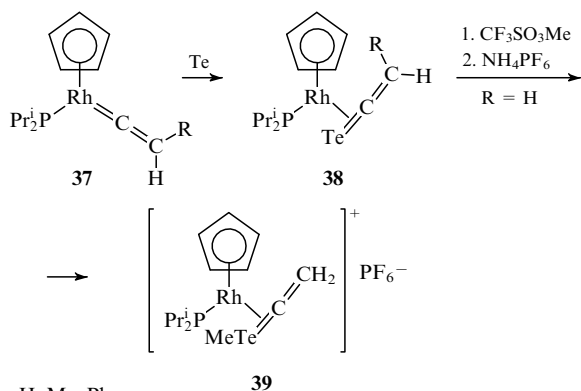
R = H (a); Ph (b).

Reactions of the complex **32b** with 1-diethylaminoprop-1-yne and bis(diethylamino)acetylene have also been studied.³⁸ They occur as [2 + 2]-cycloaddition followed by electrocyclic ring opening and give rise to telluroacrylamide complexes **36a,b**.³⁸ The complex **36b** decomposes on prolonged heating in an ethereal solution under a CO atmosphere to give $\text{W}(\text{CO})_6$, Te, and $\text{Et}_2\text{NCH}=\text{C}(\text{NEt}_2)\text{CHPh}_2$.



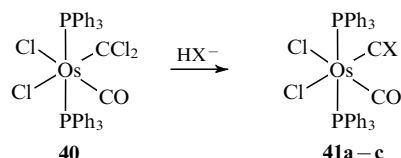
R = Me (**36a**), NEt_2 (**36b**).

Metal complexes have also been used to stabilise chalcogenokenes including telluroketenes.³⁹ Complexes **38** as well as their sulfur and selenium analogues have been synthesised in relatively high yields (68%–87%) by the reaction of vinylidene rhodium complexes **37** with chalcogens in benzene. Methylation of **38** (R = H) with methyl triflate and subsequent treatment with NH_4PF_6 results in the formation of an ionic complex **39**.³⁹



R = H, Me, Ph.

Finally, we would like to mention the synthesis of tellurocarbonyl complex **41a** (X = Te) in which the $\text{C}=\text{Te}$ group acts as a carbonyl ligand.⁴⁰ The complex **41a** as well as its sulfur (**41b**) and selenium (**41c**) analogues were obtained as crystals, stable in air, on treatment of osmium dichlorocarbene complex **40** with HX^- anions (X = S, Se, Te).

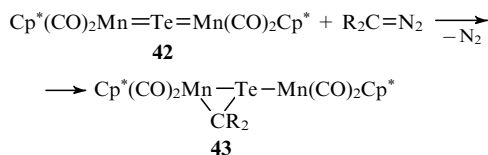


X = Te (a), S (b), Se (c).

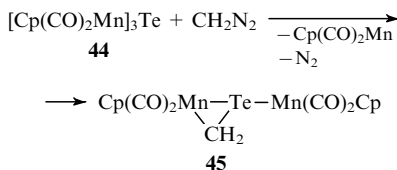
The $\nu(\text{C}=\text{X})$ absorption frequencies in the IR spectra of the complexes **41a-c** regularly decrease in the order S (1315 cm^{-1}) > Se (1156 cm^{-1}) > Te (1056 cm^{-1}).⁴⁰

The tellurium-containing groups in the complexes **32** and **38** are bound to metal atoms either through the Te atom or by the $\text{C}=\text{Te}$ double bond, i.e. these compounds are η^1 -complexes. At

the same time, a number of heterobinuclear μ -alkylidene complexes of the dimetallacyclopropane type containing C and M in three-membered rings have also been described. Complexes of this type, for example, **43** and **45**, have been prepared as blue crystalline compounds by treatment of the manganese complexes **42**⁴¹ or **44**⁴² with diazoalkanes.^{41, 43}

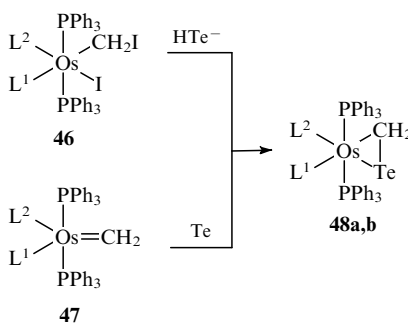


R = H, Me; Cp^* is C_5Me_5 .



Cp is C_5H_5 .

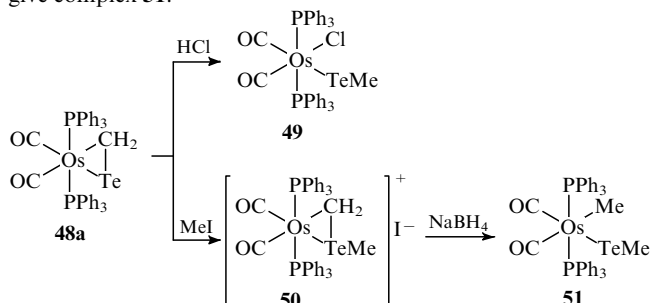
The reactions of osmium complexes **46**⁴⁴ and **47**⁴⁵ with hydrogentelluride anions⁴⁴ or elemental tellurium⁴⁵ resulted in the formation of telluroformaldehyde complexes **48a,b**.



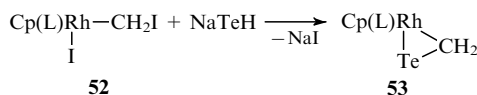
$\text{L}^1 = \text{L}^2 = \text{CO}$ (**46**, **48a**);

$\text{L}^1 = \text{NO}$, $\text{L}^2 = \text{Cl}$ (**47**, **48b**).

The reaction of the complex **48a** with HCl involves the $\text{Os}-\text{CH}_2$ bond and gives rise to complex **49**.⁴³ In the reaction with methyl iodide, the attack is directed at the tellurium atom; the cationic complex **50** thus formed is easily reduced by sodium tetrahydridoborate with opening of the three-membered ring to give complex **51**.⁴⁴



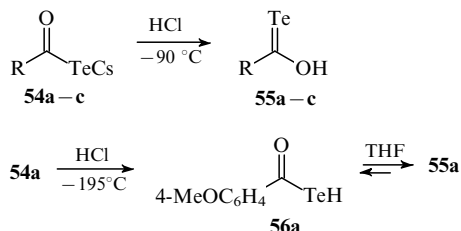
Rhodium complexes **53** containing rigid three-membered rings have been synthesised in relatively low yields by reaction of rhodium complexes **52** with sodium hydrogentelluride.^{46, 47}



L = Me_3P ,^{46, 47} Pr_3P ,⁴⁷ CO.⁴⁷

2. Telluronic acids

The synthesis and some reactions of tellurocarboxylic acids have been described only quite recently. These acids were prepared by acidolysis of the corresponding cesium tellurocarboxylates **54** with an ethereal solution of HCl.⁴⁸ At low temperatures in a polar solvent like THF, they exist mostly as the telluoroxo form **55** (telluronic acids).⁴⁸



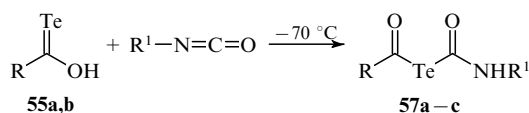
R = 4-MeOC₆H₄ (a), 4-MeC₆H₄ (b), Me₃C (c).

The structure of the acids **55** has been confirmed by their spectral characteristics. The ¹H and ¹³C NMR spectra of these compounds recorded at -90 °C contain no signals corresponding to the TeH and C=O groups present in the isomeric tellurolic acids **56**. The singlets observed at δ 16.02, 16.48 and at δ 222.9, 223.1 ppm were attributed to the OH and C=Te fragments of the acids **55a** and **55b**, respectively. When the temperature was raised to -70 °C, the signals mentioned above were markedly broadened; this was attributed⁴⁸ to a dynamic exchange process involving the formation and rupture of hydrogen bonds (Te-H...O, O-H...O) in the above equilibrium. The telluoroxo structure of these compounds is also supported by the magnitudes of ¹²⁵Te chemical shifts (δ 952 ppm for **55a** and δ 1024 ppm for **55b**). The acids of the aromatic series are coloured dark-green (λ_{max} = 652 and 673 nm for **55a** and **55b**, respectively), whereas tellurotrimethylacetic acid **55c** is blue-violet (λ_{max} = 594 nm).

The isomeric tellurobenzoic Te-acid **56a** was prepared by treatment of the salt **54a** with liquid hydrogen chloride at -195 °C followed by raising the temperature to -90 °C. At -110 °C, the dark-brown salt **54a** was converted into the solid yellow acid **56a**, which is soluble in toluene at -90 °C. The signal observed in the ¹²⁵Te NMR spectrum of this compound at δ 535 ppm was assigned to the TeH group. When THF was added to the resulting solution, the acid **56a** was converted into the isomeric acid **55a**.⁴⁸

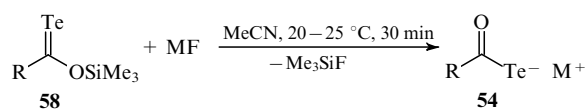
Tellurocarboxylic acids of both types are unstable at ambient temperature and are very sensitive to oxygen; on exposure to air even at -90 °C, they immediately decompose with liberation of elemental Te. The tellurolic acids **56** are appreciably less stable than telluronic acids **55**.⁴⁸

Tellurocarboxylic acids **55a,b** react with aryl isocyanates in THF or CH₂Cl₂ at -70 °C to give stable acyl carbamoyl tellurides **57a-c**, their yields exceeding 80%.⁴⁸



R = 4-MeOC₆H₄; R¹ = Ph (**57a**), 4-MeC₆H₄ (**57b**);
R = 4-MeC₆H₄; R¹ = Ph (**57c**).

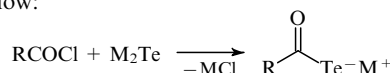
The synthesis of free acids from their salts proved to be possible only for cesium salts.⁴⁹ These salts, which are relatively stable (for R = Ar) under an inert atmosphere, as well as their rubidium analogues, have been prepared in 40%–60% yields by the reactions of *O*-trimethylsilyl tellurocarboxylates **58** (see Section II.3) with cesium and rubidium fluorides.⁴⁹



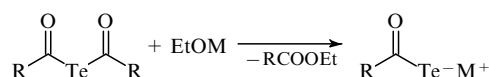
M = Cs, Rb; R = Me, Bu^t, Ph, 2-MeC₆H₄, 4-MeC₆H₄, 2-MeOC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄.

The presence of a carbonyl group in the compounds **54** was confirmed by an X-ray diffraction study of Te-cesium 2-methoxytellurobenzoate **54a**.⁴⁹

It should be noted that salts of type **54** containing lighter alkali metal cations, that is, lithium,⁵⁰ sodium^{51,52} and potassium,⁵³ have been synthesised earlier using one of the reactions presented below:



M = Li, Na.

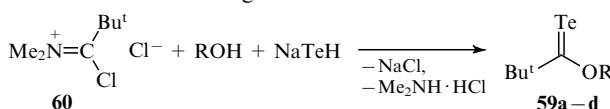


M = Na, K.

However, it was impossible to carry out X-ray diffraction analyses of these salts, because they were sensitive to oxygen and thermally unstable and, hence, it was difficult to purify them. The same features precluded preparation of the corresponding acids from these salts.

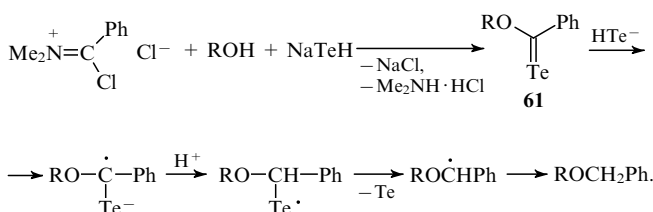
3. *O*-Alkyl and *O*-trimethylsilyl tellurocarboxylates

O-Alkyl tellurocarboxylates **59** were the first representatives of organotellurium compounds with the C=Te bond to be isolated in a pure state. These compounds were prepared by Barton *et al.*^{54,55} by the reaction of (1-chloro-2,2-dimethylpropylidene)dimethylammonium chloride **60** with alcohols and sodium hydrogentelluride, synthesised from NaBH₄ and Te in ethanol in the absence of air and light.



R = CH₂Bu^t (a), (–)-menthyl (b), adamantylmethyl (c),
5α-cholestan-3β-yl (d), Δ⁹-tigogenyl-3 (e).

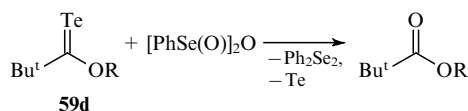
The yields of the compounds **59** varied over wide limits, namely, from 6% in the case of **59b** to 91% for **59c**. Evidently, the higher stability of the compound **59a** is due to the presence of bulky *tert*-butyl groups in their molecules. In fact, when the analogous phenyl derivative is used instead of the chloride **60**, the reactions with alcohols and sodium hydrogentelluride afford the corresponding benzyl ethers as the final products. Tellurobenzoates **61** were postulated as intermediate compounds.^{56,57}



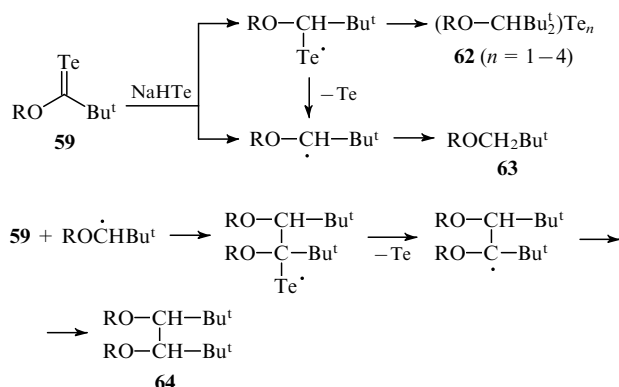
Since these reactions occur under relatively mild conditions, it was proposed^{56,57} to use them for protecting hydroxy groups in carbohydrates and other compounds, labile in alkaline media.

The compounds **59** are coloured violet, which is due to absorption of the tellurocarbonyl chromophore with $\lambda_{\max} = 584\text{--}596\text{ nm}$; the ^{13}C NMR signals for the carbon nuclei of the $\text{C}=\text{Te}$ group occur at $\delta\ 229\text{ ppm}$.^{54,55}

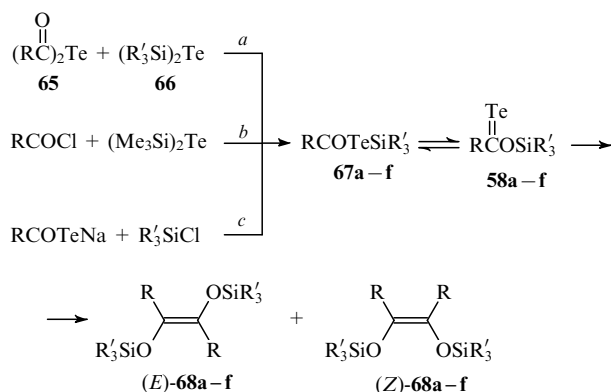
The esters **59** are quite stable to atmospheric oxygen in the dark. However, they are readily oxidised by phenylseleninic anhydride; in the case of **59d**, the ester of the corresponding carboxylic acid is formed in an almost quantitative yield.^{54,55}



The reaction of the telluroesters **59** with excess sodium hydrogentelluride initially yields a mixture of oligotellurides **62** and finally gives esters **63** and **64**. The formation of these compounds was explained in terms of the scheme given below.⁵⁵



The silyl esters **58** represent yet another type of telluroesters with $\text{C}=\text{Te}$ bonds. They have been synthesised by reactions of bis(acyl) tellurides **65** with bis(trialkylsilyl) tellurides **66** [pathway (a)], of acyl chlorides with equimolar amounts of bis(trimethylsilyl) tellurides [pathway (b)],^{58–61} and of sodium tellurocarboxylates with trialkylchlorosilanes [pathway (c)].⁵²



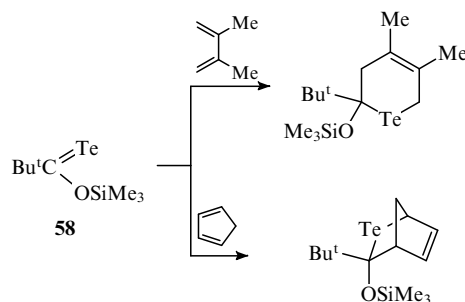
Compound	R	R'	Pathway
a	Me	Me ₃	a, b
b	Bu ^t	Me ₃	a, b
c	Me	Pr ⁱ Me ₂	a
d	2-MeC ₆ H ₄	Me ₃	c
e	2-MeC ₆ H ₄	Bu ^t Me ₂	c
f	Ph	Bu ^t Me ₂	a

The compounds **58** gradually decompose in solutions with liberation of tellurium giving mixtures of *E*- and *Z*-isomers of alkenes **68**^{58–61} (when $\text{R} = \text{R}' = \text{Me}$, the *E*:*Z* ratio amounts to 55:45⁵⁷). The stability of the esters **58** increases with increase in the size of the substituents R and R'. For example, in the reaction of bis(acetyl) telluride with bis(trimethylsilyl) telluride, the mixture of alkenes **68a** is formed in almost quantitative yield over a period of 30 min, whereas the reaction of bis(acetyl) telluride with

bis[(dimethyl)isopropylsilyl] telluride giving rise to a mixture of the alkenes **68c** is completed only over a period of 12 h.^{58,61}

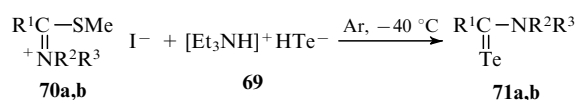
Te-Silylated derivatives **67** are the precursors of the esters **58**; they either completely isomerise into *O*-silylated esters **58** (for $\text{R} = \text{Ar}$ ⁵²) or exist as equilibrium mixtures with them. Thus the reaction of pivaloyl chloride with silyl telluride **66** ($\text{R}^1 = \text{Me}$) affords an equilibrium mixture of the compounds **67b** (35%) and **58b** (65%),⁶⁰ as indicated by the spectral parameters of the blue liquid formed in this reaction ($\lambda_{\max} = 624\text{ nm}$ ^{58,60}). The ^{13}C NMR spectrum exhibits signals at $\delta\ 207.5$ ($\text{C}=\text{O}$) and $\delta\ 251.2$ ppm ($\text{C}=\text{Te}$); the ^{125}Te NMR signal corresponding to the compound **58b** is manifested at $\delta\ 1418\text{ ppm}$.⁶⁰

Similarly to telluroaldehydes and telluroketones (see Section II.1), the esters **58** enter into [2 + 4]-cycloaddition to 2,3-dimethylbutadiene and cyclopentadiene giving the corresponding tellurium-containing heterocycles.⁶⁰

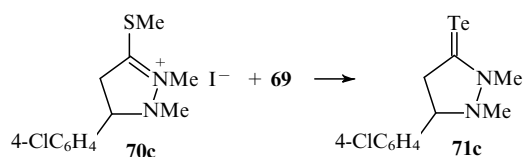


4. Telluroamides and their analogues

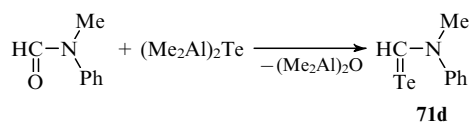
The first telluroamides and tellurohydrazides **71** were synthesised at about the same time as telluroesters, in 1979.⁶² They have been prepared similarly to selenium analogues,⁶³ namely, by treating the salts **70** with the hydrogentelluride anion **69** generated from Et_3N and H_2Te in CH_2Cl_2 .⁶² The yields of the compounds **71** were low (5%–19%).



$\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{R}^3 = \text{Me}$ (a); $\text{R}^2 = \text{Me}$, $\text{R}^3 = \text{NMe}_2$ (b).



Telluroamides have also been synthesised from bis(dimethylaluminium) telluride, which had been used previously to prepare telluroaldehydes and telluroketones.^{22,23} (see Section II.1). Treatment of *N*-methylformanilide with this telluring reagent resulted in the synthesis of telluroformanilide **71d** in a yield of about 90%.⁶⁴



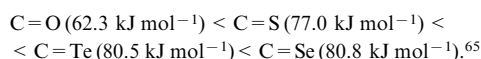
However, other telluroformanilides could not be isolated because they decomposed during purification.

The compounds **71** are stable at room temperature in the absence of water. They are rapidly hydrolysed in moist air or in wet solvents to give the corresponding amides and elemental tellurium resulting from fast oxidation of H_2Te .⁶² The hydrolysis is catalysed by alumina and silica gel; this apparently accounts for the fact that other telluroformanilides could not be isolated. The relatively high stability of telluroamides (hydrazides) **71a–c** is caused by the presence of strong electron-donating substituents

(NR₂, NR¹NR₂²) at the tellurocarbonyl carbon atom. Evidently, the stability of telluroamides, like that of telluroesters **59**, could be increased by introducing bulky substituents into their molecules. However, compounds of this type have not yet been synthesised.

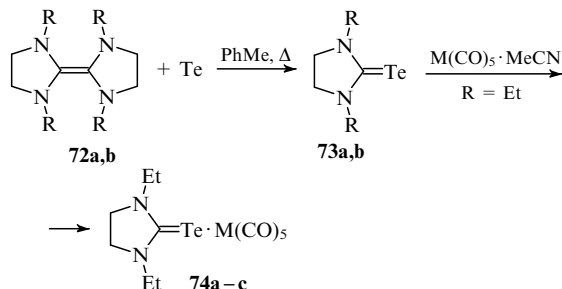
The long-wave absorption bands associated with the $n \rightarrow \pi^*$ transition in the C=Te fragment in the UV spectra of the telluroamides **71a,d** shift bathochromically with respect to those in the spectra of the analogous selenium derivatives by more than 100 nm and are located at 540 nm.^{62, 64}

The ¹H NMR data imply that the barriers (ΔG) to rotation of the NMe₂ groups in the amides PhC(X)NMe₂ vary in the following sequence:

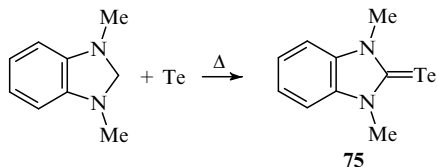


The deviation of the ΔG value for the telluroamide **71a** from the general tendency was attributed⁶⁵ to the increase in the steric strain in the ground state caused by the repulsion between the bulky Te atom and the (Z)-N-methyl group.

The stability of telluroureas **73** and **75** is also associated with the presence of electron-donating substituents at the tellurocarbonyl group. These compounds have been synthesised by the oxidation of alkenes **72**⁶⁶ or 1,3-dimethylbenzimidazoline with elemental Te. The compounds **73** were formed in 42%–45% yields, and the tellurourea **75** was obtained in ~9% yield.

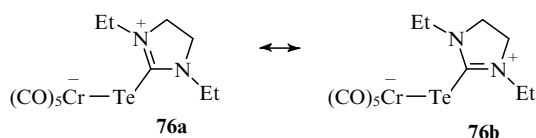


R = Me (**a**), Et (**b**); M = Cr (**74a**), Mo (**74b**), W (**74c**).



The properties of the tellurourea **75** have scarcely been studied. It has been reported⁶⁷ that the long-wave absorption bands in the UV spectra of 1,3-dimethylbenzimidazolinechalcogenones shift bathochromically in the series: thione ($\lambda = 310$ nm), selenone ($\lambda = 318$ nm), tellurone ($\lambda = 372$ nm).

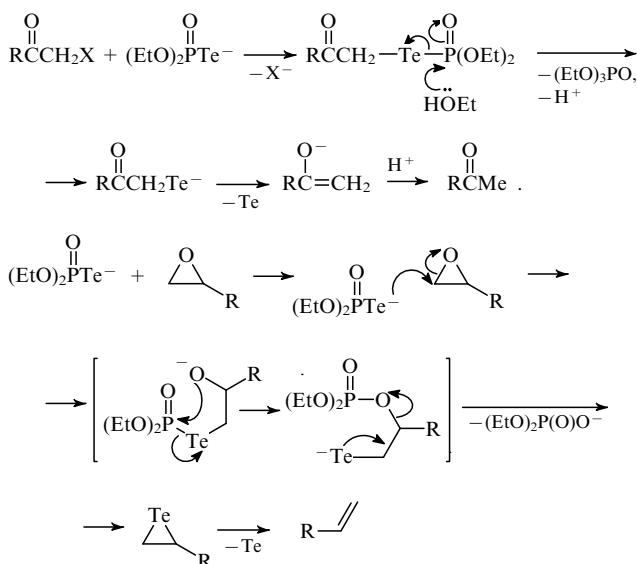
The properties of the telluroureas of type **73** have been studied somewhat more extensively.⁶⁶ These compounds are sensitive to air and decompose with the liberation of tellurium both in solutions and in the solid state. Complexes **74**, which are formed in 50%–75% yields in the reaction of the tellurourea **73b** with Cr, Mo, and W carbonyls, are more stable to air. The length of the C–Te bond in the complex **74a** corresponds to the length of a single C–Te bond and is equal to 2.12 Å; this is much longer than a similar bond in the complex **12** formed from the telluroketone **5** and tungstenpentacarbonyl (1.987 Å¹⁴). This was explained⁶⁶ by the assumption that the resonance-stabilised zwitter-ionic structures **76** make the predominant contributions to the ground state of the complexes.



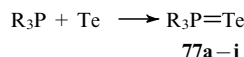
III. Synthesis, reactions, structures, and spectroscopic characteristics of phosphine tellurides R₃P=Te

1. Synthesis of phosphine tellurides

The first compound with the P–Te bond was synthesised by Foss about 50 years ago.⁶⁸ The reaction of elemental Te with an ethanolic solution of potassium diethyl phosphite has resulted in the synthesis of (EtO)₂P(O)TeK. Later, the corresponding sodium derivative was used as an efficient dehalogenating reagent for α -chloro- and α -bromoketones,⁶⁹ and also for deoxygenation of epoxides.⁷⁰

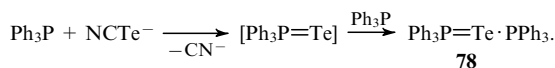


As mentioned above, the first phosphine telluride, tributyl phosphine telluride, was synthesised by Zingaro in 1963.¹ This compound and similar compounds **77** have been prepared by the interaction of triorganylphosphines with elemental tellurium in anhydrous toluene.^{1, 71, 72} The yields of the compounds **77** varied from 5% to 45%. However, the reaction of tris(*tert*-butyl)-phosphine with tellurium carried out under the same conditions gave the corresponding phosphine telluride in an almost quantitative yield.⁷³ Phosphine tellurides have been synthesised in substantially higher yields (75%–80%) by heating trialkyl(cycloalkyl)phosphines with tellurium without a solvent.⁷⁴



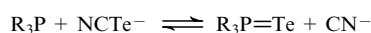
R = Me (**a**),⁷² Et (**b**),⁷¹ Pr (**c**),^{71,74} Bu (**d**),^{1,71,74} Bu^t (**e**),⁷³ C₅H₁₁ (**f**),⁷⁴ cyclo-C₆H₁₁ (**g**),⁷⁴ C₈H₁₇ (**h**),⁷⁴ R₃ = PhBu₂ (**i**).⁷¹

It should be noted that there is no direct correlation between the solubility of tellurium in phosphines and the capability of the latter of being converted into phosphine tellurides. In fact, the solubility of tellurium in dimethyl(phenyl)phosphine (defined as the ratio of the number of moles of dissolved Te to the number of phosphine moles multiplied by 100)⁷¹ is 16.7, and that for dibutyl(phenyl)phosphine is 9.1; however, only the latter compound yields phosphine telluride upon interaction with tellurium. No triorganylphosphine tellurides containing more than one phenyl group have been obtained so far. For example, all attempts to prepare triphenylphosphine telluride failed. However, this compound has been obtained as a complex with triphenylphosphine in acetonitrile in the presence of lithium perchlorate.⁷⁵



The structure of the adduct **78** was determined by X-ray diffraction analysis.⁷⁵ It contains a linear P–Te–P fragment with non-equivalent P–Te bonds. The length of one of these bonds is 2.27–2.42 Å; this falls into the range of typical P=Te bonds in phosphine tellurides (2.31–2.37 Å^{76–80}); the other bond, which is 3.41–3.95 Å long, corresponds to a ‘secondary interaction’⁸¹ between the Te atom and the phosphorus atom in triphenylphosphine.

The reversible reaction between triorganylphosphines and NCTe[–] anions was used to estimate quantitatively the ‘tellurophilicity’ of phosphines;⁷⁸ for this purpose, the equilibrium constants (*K*) for the reaction

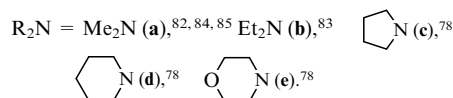
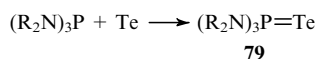


were measured. The following results were obtained:

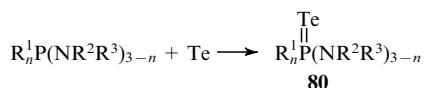
R			Me ₂ N	Et ₂ N	Bu	
<i>K</i>	8.000	0.600	0.540	0.270	0.170	0.009

R	Pr ⁱ ₃ N	EtO	MeO	BuO	Ph
<i>K</i>	0.048	~ 0.003	~ 0.001	~ 0.003	0

The *K* values are in fairly good agreement with other findings. Thus the fact that Ph₃P does not form phosphine tellurides is consistent with the *K* value found (0.000). At the same time, various triaminophosphines characterised by relatively large *K* readily react with elemental tellurium giving tris(dialkylamino-phosphine) tellurides **79** in high yields.^{78, 82–85}

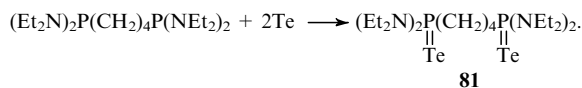


Amidophosphine tellurides of type **80**^{83, 86–88} and **81**⁸⁸ have been obtained in a similar way.

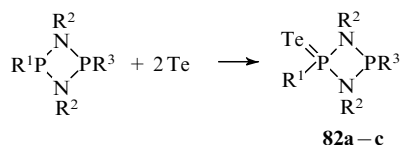


$n = 1$: $R^1 = R^2 = \text{Me}$;^{83, 87} $R^1 = \text{Me}$, $R^2 = R^3 = \text{Et}$;⁸⁸ $R^1 = \text{Ph}$, Et ;
 $R^2 = R^3 = \text{Me}$;⁸²

$n = 2$: $R^1 = \text{Bu}^t$; $R^2 = \text{H}$, $R^3 = \text{Pr}^i$, cyclo-C₆H₁₁.⁸⁶



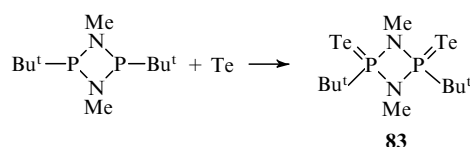
Cyclic phosphine tellurides, which are relatively resistant against water and air compared to other phosphine tellurides, have been synthesised by the reactions of the corresponding diazadiphosphetidines with tellurium.^{89–91} Depending on the ratio of the reactants, these reactions gave diazadiphosphetidine monotellurides **82**^{89–91} and ditellurides **83**.⁸⁹



82a: $R^1 = \text{Me}$, $R^2 = \text{Bu}^t$, $R^3 = \text{Cl}$;⁸⁹

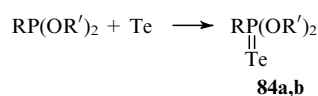
82b: $R^1 = R^3 = \text{NMe}_2$, $R^2 = \text{Bu}^t$;⁹⁰

82c: $R^1 = R^3 = \text{Bu}^t$, $R^2 = \text{Me}$.⁹¹



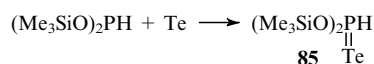
Dichloro(methyl)phosphine does not react with tellurium,⁹² although the chloro-substituted diazadiphosphetidine forms the corresponding telluride **82a** in 17% yield.⁸⁹

The fairly low tellurophilicity of trialkyl phosphites accounts for the fact that no trialkyl phosphotelluroates (RO)₃P=Te have been synthesised so far. However, phosphonites RP(OR')₂ are able to form compounds **84** with a P=Te bond. The stability of these compounds is largely determined by the nature of the hydrocarbon substituents attached directly to the phosphorus atom. For example, **84a** resulting from reaction of diethyl ethylphosphonite with Te decomposes during distillation,⁹³ whereas phosphotelluroate **84b** formed from diethyl allylphosphonite is relatively stable under an inert atmosphere.⁹⁴

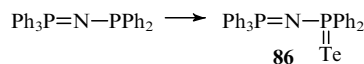


$R = R' = \text{Et}$ (**a**); $R = \text{CH}_2\text{CH}=\text{CH}_2$, $R' = \text{Et}$ (**b**).

Phosphonotelluroate **85** was obtained in 44% yield by the reaction of bis(trimethylsilyl) hydrogenphosphonite with Te in dioxane.⁹⁵



Finally, it should be noted that *N*-diphenyltellurophosphinoyl(triphenyl)phosphazene **86** is formed in a yield of 87% when the corresponding phosphazene is heated with elemental tellurium in benzene.⁹⁶



Thus, synthesis of all types of compounds containing P=Te bonds is based on the reactions of P(III) derivatives with elemental tellurium. Other sources of tellurium do not afford phosphine tellurides, although their sulfur and selenium analogues are used to prepare the corresponding phosphine chalcogenides. For example, unlike diorganyl disulfides and diselenides, which react with triorganylphosphines to give triorganylphosphine sulfides or selenides,⁹⁷ diorganyl ditellurides subjected to photolysis in the presence of tertiary phosphines yield only mixtures of organyl tellurides and elemental tellurium.⁹⁸

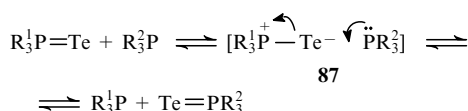
2. Reactions of phosphine tellurides

Triorganylphosphine tellurides $R_3P=Te$ are golden-yellow crystalline compounds, which partially decompose in air or during recrystallisation. Therefore, they are normally recrystallised in the presence of the corresponding phosphines. In many cases, heating of solutions of phosphine tellurides in hydrocarbon solvents results in the formation of tellurium mirrors.⁷¹ Only tris(*tert*-butyl)phosphine telluride is thermally stable both in the solid state and in solutions.⁷³ Tris(dialkylaminophosphine) tellurides are also quite sensitive to air and decompose with liberation of elemental Te.⁸² Phosphine tellurides containing residues of cyclic nitrogen-containing compounds at the phosphorus atom are more stable.⁷⁸ Diazadiphosphetidine tellurides **82** and **83** are very stable both in the crystalline state and in solutions.^{88–90}

a. Exchange reactions

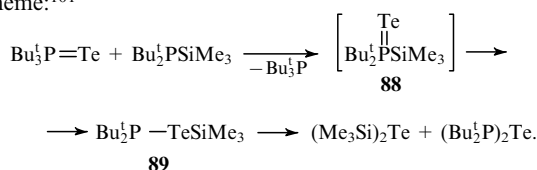
The ¹H, ³¹P and ¹²⁵Te spectra of mixtures of phosphine tellurides with phosphines recorded at room temperatures indicate that the Te atom migrates rapidly, on the NMR time scale, between the

phosphine molecules.^{73, 98–101} Apparently, this reaction occurs *via* a transition state like **87**.⁹⁹

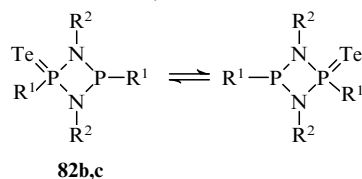


$\text{R}^1 = \text{R}^2 = \text{Bu}^t$,^{73, 99, 100} Me_2N ,⁹⁹ Bu ,¹⁰⁰
 $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Me}_2\text{N}$.^{73, 99}

However, in the $\text{Bu}_3\text{P}=\text{Te}/\text{Bu}_2\text{PSiMe}_3$ system, the Te atom is rapidly and irreversibly transferred to the silylphosphine; the intermediate phosphine telluride **88** immediately rearranges into compound **89** containing a Te–Si bond.¹⁰¹ However, this compound and also similar derivatives with Te–Ge and Te–Sn bonds have not been isolated in an analytically pure state due to disproportionation, which is described by the following scheme:¹⁰¹



Fast, on the NMR time scale, transfer of a tellurium atom between phosphorus atoms has been observed for cyclic phosphine tellurides **82b,c**.^{90, 91}



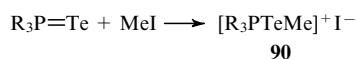
$\text{R}^1 = \text{Me}_2\text{N}$, $\text{R}^2 = \text{Bu}^t$ (**b**);⁹⁰ $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Me}$ (**c**).⁹¹

The concentration dependence of the coalescence temperature indicates that this process can occur not only as intramolecular exchange, which is facilitated by the non-planarity of the diazadi-phosphetidine ring,⁷⁶ but also intermolecularly.

b. Protonation and alkylation

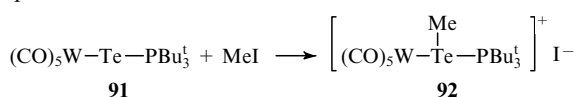
The protonation of phosphine tellurides with strong acids affords cations $[\text{R}_3\text{PTeH}]^+$.¹⁰² However, no salts with these cations have been isolated in a pure state; their formation in solutions has been judged only by NMR spectra.

Under mild conditions (benzene, room temperature), phosphine tellurides are alkylated with methyl iodide to give methyl-telluorophosphonium salts **90**, their yields being about 90%.¹⁰³ The salts **90** are soluble in nitromethane but decompose soon after dissolution.

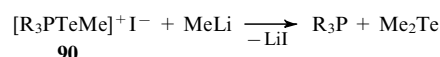


$\text{R} = \text{Me}$, Pr^i , Bu , Bu^t , Me_2N .

It is of interest that not only phosphine tellurides but also their complexes with metal carbonyls can be methylated.¹⁰⁴ Thus the reaction of the complex **91** with methyl iodide gave cationic complex **92**.⁴

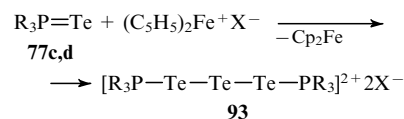


The P–Te bonds in the salts **90** tend to be cleaved by strong nucleophiles. For instance, treatment of these salts with methyl-lithium affords dimethyl telluride and triorganylphosphines.¹⁰³



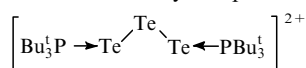
c. Oxidation

The phosphine tellurides **77c,d** are oxidised with the ferrocenium salts $\text{Cp}_2\text{Fe}^+\text{X}^-$ ($\text{X} = \text{BF}_4$, PF_6 , SbF_6) at low temperatures to give dications **93**, the yields of which are about 30%, and ferrocene.¹⁰⁵



$\text{R} = \text{Pr}^i$ (**c**), Bu^t (**d**); $\text{X} = \text{BF}_4$, PF_6 , SbF_6 .

The salt **93** ($\text{R} = \text{Bu}^t$, $\text{X} = \text{SbF}_6$) was studied by X-ray diffraction analysis.¹⁰⁵ Based on the bond lengths Te–Te (2.71 Å) and P–Te (2.50 Å), which corresponds to a single bond between Te and P atoms) and on the Te–Te–Te (109°) and Te–Te–P (108.6°) bond angles, this compound was described¹⁰⁵ as a Te_3^{2+} dication stabilised by complex formation with Bu_3P .



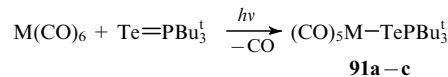
In a more recent study,¹⁰⁶ tributylphosphine telluride has been used to stabilise the tellurenyl cations RTe^+ . These species were generated by oxidation of diorganyl ditellurides with the nitrosonium salts NO^+X^- ($\text{X} = \text{BF}_4$, ClO_4) and isolated as stable complexes $[\text{Bu}_3\text{P} \rightarrow \text{TeP}]^+\text{X}^-$.

d. Complex formation

Phosphine tellurides form complexes with some metal salts. Like their sulfur and selenium analogues, phosphine tellurides act as donors in complex formation. Moreover, since in this case the bipolar character of the $(\text{P}=\text{Te} \leftrightarrow \text{P}^+-\text{Te}^-)$ bond is more pronounced, phosphine tellurides are stronger donors than phosphine sulfides or phosphine selenides.

Thus tributylphosphine telluride reacts with mercury(II) bromide to give a complex of the composition $(\text{HgBr}_2)_4(\text{TePBu}_3)_3$, which is fairly sensitive to oxygen and heating.¹⁰⁷ According to X-ray diffraction data, this complex consists of dimeric $[(\text{HgTePBu}_3)_3\text{Br}_3]^{2+}$ cations and binuclear $[\text{Hg}_2\text{Br}_6]^{2-}$ anions. The reactions of trimethylphosphine telluride with nickel and cobalt salts follow a different pathway, which includes decomposition of phosphine telluride and liberation of elemental tellurium even at -30°C .⁷²

The first phosphine telluride complexes **91a–c** were prepared in almost quantitative yields on irradiation of mixtures of Cr, Mo, and W carbonyls with tris(*tert*-butyl)phosphine telluride in THF.¹⁰⁴ They appear as dark-red crystals fairly stable in air and at elevated temperatures.

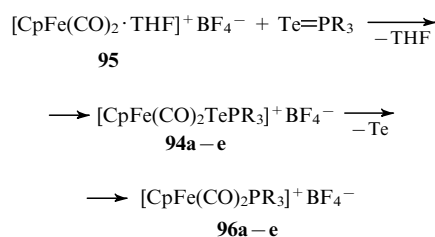


$\text{M} = \text{Cr}$ (**a**), Mo (**b**), W (**c**).

The relatively high donor ability of the phosphine telluride ligands is indicated by the substantial upfield shift of the signals of the CO groups in the ^{13}C NMR spectra of the complexes **91**. This is also confirmed by the fact that the phosphine telluride ligands in the complexes **91**, unlike those in similar complexes derived from phosphine sulfides $(\text{CO})_5\text{M}-\text{S}=\text{PR}_3$,¹⁰⁸ are not replaced by Ph_3P or CO on heating in solutions at 80°C .¹⁰⁴ The length of the P–Te bond in the complex **91c** is 2.439 Å, which corresponds to a single P–Te bond.¹⁰⁴

The results of NMR studies of complexes **94** also indicate that phosphine tellurides are stronger donors than other phosphine

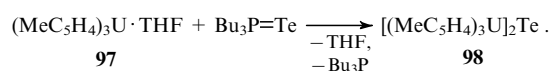
chalcogenides. These compounds have been synthesised¹⁰⁹ by a reaction similar to that used earlier¹¹⁰ to prepare the corresponding sulfur and selenium derivatives. The dark-brown complexes **94** were formed in almost quantitative yields on the interaction of salts **95** with phosphine tellurides in dichloromethane at room temperature.



R = Me (**a**), Prⁱ (**b**), Bu^t (**c**), Me₂N (**d**),  (**e**).

The compounds **94** are stable in air in the solid state but slowly decompose in solutions with liberation of tellurium to give complexes **96**.¹⁰⁹ The complex **94e**, which is the least stable in this series, decomposes yielding [CpFe(CO)₃]⁺BF₄[−] and the corresponding phosphine telluride. The attempts to replace one of the CO groups in the cation **94** by a second R₃P=Te molecule, which would have resulted in the formation of the cations [CpFe(CO)(TePR₃)₂]⁺, failed; heating or irradiation of mixtures of **94** with R₃P=Te was accompanied by intense decomposition. Meanwhile, treatment of the cations **94** with iodine resulted in the rupture of the Fe–Te bonds and in the formation of [CpFe(CO)₂I]₂.¹⁰⁹

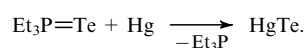
It should be noted that the reaction of the uranium cyclopentadienyl complex **97** with tributylphosphine telluride, unlike the reactions of the salts **95**, is accompanied by elimination of tributylphosphine giving rise to compound **98**.¹¹¹



Triphenylphosphine sulfide and selenide react with the complex **97** yielding compounds with similar structures. In the case of triphenylphosphine oxide, this gives the complex (MeC₅H₄)₃U · OPPh₃.¹¹¹

e. Phosphine tellurides as synthetic equivalents of elemental tellurium. Preparation of metal tellurides

The use of phosphine tellurides as synthetic equivalents of elemental tellurium to introduce tellurium into molecules of organic and organoelement compounds is based on the fact that phosphine tellurides readily dissociate on heating. In some cases, phosphine tellurides are preferred over elemental tellurium, since the reactions can be carried out at lower temperatures and the products can be obtained in higher yields. Moreover, some telluration reactions can occur only with phosphine tellurides. Low-temperature synthesis of metal tellurides is among the most significant synthetic applications of phosphine tellurides. Thus triethylphosphine telluride reacts with metallic mercury in toluene at room temperature to give mercury telluride in an almost quantitative yield.¹¹²

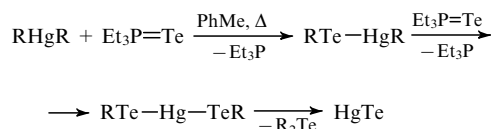


Phosphine tellurides eliminate metallic tellurium at lower temperatures than the majority of widely used sources of tellurium such as Me₂Te and Et₂Te, which generate tellurium at temperatures above 200 °C.^{5, 113}

The easy thermal dissociation of phosphine tellurides has served as the basis for the recently developed synthesis of semiconductor nanosized crystals¹¹⁴ by pyrolysis of a mixture of organometallic substrates upon their injection into a hot coordinating solvent. Thus cadmium telluride with a size of crystals

ranging from 12 to 115 Å was obtained by the introduction of (C₈H₁₇)₃P=Te and Me₂Cd into (C₈H₁₇)₃P=O at 240 °C followed by keeping the reaction mixture at 190–220 °C to grow the crystals.¹¹⁴

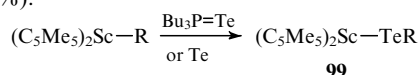
The reactions of phosphine tellurides with some organoelement compounds result in insertion of tellurium into C–element bonds. For example, the formation of mercury telluride in the reaction of Et₃P=Te with diorganylmercury derivatives occurs according to the following scheme:¹¹²



R = Et, Ph.

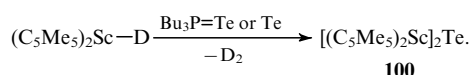
It should be noted that various Ar₂Hg react with elemental tellurium only under fairly drastic conditions (> 200 °C) to give diaryl tellurides.^{8,9}

Insertion of Te atoms into Sc–C(sp³) or Sc–C(sp²) bonds occurs relatively easily when permethylscandoceno-alkyls or -aryls are made to react with tributylphosphine telluride or elemental tellurium.^{115–118} The reactions of scandocenes with phosphine telluride occur faster than the reactions with elemental tellurium, and compounds **99** are formed in higher yields (31%–71%).

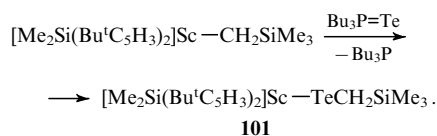


R = Me₃SiCH₂, PhCH₂, *erythro*-CHDCHDBu^t, CH₂CHDCH₂CH₂CH=CMe₂, Ph, cyclo-C₅H₉CH₂.

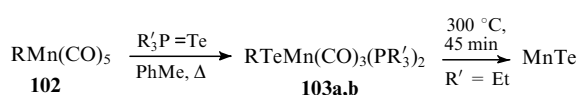
The dimeric scandium μ-telluride **100** has been prepared in a similar way;^{115, 117} its structure was determined by X-ray diffraction analysis.



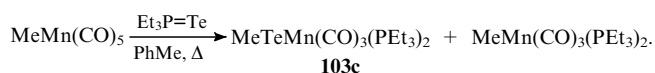
The advantages of Bu₃P=Te over elemental tellurium are illustrated by the synthesis of the scandocene derivative **101**.¹¹⁸ When elemental tellurium is used, the reaction is completed over 4–5 h, whereas in the case of Bu₃P=Te, this reaction occurs immediately after mixing the reactants.



Yet another example of the insertion of a Te atom into a C–element bond is the reaction of complexes **102** with trialkylphosphine tellurides yielding alkyltelluride manganese complexes **103**.^{119, 120} Pyrolysis of one of these products (**103b**) gives rise to manganese telluride.

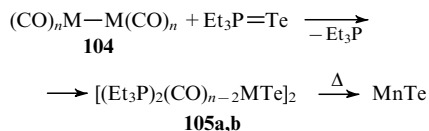


R = CH₂Ph: R' = Me (**103a**), Et (**103b**);



A series of metal tellurides including manganese telluride have been prepared using complexes of metals in low oxidation states. Depending on the reaction conditions, the reactions involving these compounds either directly afford metal tellurides or initially

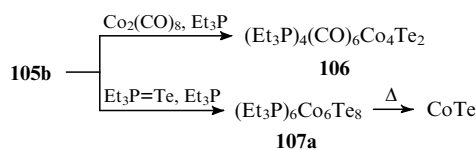
afford clusters the pyrolysis of which under relatively mild conditions leads to tellurides. Manganese¹²¹ and cobalt^{122, 123} tellurides have been obtained using carbonyls of the corresponding metals **104** the reactions of which with triethylphosphine telluride in toluene give rise to binuclear complexes **105**; these products result from the insertion of two tellurium atoms into metal–metal bonds in the initial complexes.



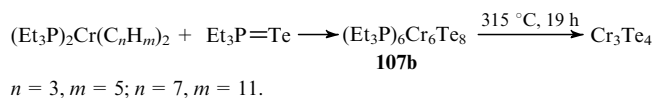
M = Mn, $n = 5$ (**a**); M = Co, $n = 4$ (**b**).

The dimeric molecules of **105** are built like diorganyl ditellurides R–Te–Te–R, but contain $(\text{Et}_3\text{P})_2(\text{CO})_{n-2}\text{M}$ groups instead of the organic radicals. The Te–Te bond lengths (2.763 Å in **105a**¹²¹ and 2.765 Å in **105b**¹²²) are somewhat larger than that in diphenyl ditelluride (2.712 Å¹²⁴). The pyrolysis of the complex **105a** giving crystalline manganese telluride occurs under substantially milder conditions (300 °C, 16 h) than does the synthesis of this telluride from the elements (heating to 800 °C followed by keeping the reaction mixture at 500 °C¹²¹).

When the $\text{Co}_2(\text{CO})_8 : (\text{Et}_3\text{P}=\text{Te}) : \text{Et}_3\text{P}$ ratio was varied, clusters **106**¹²² and **107a**^{122, 123} were isolated in addition to the compound **105b**. The former of these clusters can also be obtained from **105b**, $\text{Co}_2(\text{CO})_8$, and Et_3P ;¹²² treatment of the complex **105b** with $\text{Et}_3\text{P}=\text{Te}$ and Et_3P affords the cluster **107a**.¹²²



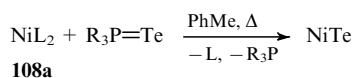
The chromium-containing cluster **107b**, similar to the cobalt derivative **107a**, was prepared by treatment of bis(triethylphosphinediallyl)chromium or bis(2,4-dimethylpentadienyl)chromium with triethylphosphine telluride.¹²⁵



According to X-ray diffraction data, the clusters **107a,b** are built of octahedra consisting of six cobalt (the Co–Co bond length is 3.23 Å¹²²) or chromium (the Cr–Cr bond length is 2.94 Å¹²⁵) atoms; the octahedra are incorporated into a cube combining 8 tellurium atoms; the triethylphosphine groups are bound only to metal atoms.

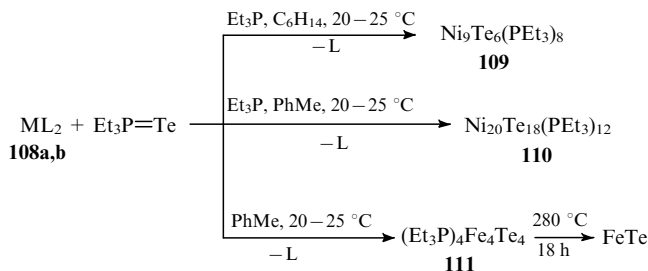
Pyrolysis of the clusters **107a** (300 °C, 45 min^{122, 123}) and **107b** (315 °C, 19 h¹²⁵) gives rise to polycrystalline β -CoTe and Cr_3Te_4 , respectively. In a relatively recent study,¹²⁶ the cluster $(\text{Ph}_2\text{PPr})_6\text{Co}_6\text{Te}_8$ the composition of which is close to that of **97a** was synthesised by the reaction of CoCl_2 with Ph_2PPr and trimethyl(phenyltelluro)silane.

The complexes bis(cyclooctadiene)nickel **108a**¹²⁷ and (cyclooctatetraene)iron **108b**¹²⁸ served as the starting compounds for the preparation of the tellurides of these metals. Thus heating of bis(cyclooctadiene)nickel **108a** in boiling toluene, which normally results in its dissociation to Ni and cyclooctadiene, affords polycrystalline nickel telluride when carried out in the presence of $\text{Et}_3\text{P}=\text{Te}$.¹²⁷ The synthesis of this telluride from the elements is possible only upon prolonged heating at 400–600 °C.



L = cyclooctadiene.

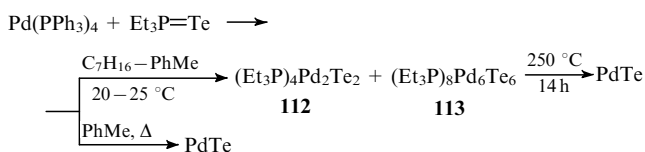
Nickel telluride¹²⁷ as well as a mixture of β - and γ -FeTe¹²⁸ have been synthesised by pyrolysis of clusters **109–111** formed initially. These clusters, like those considered above, are intermediate compounds on the way from organic substrates to inorganic solid materials. The nickel clusters **109** and **110** contain $\text{Et}_3\text{P} - \text{Ni} - \text{Te}$ fragments with tetracoordinated nickel and tellurium atoms;¹²⁷ in the cluster **111**, the tellurium atoms are tricoordinated, and the iron atoms are tetracoordinated.¹²⁸



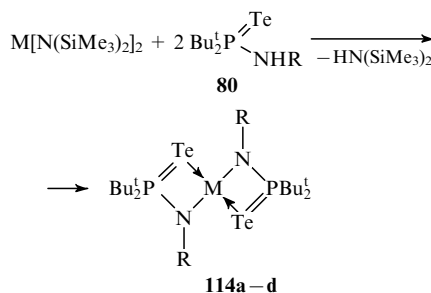
M = Ni, L = cyclooctadiene (**108a**);

M = Fe, L₂ = cyclooctatetraene (**108b**).

Like nickel telluride, palladium telluride was synthesised using two procedures: by heating of an equimolar mixture of $\text{Pd}(\text{PPh}_3)_4$ and $\text{Et}_3\text{P}=\text{Te}$ in toluene¹²⁹ and *via* the clusters **112** and **113**; however, the clusters were isolated in fairly low yields (10% and 2%, respectively).



To complete the discussion of the methods for synthesis of metal tellurides, we shall mention a new approach developed recently,¹³⁰ which is based on the use of phosphine tellurides other than $\text{R}_3\text{P}=\text{Te}$. Complexes **114**, which have been obtained in almost quantitative yields by the reaction of phosphine tellurides **80** with zinc and cadmium bis[*N*-di(trimethylsilyl)amides], provide an example.^{130, 131}

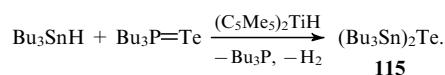


M = Zn: R = Prⁱ (**114a**), cyclo-C₆H₁₁ (**114b**);

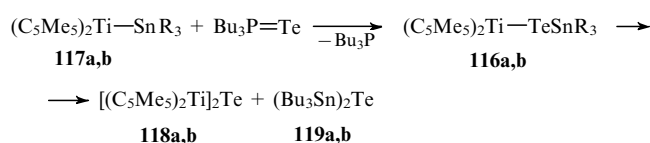
M = Cd: R = Prⁱ (**114c**), cyclo-C₆H₁₁ (**114d**).

The complexes **114** are crystalline compounds readily soluble in toluene. Based on the results of X-ray diffraction analysis of the selenium analogue of **114a**,¹³¹ a distorted tetrahedral structure has been ascribed to these complexes. Pyrolysis of the complexes **114a,b** at 300 °C and **114d** at 320 °C gives rise to cubic zinc telluride with an admixture of elemental tellurium and to cubic cadmium telluride, respectively.¹³⁰

Phosphine tellurides have also been used to synthesise compounds containing M–Te–M fragments. For example, the reaction of tributyltinhydride with tributylphosphine telluride in the presence of catalytic amounts of (C₅Me₅)₂TiH resulted in the formation of bis(tributylstannyl) telluride **115**.¹³² We shall not discuss the mechanism of the catalytic action of (C₅Me₅)₂TiH;¹³² however, it should be noted that without this compound, the formation of the telluride **115** proceeds very slowly.

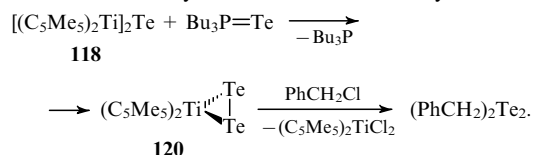


Compounds **116** containing the M–Te–M' fragment (M and M' are atoms of different elements) were prepared by the reactions of dimetal derivatives **117** with tributylphosphine telluride.¹³² However, unlike **116a**, which rapidly disproportionates to give symmetrical tellurides **118a** and **119a**, its phenyl analogue disproportionates quite slowly.



R = Bu (a), Ph (b).

The reaction of the telluride **118** with tributylphosphine telluride giving rise to compound **120** is the only example of transformation of a telluride into a ditelluride known at present.^{132, 133} It is of interest to verify whether diorganyl tellurides R₂Te would be converted into diorganyl ditellurides R₂Te₂ upon treatment with tributylphosphine telluride. The compound **120** can be regarded as a synthetic equivalent of Te₂^{2–}, because its interaction with benzyl chloride affords dibenzyl ditelluride.¹³³



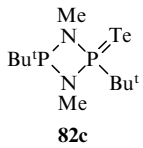
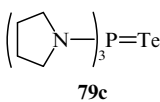
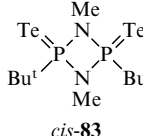
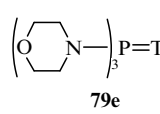
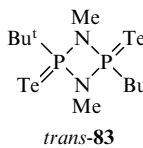
3. X-Ray diffraction analysis and spectroscopic characteristics of phosphine tellurides.

a. X-Ray diffraction analysis of phosphine tellurides

The data considered in this Section are mostly concerned with the lengths of P–Te bonds. Detailed information about the fine structure of phosphoryl groups R₃P can be found in original publications. The molecular and crystal structures of six compounds with P=Te bonds have been studied by X-ray diffraction analysis. The corresponding bond lengths are listed in Table 1.

It can be seen from Table 1 that the P=Te bond lengths vary over a narrow range and are intermediate between the theoretically predicted lengths of single (2.48 Å¹³⁴) and double (2.27 Å¹³⁴) P=Te bonds. These lengths have been reported⁸⁰ to correspond to a bond order of 1.5; this implies a substantial contribution of the bipolar P⁺–Te[–] structure to the ground state of phosphine telluride molecules. Comparison of the P–chalcogen bond lengths in tris(morpholinophosphine) telluride **79e** and its selenium analogue⁷⁸ with the sums of the radii of double bonds formed by the corresponding elements indicates that the contribution of the bipolar structure to the resonance hybrid in compounds with the P=Te bonds is larger than that in compounds with the P=Se bonds. This is indirectly supported by the conclusion, based on measurements of the dipole moments of phosphine chalcogenides, that the polarity of compounds increases in the sequence oxide < sulfide < selenide.¹³⁵ However, the values of the bond dipole moments of P=X bonds (X = O, S, Se, Te) calculated from the dipole moments of (C₈H₁₇)₃P=X¹³⁶ do not confirm this conclusion.

Table 1. Lengths of the P=Te bonds in phosphine tellurides.

Compound	Bond length / Å	Ref.	Compound	Bond length / Å	Ref.
Bu ₃ P=Te	2.368	80		2.354	76
	2.355	79		2.305	77
	2.357	78		2.327	77

The diazadiphosphetidine rings in the compounds **82c**⁷⁶ and *cis*-**83**⁷⁷ are markedly non-planar, whereas *trans*-**83**⁷⁷ is planar.

Although tellurium atoms in other types of organotellurium compounds tend to form both intramolecular⁶ and intermolecular bonds with atoms of other elements,¹³⁷ none of the phosphine tellurides has been found to contain any intermolecular contacts between tellurium and phosphorus atoms that would be shorter than the sum of their van der Waals radii.

b. Spectroscopic characteristics of phosphine tellurides.

Ultraviolet spectra of phosphine tellurides have been relatively little studied, which is apparently due to the fact that these compounds readily decompose in solutions. Therefore, the UV spectra have been reported only for the most stable compounds **79** in which the phosphorus atom is bound to nitrogen atoms incorporated into heterocycles. The absorption maxima of these compounds are observed at 280 nm.⁷⁸ Although the nature of the electronic transition responsible for this absorption is not known exactly, presumably,⁷⁸ it is the *n*→*π** transition. Particular interest is aroused by comparison of the UV spectra of compounds of the Ph₃P=X type containing O, S, Se, and Te atoms. The data for these derivatives presented in Table 2 indicate that the absorption bands shift bathochromically in the series O, S, Se, and Te.

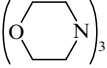
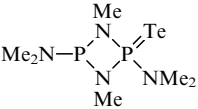
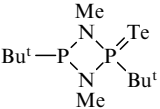
Table 2. Data of the UV spectra for compounds R₃P=X.⁷⁸

R	X	λ _{max} / nm	lg ε
	O	< 205	
	S	~ 210	~ 3.70
	Se	~ 225	~ 3.56
	Te	286	2.79
	Te	288	2.85
	Te	281	2.80

According to several publications,^{73, 74, 78, 84, 96} the P=Te stretching bands lie in the range of 445–526 cm⁻¹. However, Watari,¹³⁸ who studied the IR and Raman spectra of Me₃P=Te and (CD₃)₃P=Te, did not find any absorption bands between 400 and 450 cm⁻¹; the bands for the P=Te stretching vibrations were observed at 376 cm⁻¹. It should be noted that the order of variation of the force constants of the P=X bonds in the series of phosphine chalcogenides R₃P=X differs depending on R. For R = Me₂N, the force constants change in the order O > Te > Se > S,⁸⁴ whereas in the case of R = Me, this order is O > S > Se > Te.¹³⁸

Data on the ³¹P and ¹²⁵Te NMR spectra of phosphine chalcogenides of various types are listed in Table 3.

Table 3. Chemical shifts (δ, ppm) and spin-spin coupling constants (J/ Hz) in the ³¹P and ¹²⁵Te NMR spectra of phosphine tellurides.

Compound	δ (³¹ P) ^a	δ (¹²⁵ Te) ^b	J(³¹ P– ¹²⁵ Te)	Ref.
Me ₃ P=Te		–513.4		80
Et ₃ P=Te		–875.2	1743	80
Pr ₃ P=Te		–1000.3	1735	80
Bu ₃ P=Te	+11.0		1720	83
		–807.0	1730	80
		–803.2	1732	139
Bu ₃ ^t P=Te	+75.2			99
		–836.5	1663	139
	+77.5		1600	73
(Me ₂ N) ₃ P=Te	+54.5		2003	85
	+58.8			99
		–826.4	2105	80
		–821.7	2095	139
(Et ₂ N) ₃ P=Te	+48.0		2037	83
			2040	80
() ₃ P=Te		–812.6	2153	139
			1821	80
Me(Me ₂ N) ₂ P=Te	+51.8		1950	83, 87
	+16.7			90
	+119.5			91
Et ₂ (EtO)P=Te	+83.0		1964	83

^a In relation to 85% H₃PO₄; ^b in relation to Me₂Te.

The ¹²⁵Te NMR spectra (provided that the solution contains no free phosphine) are well resolved doublets arising due to ³¹P–¹²⁵Te spin-spin coupling.¹³⁹ In the case of triphenylphosphine telluride which exists, as shown above, as a complex with triphenyl phosphine, the ¹²⁵Te signal is exhibited as a broad singlet at δ –491.8 ppm, owing to rapid migration of the Te atom between the Ph₃P groups.¹³⁹

The ¹²⁵Te chemical shifts range from δ –513 to –1000 ppm (in relation to Me₂Te) indicating that the Te nuclei are appreciably shielded and that the bipolar structures R₃P⁺–Te[–] make substantial contributions to the ground states of phosphine telluride molecules.

The ³¹P–¹²⁵Te spin-spin coupling constants are 1660–2150 Hz, the values for tris(dialkylaminophosphine) tellurides

being approximately 300–400 Hz greater than those for phosphine tellurides R₃P=Te.

IV. Conclusion

The data presented in this review demonstrate certain progress in the chemistry of organic derivatives of monocoordinated tellurium achieved over the past decade. Efficient methods for the generation of telluroaldehydes and telluroketones have been developed and the first relatively stable telluroketone was synthesised. Dimerisation and Diels–Alder reactions of these compounds have led to the synthesis of ditelluretanes, 1-telluracyclohex-3-enes and 2-tellurabicyclo[2.2.1]hept-5-enes. New complexes of tellurocarbonyl derivatives with transition metal compounds have been prepared and their chemical transformations have been studied. It has been shown that at low temperatures in polar solvents like THF, tellurocarboxylic acids exist in the telluroxo-form. The chemistry of telluroesters and telluroamides has been developed to a lesser extent. Development of new methods for the synthesis of compounds with C=Te bonds, study of the possibility of using these derivatives in the preparation of tellurium-containing heterocycles, and attempts to synthesise stable telluroaldehydes and telluroketones by introducing substituents, able to form intramolecular coordination bonds with the C=Te groups, into their molecules appear to be promising lines of research in this field.

As regards phosphine tellurides, the main progress has been achieved in the investigation of their reactivity towards alkylation, complex formation, oxidation, and other types of transformation. However, the discovery and study of reactions in which phosphine tellurides act as synthetic substitutes of elemental tellurium is the most important achievement. This property of phosphine tellurides forms the basis for using them in low-temperature syntheses of metal tellurides and new types of tellurium-containing clusters. In addition to further development of these studies, it appears of interest to attempt using phosphine tellurides as tellurating reagents in the synthesis of some organotellurium derivatives (the transformation of diorganyl tellurides into diorganyl ditellurides, reactions with halogen-containing substrates, etc.)

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Azorhodanines, azothiopropiorhodanines, and their analytical application

R F Gur'eva, S B Savvin

Contents

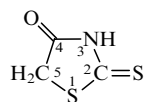
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Abstract. The methods of synthesis, properties, and reactivities of azo-compounds based on rhodanine and thiopropiorhodanine are examined. The possibilities of the wide scale practical employment of this series of reagents, including their modified and immobilised forms, in the analytical chemistry of platinum and heavy metals are discussed. The bibliography includes 115 references.

I. Introduction

Azo-compounds based on rhodanine (2-thioxo-4-thiazolidinone), thiorhodanine (2,4-dithioxothiazolidine), and aromatic amines containing salt-forming groups were first synthesised in 1971; these azo-compounds were obtained at the same time as analytical reagents.^{1,2} A distinctive feature of these reagents is their ability to enter into highly sensitive, selective, and contrasting colour reactions with noble (NM) and heavy (HM) metals in solutions and in the solid phase.^{3–13} Systematic studies on azo-compounds synthesised from 3-substituted derivatives of rhodanine, thiohydantoin (2-thiazolidine), selenisorhodanine [4-thioxo-2-(1,3-selenazolidinone)], the six-membered analogue thiopropiorhodanine (2,4-dithioxo-1,3-thiazane), as well as bisazo-compounds based on rhodanine resulted in the creation of a whole series of promising analytical reagents.^{14–24} By virtue of their exceptionally valuable properties, azorhodanines and azothiopropiorhodanines have found extensive applications in analytical chemistry. For example, various methods for the determination of 17 elements (photometric, differential photometric, extraction-photometric, sorption-photometric, including those using sensitive photometric cells, *etc.*) have been developed using these compounds. The method may be applied in the analysis of objects of different composition and with different contents of the components. It may be that azorhodanines and azothiopropiorhodanines are some of the most promising analytical reagents proposed during the last 25 years.

Rhodanine is known as the analytical reagent for the precipitation and gravimetric determination of silver, mercury, and other platinum metals.^{25–30}



However, the low sensitivity of rhodanine (as well as the products of its interaction) and the low sensitivity of the reactions precluded the wide scale employment of this reagent for the requirements of analytical chemistry, especially photometry. Because of the enhanced reactivity of the 5-methylene group, rhodanine interacts with compounds of different classes — aldehydes, ketones, and diazo-compounds.^{31–42} This leads to the possibility of obtaining from it new reagents containing the chromophoric groups $=C=CH-$ and $-N=N-$. The sensitivity and contrasting properties of the reactions of rhodanine condensation products with metal ions are greatly superior to those of rhodanine. Thus *p*-dimethylaminobenzylidenerhodanine has found fairly extensive applications in the photometric determination of silver and gold.^{29, 30, 43–49}

In contrast to the 5-condensed derivatives, the azo-compounds based on rhodanine and aromatic amines containing salt-forming groups (OH, SO_3H , $COOH$, AsO_3H_2)^{1–3, 13, 14, 16, 21, 24} are of interest for the determination of not only gold and silver but also of platinum, palladium, rhodium, iridium, ruthenium, and heavy metals. Such compounds are more stable in solution, dissolve relatively easily, and their reactions with the elements are characterised by an unusually high sensitivity [the molar absorption coefficient (ϵ) reaches $(3–9) \times 10^5$ in certain cases], good contrasting properties, and high selectivity. The selectivity is based on the sharp differences between the conditions and kinetics of the colour reactions with the elements and the spectroscopic characteristics and stability of the complexes formed.^{50–58}

II. Synthesis of the reagents and methods for their identification

About forty 5-azo-compounds based on rhodanine (**1a–m**), thiorhodanine (**2a–c**), thiohydantoin (**3a, b**), pseudothiohydantoin (**4a–d**), 3-aminorhodanine (**5a–f**), N-substituted 3-aminorhodanine (**6a, b**), bisazo-compounds based on rhodanine (**7a–c**), selenisorhodanine (**8a–d**), a six-membered structural analogue

R F Gur'eva, S B Savvin V I Vernadskii Institute of Geochemistry and Analytical Chemistry, Russian Academy of Sciences, ul. Kosygina 47a, 117975 Moscow, Russian Federation. Fax (7-095) 938 20 54. Tel. (7-095) 137 28 78 (S B Savvin)

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of rhodanine — thiopropiorhodanine (**9a–d**), as well as aromatic amines containing predominantly salt-forming groups have been synthesised as possible analytical reagents.^{1–3, 13, 14, 16, 21, 24} The structural formulae and names of reagents of each group are presented in Table 1.

The azo-compounds are synthesised in accordance with a general scheme: by treating the heterocyclic azo-component with the corresponding diazotised amine under conditions suitable for each reaction (nature of the solvent, pH, time during which the reaction mass is allowed to stand, and the temperature regime). This ensures the preparation of reagents in high yields and reduces to the maximum extent the possibility of the formation of side products. The heterocyclic azo-components are obtained as follows: rhodanine — by the condensation of monochloroacetic acid with ammonium thiocyanate on heating;²⁵ thiorhodanine — from rhodanine by replacing the carbonyl group by the thiocarbonyl group on treatment with P_2S_5 ;¹ thiohydantoin — by the reaction of potassium thiocyanate with the hydrochloride of the ethyl ester of glycine;⁵⁹ pseudothiohydantoin — by condensing urea with monochloroacetic acid on heating;²⁵ 3-aminorhodanine — by condensing sodium monochloroacetate with hydrazine dithiocarbazine;^{60, 61} 3-aminobenzylidenerhodanine — by condensing 3-aminorhodanine with aldehydes in acetic acid; thiopropiorhodanine — by treating propiorhodanine with P_2S_5 in dry dioxane;⁶² propiorhodanine — by condensing chromotropic acid with freshly prepared ammonium dithiocarbamate and subsequent heating of thiocarbamoyl- β -thiolactic acid with acetic anhydride;⁶³ selenisorhodanine — by the interaction of 1,3-selenazolidine-2,4-dione with P_2S_5 in dry dioxane;⁶⁴ 1,3-selenazolidine-2,4-dione — by condensing monochloroacetic acid with selenourea on heating.

In order to obtain purer products and higher yields of the main substances, the synthesis is carried out in the presence of metal (calcium, lead) salts, but the solubility of the reagents is then reduced. The azo-compounds based on aminophenols and selenisorhodanine could not be isolated.

The azo-compounds are identified by paper chromatography, column chromatography, electrophoresis using various buffer systems and also from the characteristic absorption spectra of the reagents themselves (concentrated H_2SO_4 , neutral and alkaline solutions) and their complexes. The purity of the preparations is established by the potentiometric titration of the reagents with alkali and by spectrophotometric titration with solutions of metal salts.^{3, 7, 16, 65}

The study of 5-azo-compounds based on propiorhodanine [2-thioxo-4-(1,3-thiazanone)] showed that, in contrast to rhodanine, propiorhodanine does not react with diazonium salts even in the presence of activators of the azo-coupling reactions (pyridine, alkoxides). The reduced reactivity of the methylene group in the 5-position is due to the fact that the activating effect of the carbonyl group in the 4-position extends to the 5-methylene group, while the thioxo-group activates the 6-methylene group. On the other hand, in rhodanine the activating effect of the two groups is directed to the 5-methylene group of propiorhodanine. At the same time, the azo-coupling of thiopropiorhodanine with diazonium salts becomes possible as a result of the increase in electron density on the carbon atom in the 5-position as a consequence of enolisation and the formation of a thioenolate anion.^{62, 63}

III. Properties of the reagents

The reagents are powdered substances the colour of which varies from yellow to dark-red depending on the nature of the diazo- and azo-components; they dissolve in dioxane, dimethylformamide, ethanol, acetic acid, solutions of alkalis, and concentrated acids. The reagents containing sulfo-groups are readily soluble in water. In a dry form, they retain their analytical properties for more than three years.

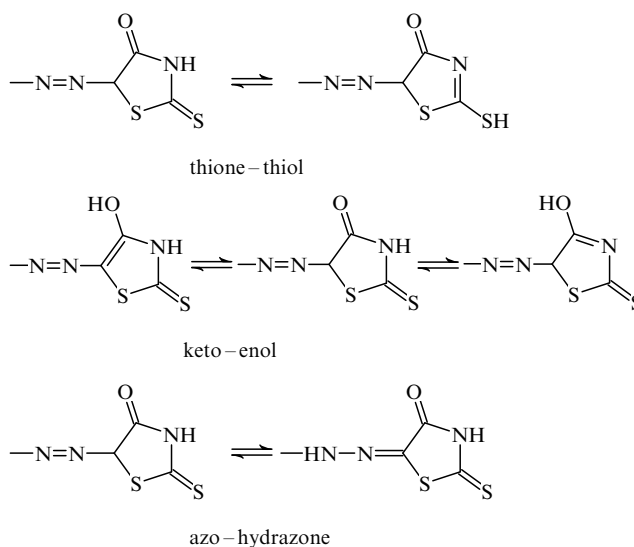
The state of the reagents in solution is one of the principal factors determining the reactivity, the mechanism of the complex formation reaction, and the nature of the colour reactions with the elements. Solutions of the reagents undergo a sharp colour change as the pH is altered, which is due to the dissociation of the acid groups and the protonation of the basic groups as well as tautomeric transformations. For the azo-substituted rhodanines **1a–m**, the diazo-component of which contains a OH group, it is possible to identify several coloured forms: red (conc. H_2SO_4), yellow (pH 1–4), orange (pH 4–8), red (pH 8–10), and violet (pH > 11). For reagents without OH groups, a colour change from lemon-yellow (acid and neutral media) to yellow-orange (pH 9–10) and red (pH 11–13) is observed. Only three coloured forms have been identified for the azothiorhodanines **2a–c**, which contain an OH group: dark-red (acid and neutral media), violet (weakly alkaline media), and blue (strongly alkaline media). The azothiorhodanines are unstable in strongly acid media.

The above pH values and the sequence in which the acid groups of the reagents ionise have been established on the basis of the results of potentiometric and high-frequency titrations as well as the analysis of the absorption spectra at the pH corresponding to the potential jumps.^{3, 7, 16, 22, 65} The nature of the heteroatom (O, S) influences appreciably the pK for the dissociation of the NH group of the heterocycle. In the azothiorhodanines **2a–c**, the NH group is titrated at lower pH; on the other hand, the nature of the substituents in the diazo-component influences the pK of the OH group in the benzene ring.

For the majority of azorhodanines, $pK_{NH} < pK_{OH}$. However, in the case of disulfophenolazorhodanine **1b**, the NH and OH groups are titrated simultaneously, whilst in picramineazorhodanine **1e**, containing two strong electron-accepting substituents, the dissociation of the OH group in the benzene ring precedes that of the NH group.

In concentrated H_2SO_4 , a shift of the long-wavelength absorption band ($\Delta\lambda = 70$ nm) is observed for all 5-azo-substituted rhodanines relative to their absorption band in neutral solutions. According to calculated data,⁶⁵ the bathochromic shift in strongly acid media is due to the protonation of the reagents: the heteroatoms of the rhodanine ring are protonated but not the hydroxy-group in the benzene ring or the nitrogen atom of the azo- or hydrazo-group, because the highest negative charge is present on the heteroatoms of the rhodanine ring.

Several types of tautomerism are possible for azo-substituted rhodanines:



If the reagent contains a OH group in the benzene ring, there is yet another form of tautomerism: hydroxyazoquinone – hydrazone.

Table 1. Structural formulae and names of the reagents.

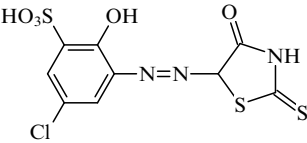
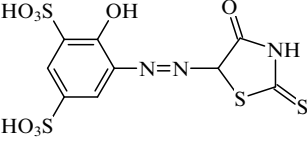
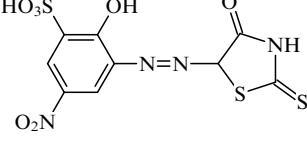
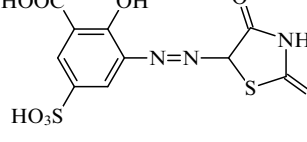
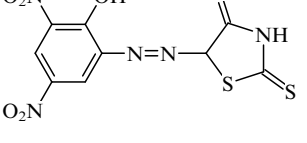
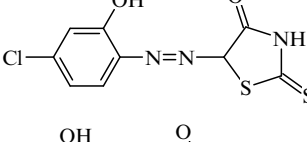
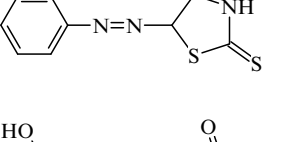
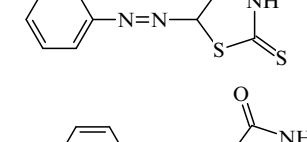
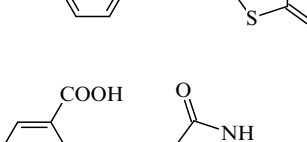
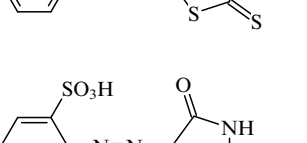
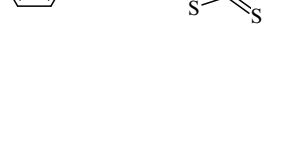
Azo-compound	Number	Name according to IUPAC nomenclature	Trivial name
	1a	5-chloro-2-hydroxy-3-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	sulfochlorophenolazo-rhodanine (SCPAR), rhodazol KhS
	1b	3,5-disulfo-2-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	disulfofphenolazo-rhodanine
	1c	2-hydroxy-5-nitro-3-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	sulfonitrophenolazo-rhodanine
	1d	3-carboxy-2-hydroxy-5-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	carboxysulfofphenol-azorhodanine
	1e	3,5-dinitro-2-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	picramineazorhodanine
	1f	4-chloro-2-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	rhodazol Kh
	1g	2-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	<i>o</i> -phenolazorhodanine
	1h	3-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	<i>m</i> -phenolazorhodanine
	1i	4-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	<i>p</i> -phenolazorhodanine
	1j	2-carboxy-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzene	carboxybenzene-azorhodanine
	1k	2-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	<i>o</i> -sulfobenzeneazo-rhodanine

Table 1 (continued).

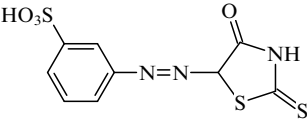
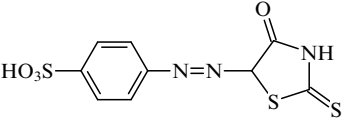
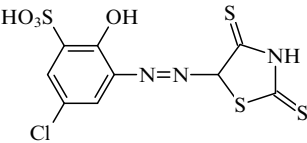
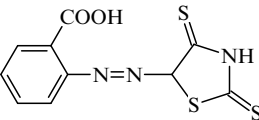
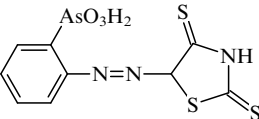
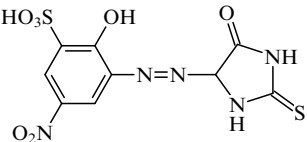
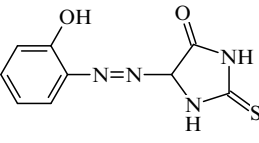
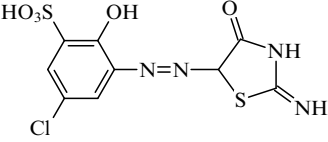
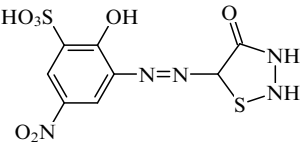
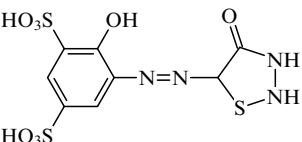
Azo-compound	Number	Name according to IUPAC nomenclature	Trivial name
	1l	3-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	<i>m</i> -sulfobenzeneazo-rhodanine
	1m	4-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	<i>p</i> -sulfobenzeneazo-rhodanine
	2a	5-chloro-2-hydroxy-3-[2,4-dithioxo-5-thiazolidinyl]azobenzenesulfonic acid	sulfochlorophenol-azothiorhodanine
	2b	2-carboxy-[(2,4-dithioxo-5-thiazolidinyl)azo]benzene	carboxybenzeneazo-thiorhodanine
	2c	2-arsono-[(2,4-dithioxo-5-thiazolidinyl)azo]benzene	arsonobenzenazo-thiorhodanine
	3a	2-hydroxy-5-nitro-3-[(4-oxo-2-thioxo-5-imidazolidinyl)azo]benzenesulfonic acid	sulfonitrophenolazothiohydantoin
	3b	2-[4-oxo-2-thioxo-5-imidazolidinyl]azo-phenol	<i>o</i> -phenolazothiohydantoin
	4a	5-chloro-2-hydroxy-3-[(2-imino-4-oxo-5-imidazolidinyl)azo]benzenesulfonic acid	sulfochlorophenolazopseudothiohydantoin
	4b	2-hydroxy-5-nitro-3-[(2-imino-4-oxo-5-imidazolidinyl)azo]benzenesulfonic acid	sulfonitrophenolazopseudothiohydantoin
	4c	3,5-disulfo-2-[(2-imino-4-oxo-5-imidazolidinyl)azo]phenol	disulfophenolazopseudothiohydantoin

Table 1 (continued).

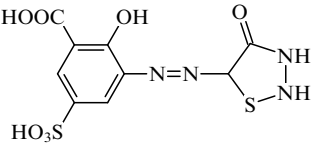
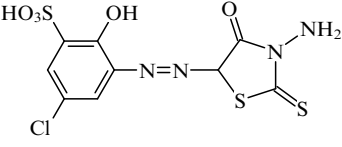
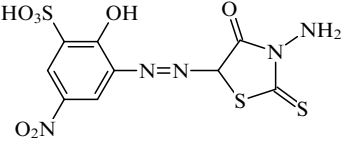
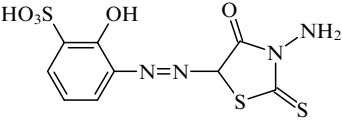
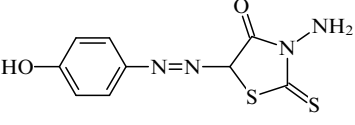
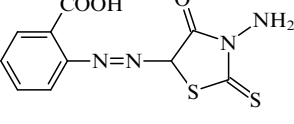
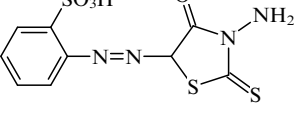
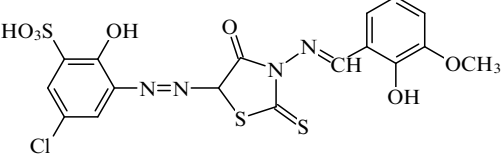
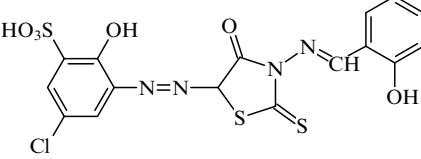
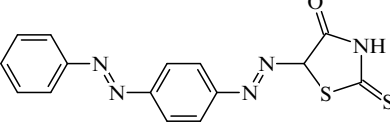
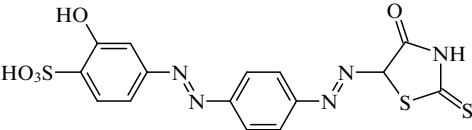
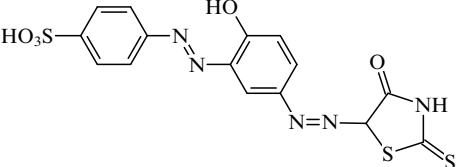
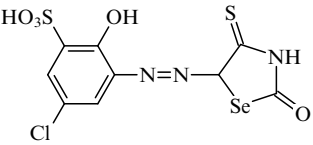
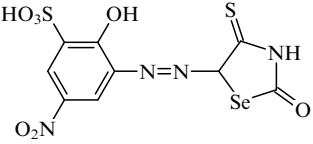
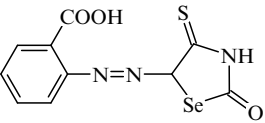
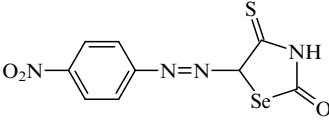
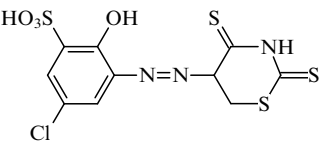
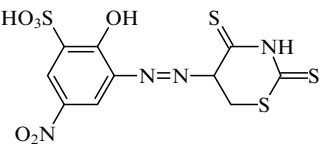
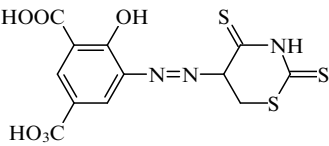
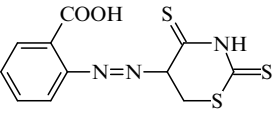
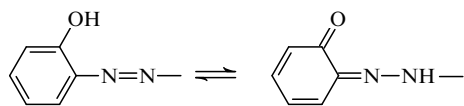
Azo-compound	Number	Name according to IUPAC nomenclature	Trivial name
	4d	3-carboxy-5-sulfo-2-[(imino-4-oxo-5-thiazolidinyl)azophenol]	carboxysulfophenol-azopseudothiohydantoin
	5a	5-chloro-2-hydroxy-3-[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	sulfochlorophenolazo-3-aminorhodanine
	5b	2-hydroxy-5-nitro-3-[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)azo]benzene-sulfonic acid	sulfonitrophenolazo-3-aminorhodanine
	5c	3-[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)azo]-2-hydroxybenzenesulfonic acid	sulfophenolazo-3-amino-rhodanine
	5d	4-[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)azo]phenol	<i>p</i> -phenolazo-3-amino-rhodanine (PATAR)
	5e	[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)-azo]-2-carboxybenzene	carboxybenzeneazo-3-aminorhodanine
	5f	2-[(3-amino-4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	<i>o</i> -sulfonbenzeneazo-3-aminorhodanine
	6a	5-chloro-2-hydroxy-3-[(2-thioxo-3-[(2'-hydroxy-3'-methoxyphenyl)methyleneamino]-4-oxo-5-thiazolidinyl)azo]benzenesulfonic acid	—
	6b	5-chloro-2-hydroxy-3-[(2-thioxo-3-[(2'-hydroxyphenyl)methyleneamino]-4-oxo-5-thiazolidinyl)azo]benzenesulfonic acid	—
	7a	4-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]-benzene	benzeneazobenzeneazo-rhodanine (BABAR)

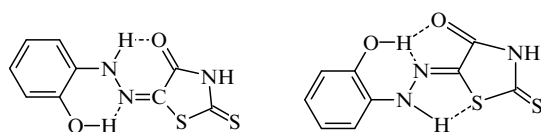
Table 1 (continued).

Azo-compound	Number	Name according to IUPAC nomenclature	Trivial name
	7b	3-hydroxy-4-[(4-oxo-2-thioxo-5-thiazolidinyl)azo]benzenesulfonic acid	sulfophenolazobenzeneazorhodanine (SPABAR)
	7c	2'-hydroxy-5'-[4-oxo-2-thioxo-5-thiazolidinyl]azo]benzeneazobenzenesulfonic acid	sulfobenzeneazophenolazorhodanine
	8a	5-chloro-2-hydroxy-3-[(2-oxo-4-thioxo-5-selenazolidinyl)azo]benzenesulfonic acid	sulfochlorophenol-selenisorhodanine
	8b	2-hydroxy-5-nitro-3-[(2-oxo-4-thioxo-5-selenazolidinyl)azo]benzenesulfonic acid	sulfonitrophenolazo-selenisorhodanine
	8c	2-carboxy-[(2-oxo-4-thioxo-5-selenazolidinyl)azo]benzene	carboxybenzeneazo-selenisorhodanine
	8d	4-nitro-[(2-oxo-4-thioxo-5-selenazolidinyl)azo]benzene	nitrobenzeneazo-selenisorhodanine
	9a	5-chloro-2-hydroxy-3-[(tetrahydro-2,4-dithioxo-1,3-thiazin-5-yl)azo]benzenesulfonic acid	sulfochlorophenolazothiopropiorhodanine, tyrodine
	9b	2-hydroxy-5-nitro-3-[(tetrahydro-2,4-dithioxo-1,3-thiazin-5-yl)azo]benzenesulfonic acid	sulfonitrophenolazothiopropiorhodanine
	9c	2-carboxy-2-hydroxy-5-[(tetrahydro-2,4-dithioxo-1,3-thiazin-5-yl)azo]benzenesulfonic acid	carboxysulfochlorophenolazothiopropiorhodanine
	9d	2-carboxy-[(tetrahydro-2,4-dithioxo-1,3-thiazin-5-yl)azo]benzene	carboxybenzeneazothiopropiorhodanine



The molecules of azo-substituted rhodanines exist in aqueous solutions predominantly in the azodiketo-form. On complex formation, the equilibrium shifts towards the enolic form. This is confirmed by data concerning the number of protons liberated on formation of the complex between copper ions and SCPAR **1a**. The formation of a 1 : 1 complex is accompanied by the liberation of two protons.³ The concentration of the azothiol tautomer is low. Picramineazorhodanine **1e**, for which the contents of the diketo- and thiol forms are approximately the same, is an exception. For the reagents containing a OH group, the first bathochromic shift (pH 6–10) is due to the transition from the azo-form of the reagent to the quinone hydrazone form. In strongly alkaline solutions, a shift of the thione–thiol equilibrium towards the thiol azo-tautomer is observed, this being accompanied by a bathochromic shift of the long-wavelength absorption band. The presence of electron-accepting substituents in the benzene ring, for example in compounds such as sulfonitrophenolazorhodanine **1c** and picramineazorhodanine **1e**, ‘shifts’ the pH of the thione–thiol transition towards lower values.⁶⁵

A series of azorhodanines have been investigated by ¹³C NMR. It was concluded that the reagents containing OH groups in the benzene ring exist in the form of two isomers in organic solvents (OS) such as CD₃OD, DMSO, and CD₃COOD.^{66, 67}



Analysis of IR spectroscopic data for azo-derivatives of rhodanine, 3-aminorhodanine, and thiopropiorhodanine showed that the transition from rhodanine to thiopropiorhodanine entails significant changes in the nature of the interaction of the individual fragments of the heterocycle and a displacement of the equilibrium towards the quinone hydrazone tautomer.⁶⁸

5-Azo-substituted thiohydantoins **3a, b** and pseudothiohydantoins **4a–d** represent the least investigated series of reagents. Their stability is inferior to that of the azorhodanines **1a–m** and azo-3-aminorhodanines **5a–f**. The ionisation sequence of the acid groups is retained.

In the case of 5-azo-compounds based on 3-aminorhodanine and *N*-substituted rhodanines **6a, b**, the same features of the influence of substituents in the diazo-component on the spectroscopic characteristics and acid–base properties of the reagents are observed as for azorhodanines. For the same sequence of the dissociation of the acid groups, a strengthening of the acid properties of the OH groups in the benzene ring is observed. For example, $pK_{OH} = 8.5$ for sulfochlorophenolazorhodanine **1a**, while $pK_{OH} = 7$ for sulfochlorophenolazo-3-aminorhodanine **5a**. The bathochromic effect in concentrated H₂SO₄ is weaker than in the case of azo-substituted rhodanines.¹⁶

The introduction of a second areneazo-group into the reagent molecule affects the state of the reagent in acid media. Whereas the protonation of azorhodanines, accompanied by a deepening of the colour † (from 420 to 500 nm), is observed in 10–15 M H₂SO₄, the bisazo-compounds based on rhodanines **7a–c** are protonated already in 1–2 M H₂SO₄ whereupon the colour becomes even deeper (from 420 to 580 nm). The influence of thermochromism — the change in colour on heating in acid media — has been observed for the bisazo-compounds. A sharp change in the colour

of benzeneazobenzeneazorhodanines as a function of pH is observed in the presence of surfactants (for example, cetylpyridinium chloride) and certain organic solvents (ethanol, propanol, acetone), provided that the content of the latter exceeds 85%. At least two new coloured forms of the reagents, undetected in aqueous solutions in the absence of organic additives, appear under these conditions. It has also been noted that, in the presence of surfactants, the reagents are protonated in more acid media. The deepening of the colour in alkaline and acid solutions is accompanied by an increase in optical density at the absorption maximum.^{21–23}

5-Azo-substituted selenisorhodanines **8a–d** are unstable in solutions. When the pH changes, the colour of solutions of the reagents is altered. The nature of the heteroatom (Se) intensifies the acid properties of azoselenisorhodanines. The protonation of reagents takes place in more dilute acid solutions and is accompanied by a more pronounced deepening of the colour compared with azorhodanines ($\lambda_{max} \approx 530$ and 490 nm respectively).

5-Azo-substituted derivatives of thiopropiorhodanine have a deeper colour in neutral and alkaline solutions than the corresponding rhodanines ($\lambda_{max} \approx 540$ and 430 nm respectively). A change in the dissociation sequence of the NH and OH groups has been noted for these reagents. The OH group in the benzene ring is the first to dissociate (at lower pH). This can be due both to the difference between the acid properties of the azo-components themselves ($pK_{NH} = 5.8$ for rhodanine and 8.1 for thiopropiorhodanine) and to the difference between the mechanisms of the tautomeric transformations. A deepening of the colour of the reagents, as in the case of azorhodanines and azo-3-aminorhodanines, is not observed for azothiopropiorhodanines in strongly acid media. The yellow colour of the reagents in weakly acid media, characteristic of the neutral form, is retained even in concentrated H₂SO₄. A strong influence of surfactants and organic solvents on the colour of the reagents over a wide pH range is observed both for azothiopropiorhodanines and for azorhodanines and rhodanine-based bisazo-compounds.^{22, 23}

IV. Reactions with metal ions and the properties of the complexes formed

The reagents based on aminophenols give rise to the most sensitive and contrasting colour reactions. In the case of 5-azorhodanines, it is possible to identify three complex-formation pH ranges.^{1, 5, 7, 9, 65} Pd, Ag, Cu, Fe, Co, Ni, Zn, Cd, Pb, and Be react in the pH range 6–10. The colour then changes from orange (480 nm) to violet (530–580 nm); $\epsilon = 2 \times 10^4$. Cu, Pd, Ag, and Hg interact at pH 1–6, the colour changing from yellow (430 nm) to red-orange (430–500 nm); $\epsilon = (1.5–3) \times 10^4$. In acid and strongly acid media, noble metals (Pt, Pd, Rh, Ir, Ru, Au, Ag) and Hg interact with the reagent; the reactions are contrasting (430 → 500–530 nm) and highly sensitive; $\epsilon = (2–12) \times 10^4$. The reactions in strongly acid media proceed as a rule over a period of time and in the presence of a 30–50-fold excess of the reagent. The sensitivity and rate of the reaction as well as the solubility of the reaction products depend on the nature and concentration of the acids (mixture of acids) in which the reaction is performed. Heating increases the rate of the reactions of noble metals with azorhodanines, but the yield of the complexes of certain metals diminishes under these conditions. For example, the chloride complexes between platinum(IV) and SCPAR give rise to a colour reaction in the presence of reductants both in HCl and in a mixture of HCl with H₂SO₄ or H₃PO₄; heating decreases the yield of the complex. The colour development time is 20 and 4 h, while $\epsilon = 3.3 \times 10^4$ and 1.0×10^5 in HCl and in the HCl–H₃PO₄ mixture respectively (Table 2).

Rhodium and iridium give rise to a colour reaction with azorhodanines in H₃PO₄ and H₂SO₄; in the presence of CH₃COOH, the sensitivity of the reactions increases; heating to 70 and 90 °C respectively increases the rate of the reaction.

† The bathochromic shift of the main absorption band.

Table 2. Analytical characteristics of the colour reactions of azorhodanines and tyrodine.

Initial form of the elements	Reaction conditions	$\lambda_{\max}$ /nm	$10^{-3} \epsilon$	Ref.
Sulfochlorophenolazorhodanine				
Pt(IV), chloride	3 M HCl, 4 h	500	32	1, 5, 50
	2 M HCl + 2 M H ₃ PO ₄ , 4 h ^b	500	100	1, 5, 50
Pt(III), sulfate	2 M H ₂ SO ₄ + 11 M H ₃ PO ₄ , 30 min, 50 °C	500	100	18, 51, 54, 74
Pt(III), phosphate	12–15 M H ₃ PO ₄ , 50 min, 50 °C	500	100	18, 54, 58
Pd(II), chloride ^a	2 M H ₂ SO ₄ + 8 M H ₃ PO ₄	520	120	1, 5, 75
	1 M HCl	520	50	
Rh(III), chloride	7 M H ₂ SO ₄ (H ₃ PO ₄) + 6 M CH ₃ COOH, 60 min, 70 °C	510	65	4, 5, 51
Rh(II), phosphate	14 M CH ₃ COOH, 60 min, 70 °C	510	8	8, 9
Rh(II), sulfate	7 M H ₂ SO ₄ + 6 M CH ₃ COOH, 10 min, 70 °C	510	17	76
Rh(III), acetate	7 M H ₂ SO ₄ + 6 M CH ₃ COOH, 15 min	510	11	76
Ir(IV), chloride	10 M H ₂ SO ₄ + 6 M CH ₃ COOH, 1 h, 90 °C	510	45	5, 8, 9
Ir(IV), sulfate, phosphate		weak reaction	< 5	5, 8, 9
Ru(III), Ru(IV), sulfate, phosphate, chloride	2 M HCl + 10 M CH ₃ COOH, 30 min, 80 °C	500	16	18, 53, 54, 56, 74
Au(III), chloride	1 M HCl, 10 min	530	53	1, 51
Ag, nitrate	pH 2–6	480	16	1, 7, 77
	pH 6–10	560	15	1, 7, 77
	1–6 M H ₂ SO ₄ , 30 min	500	40	1, 7, 77
Tyrodine				
Pt(IV), chloride	7.6 M H ₃ PO ₄ , 3 h ^b	510	65	14, 16
Pt(III), phosphate, sulfate	3 M H ₂ SO ₄ + 5 M CH ₃ COOH, 30 min ^b	510	65	18, 74
Ag, nitrate	1 M H ₃ PO ₄ + 10 M CH ₃ COOH	535	53	16, 17
	Extraction, pH 5 ^c	550–580	450–900	57, 78
Pb(II), nitrate	pH 2–6	590	42	20, 69
Cd(II), sulfate	pH 4–5.5, 10 min	520	30	72
p-Phenolazo-3-aminorhodanine				
Hg(I), Hg(II), nitrate	15 M H ₃ PO ₄ or 7–10 M H ₂ SO ₄	510	20	19, 73
Cu(III), chloride	1 M HCl, pH 1 ^b	520	40	12
Benzeneazorhodanine				
Hg(I), Hg(II), nitrate	pH 7–9, surfactant	570	100	21–23
Cu(II), chloride	pH 7–9, surfactant	570	20	21–23
Au(III), chloride	pH 7–9, surfactant	570	100	21–23
Re(IV)	2 M NaOH + 0.1 M SnCl ₂	570	$c_{\min} = 0.052 - 0.005 \mu\text{g ml}^{-1}$	79–81
Sulfobenzeneazophenolazorhodanine				
Pd(II), chloride	pH 1–3, surfactant	540	300	21–23
Au(III), chloride	pH 1–3, surfactant	540	600	21–23
Rh(III), chloride	pH 1–3, surfactant	540	100	21–23
Ru(III), Ru(IV), chloride	pH 1–3, surfactant	540	40	21–23

^a For the same sensitivities of the reactions of Pd(II) in the form of chlorides and in the form of sulfates, phosphates, and nitrates, the rates of the last three reactions are higher. ^b The reaction is carried out in the presence of reductants. ^c The two reagents 'tyrodine–macrocylic compound' method.

Gold interacts with azorhodanines in HCl solutions at room temperature, the reaction being completed after 5–10 min. The presence of H₂SO₄ and H₃PO₄ does not affect the sensitivity and rate of the reaction, but the solubility of the complexes increases and the permissible acidity range expands in H₃PO₄. Thus the optical density of solutions of the gold complexes of SCPAR is constant in 2–10 M H₃PO₄ and 0.5–1.3 M HCl, whereas in the absence of H₃PO₄ the maximum development of colour is observed in 1 M HCl.

The silver complexes, like the palladium complexes, have different molar absorption coefficients at the absorption maximum ($\lambda_{\max}$), compositions (reactant : metal ratio in the complex), solubilities, and other characteristics depending on the reaction conditions. In neutral and weakly acid solutions, palladium and silver form readily 1 : 1 complexes with azorhodanines. Saturation is then attained in the presence of a 2–3-fold excess of the reagent.

Among the reagents of the azorhodanine series, those which exist predominantly in the form of the diketo-tautomers in acid and neutral media are best, for example SCPAR, carboxysulphophenolazorhodanine **1d**, and *o*-phenolazorhodanine **1g**. Reagents which contain comparable amounts of diketo- and thiol forms in weakly acid media, for example sulfonitrophenolazorhodanine **1c** and picramineazorhodanine **1e**, are less sensitive. According to quantum-chemical studies, the reactions of silver with benzeneazorhodanines containing electron-donating substituents in the benzene ring should be characterised by a high sensitivity. The presence of a hydroxy-group enhances the contrasting properties of the reaction as a result of the hydroxyazoquinone–hydrazone tautomeric transition. In strongly acid media, the reactions of Ag and Pd as well as those of Rh, Ir, Ru, and Pd proceed over a period of time and in the presence of a large excess of the reagent. The sensitivity of the reactions in strongly acid media is higher than in

neutral and weakly alkaline solutions (pH 7–9). In terms of selectivity, the colour reactions of silver and palladium supplement one another. In strongly acid media, the selectivity of the determination in relation to nonferrous metals is higher and in relation to platinum metals is lower than in weakly acid and neutral solutions (pH 1–6).

5-Azothiorhodanines enter into colour reactions with gold, platinum, and palladium in 1–6 M HCl. The colour changes from red to blue-violet; $\varepsilon = (2-5) \times 10^4$. Silver interacts with 5-azothiopropiorhodanines at pH 1.5, the sensitivity of the reactions being low.

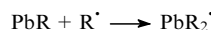
5-Azothiopropiorhodanines and 5-azothiopropiorhodanines do not react with rhodium and iridium, whereas thiopropiorhodanine-based azo-compounds enter into highly sensitive colour reactions with Pt, Pd, Au, and Ag in acid and strongly acid media; the colour changes from yellow to red. The presence of HCl has a negative influence on the reactions of gold and platinum. For platinum and gold, the optimum acid mixture comprises H_3PO_4 (H_2SO_4) and CH_3COOH . For platinum, the rate of reaction and the yield of the complexes increase in the presence of reductants.^{16, 17}

For silver, it is possible to identify two regions of interaction with azothiopropiorhodanines: neutral (pH 5–9, $\Delta\lambda = 30$ nm, $\varepsilon = 2.0 \times 10^4$) and acid (CH_3COOH – H_3PO_4 mixture, $\Delta\lambda = 75$ nm, $\varepsilon = 5.3 \times 10^4$) media. The formation of a coloured silver compound in strongly acid media was first noted for azorhodanines. The interaction of silver with azothiopropiorhodanines has a series of characteristic features compared with azorhodanines. In the case of azothio propiorhodanines, the most sensitive colour reaction with silver takes place in a CH_3COOH – H_3PO_4 acid mixture, while in the case of azorhodanines the addition of even insignificant amounts of CH_3COOH masks the reaction with silver, which can be accounted for by the greater stability of the silver complexes of azothiopropiorhodanines. The reaction of silver with azothiopropiorhodanines takes place in the presence of a 2–5-fold excess of the reagent, while that with azorhodanines requires a 20–50-fold excess of the reagent for saturation. Among the characteristic features of the reactions of silver with azothiopropiorhodanines, one should include also their high selectivity in relation to copper and other nonferrous metals, which is of great practical interest.

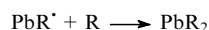
Tyrodine **9a** proved to be a promising reagent for lead.^{20, 69–71} Lead(II) interacts with tyrodine, forming a violet complex. The colour reaction develops over a period of 20–30 min. An increase in the temperature of the reaction mixture and changes in pH and in the reagent concentration do not lead to an increase in the rate of reaction. The curve for the time dependence of the optical density $A = f(\tau)$ is characterised by an induction period of 15–20 min, after which the reaction goes to completion in 1–2 min. It has been noted that the presence of up to 2% of the lead complex of tyrodine accelerates the reaction so much that the induction period is eliminated. An autocatalytic mechanism of the colour reaction between lead and tyrodine has been proposed and can be described as follows in general terms.⁷⁰

The first stage — the formation of a simple lead salt PbR involving the sulfo-group which is ionised under these conditions — is not accompanied by a colour change. This reaction is rapid (pH 3–4), the salt formed is sparingly soluble under the reaction conditions, and a weak opalescence of the solutions is observed. The first stage involves the formation of a 1 : 1 complex (PbR) with participation of the hydroxyazothioketone group of the reagent as a result of either an intramolecular rearrangement or interaction with a second molecule of the reagent (which is present in solution in an excess relative to lead). This stage is slow; 2–3 min after its onset, a change in the colour of the solution is observed and the opalescence vanishes. The third stage — the appearance of the final reaction product PbR_2 — is also slow, since both interacting species, PbR and R , are relatively unreactive: lead is partially hydrolysed and the hydroxy-group in the benzene ring of the reagent is undissociated;¹⁶ both species are to a considerable extent hydrated. It has been suggested that the final product PbR_2 actually possesses catalytic activity: in the fourth

stage, it dissociates, as a result of which compounds or radicals (PbR' and R') appear and are in the most active form at the instant of their formation (for example, as a result of minimal solvation). In the subsequent rapid reactions



and



the number of PbR_2 molecules increases, which is in fact the basis of the catalytic effect. Other mechanisms for the reaction of lead with tyrodine have also been proposed.⁷⁰

From the practical point of view, it is important that the development of the colour reaction between lead and tyrodine is not affected by large amounts of Ni, Co, Fe, Zn, Au, Pt, Rh, Be, Mn, Sn, and Ca; Ag, Hg, and Cu interfere. The high selectivity of the reaction permits the direct determination of lead in a series of systems (for example, in waste waters of the lead industries, anodic and cathodic copper, sulfuric acid) without preliminary separation from the accompanying elements.²⁰

A series of quantitative characteristics of the colour reaction of cadmium with tyrodine have been obtained.⁷² The colour reaction of cadmium is unaffected by 500–10 000-fold excess amounts of alkali and alkaline earth elements and 10–100-fold excess amounts of heavy metals; Pb, Hg, Ag, and Cu interfere. The influence of copper and mercury may be eliminated with the aid of thiourea. The colour reaction between cadmium and tyrodine has served as the basis of methods for the determination of cadmium in various types of water. Like lead, cadmium forms complexes with Cd : R = 1 : 2 under analytical conditions.⁷²

The colour reactions of azo-compounds based on 3-aminorhodanine **5a–f** and substituted 6-aminorhodanine **6a,b** with Pt, Pd, Au, and Ag are close to the corresponding reactions of azorhodanines as regards sensitivity, contrasting properties, and rate of development of the colour. On the other hand, like azothiorhodanines and azothiopropiorhodanine, these compounds do not react with rhodium and iridium, which is apparently associated with their instability in strongly acid media on heating, *i.e.* under conditions where the kinetically inert rhodium and iridium complexes react. The azo-compounds based on 3-aminorhodanine, for example *p*-phenolazo-3-aminorhodanine **5d**, are of considerable interest for the determination of monovalent and divalent mercury primarily by virtue of their high selectivity. Mercury interacts with the reagent in strongly acid media at room temperature with formation of a stable raspberry-red complex. Large amounts of Pb, Zn, Bi, Be, Ba, Ca, Mo, Ir, Ru, and Rh do not interfere with the determination; Ag, Au, and Pd do interfere. The reagent has been used in the analysis of biological objects and industrial waters without preliminary separation of mercury from the accompanying elements (in contrast to the widely familiar method for the determination of mercury with the aid of pyridyl-lazoresorcinol).¹⁹

Derivatives of benzeneazobenzeneazorhodanine **7a–c** enter into colour reactions with noble and heavy metals, but the sensitivity of the reactions is low. In terms of sensitivity, these reactions are inferior to the corresponding reactions with rhodanine-based monoazo-compounds. The colour reactions of azobenzeneazorhodanines proceed in less acid media. This can apparently be accounted for by the characteristic features of the structure of the reagents, namely by the presence of an extended π -electron system. This decreases the acidity required for the protonation of the reagents, which is accompanied by a pronounced deepening of the colour (λ_{max} for the neutral forms of benzeneazobenzeneazorhodanines is 440–480 nm, while that for the protonated forms is 580–620 nm). One of the important features of these reagents is that they enter into highly sensitive and contrasting colour reactions with noble and heavy metals in the presence of surfactants [$c_{\text{surf}} < \text{CMC}$ (CMC is critical micelle concentration)] and certain organic solvents when the content of the latter is more than 80%–85%.^{21–23} Two types of colour

reactions are characteristic of modified derivatives of benzene-azobenzeneazorhodanine. The first type of the interactions of these reagents includes those with Cu, Hg, Ag, Pd, and certain other elements in neutral and alkaline solutions, the reactions being characterised by effective contrasting properties ($\Delta\lambda = 250$ nm) and a higher sensitivity, the absorption coefficients ε increasing by a factor of 5–10. The interactions of the second type are those with Pt, Pd, Rh, and Ru (heavy metals and silver do not enter into reactions of this kind). The reactions proceed at pH 1–3 and are characterised by an even more pronounced increase in sensitivity with virtually unchanged contrasting properties. The reactions of Au and Pd with modified SBAPAR **7c** are the most sensitive, the absorption coefficients ε being 3×10^5 and 6×10^5 respectively. The sensitivity of reactions of the second type is greatly superior to that of the most sensitive reactions of noble metals with SCPAR and tyrodine. A high rate of development of the colour in these reactions should also be noted.

The ratio of the reagent to the metal in the complex (molar ratios method) is 2 : 1 in the presence of cetylpyridinium chloride in the case of reactions of the first type. Compounds even more 'saturated' with respect to the reagent are formed by reactions of the second type. The cause of such an increase may be associated both with the increase in the coordination capacity of the metal (for example, by virtue of dehydration on treatment with a surfactant or organic solvent) and with a change in the state of the reagent itself (for example, its aggregation, preceding the formation of the complexes).

Table 2 presents the characteristics of reactions of metal ions with the reagents (including their modified forms). The compounds examined apparently belong to the class of the most promising reagents of the azorhodanine and azo-thiopropiorhodanine series for the determination of noble and heavy metals both in solutions and in the solid phase.^{13, 73}

V. Characteristic features of the interaction with acido-complexes of platinum metals

The reactions of sulfate (Pt, Pd, Rh), phosphate (Pt, Pd, Rh, Ir), acetate (Rh), and hydroxynitrate (Pd) complexes have been investigated together with the traditional chloride complexes using sulfochlorophenolazorhodanine and tyrodine as the reagents^{1, 4, 8, 9, 53–56, 82} (see ‡).

The vast majority of methods for the determination of platinum elements are known to be applicable only to chloride systems. Analysis of other systems involves as a rule an additional stage in which the initial complexes are converted into chloride complexes. On the other hand, from the practical standpoint it is important to investigate the reactivities of acido-complexes of platinum metals based on various oxygen-containing acids (H_2SO_4 , HClO_4 , H_3PO_4 , CH_3COOH). These acids are in fact largely employed at various stages in the processing of natural and industrial materials and in refining. Studies of the reactivities of dimeric complexes of platinum elements with a metal–metal bond have acquired special importance. Such compounds have unusual thermodynamic and kinetic characteristics. They are readily aquated and enter into substitution reactions more vigorously than the chlorides. This leads to new possibilities in the analytical chemistry of the platinum elements. In the dimeric complexes, the

platinum elements can manifest unusual chemical properties. Many of the difficulties in the development of methods for the photometric determination of platinum metals, for example in the sulfate or phosphate form, are known to be associated with hydrolysis and the formation of unreactive polymeric forms in dilute acid solutions. A characteristic feature of azorhodanines and their analogues consists in their ability to enter into highly sensitive colour reactions with noble metals in strongly acid media, in which readily hydrolysable forms of the platinum elements may retain their reactivity. Simultaneously with the investigation of the colour reactions of acido-complexes of platinum metals, the behaviour of the initial forms of the complexes under the conditions of their colour reactions has been investigated spectrophotometrically. Taking into account the results of such studies, a hypothesis has been put forward concerning the nature of the active forms of the platinum elements and the factors determining their yield. Procedures have also been proposed for the stabilisation (standardisation) of the active forms and in certain cases procedures for the conversion of the initial forms into active ones.^{53, 56}

Dimeric platinum(III) phosphate and sulfate complexes as well as their chloride forms give rise to brightly coloured compounds with sulfochlorophenolazorhodanine and tyrodine.^{8, 53–56} Depending on the nature of the ligand and the oxidation state of the central atom in the initial complex, the conditions, kinetics, sensitivity, and selectivity of the colour reactions are different. Platinum phosphate and sulfate complexes interact with organic reagents in more acid media and a higher kinetic reactivity, compared with platinum(IV) chloride complexes, is characteristic of them. Markedly different effects of reductants on the colour reactions of acido-complexes of platinum have also been observed. Thus the reactions of platinum(IV) chloride complexes with organic reagents are strongly accelerated in the presence of reductants, whereas the influence of the latter on the colour reactions of the phosphates and sulfates is insignificant. The absorption spectra of platinum complexes with organic reagents are independent of the initial form of platinum.

The characteristics (reaction conditions, solubility of the products, behaviour in relation to reductants) of the colour reactions of dimeric platinum sulfate and phosphate complexes are similar. The coloured compounds of platinum sulfate and phosphate with organic reagents are more soluble and more stable on heating than the chloride forms of platinum. In the reactions of the chloride complexes, heating of the solutions even to 40–50 °C reduces the yield of the coloured compound, although the rate of reaction increases. Heating of the sulfate and phosphate complexes to 50–70 °C shortens the reaction time from 4 h to 30–60 min. Regardless of the nature of the ligand in the initial complex, the reaction with the organic reagent is apparently preceded by the stage involving the reduction of platinum(IV) to platinum(II). In the case of platinum(III) sulfate and phosphate complexes, the Pt–Pt bond is initially dissociated with formation of platinum(II) and platinum(IV), after which platinum(IV) is reduced to platinum(II). The reduction of platinum in the sulfate and phosphate complexes is faster than in the platinum(IV) chloride complexes and takes place at lower concentrations of the reductants in solution. One of the causes of the appreciable difference between the reactivities of the acido-complexes of platinum investigated in relation to organic reagents probably consists in the difference between the rates and conditions in the aquation and reduction of the initial forms. Evidently, the similarity of the behaviour of platinum sulfate and phosphate complexes and the characteristics of the colour reactions can be accounted for by the similar structures of such complexes.

The reactions of dimeric platinum sulfate and phosphate complexes are highly sensitive and selective. The complexes exhibit a high kinetic reactivity. All these features make it possible to classify the reactions considered as the most promising for the determination of platinum. Whilst showing equal resistances to the interfering effects of alkaline earth and alkali metals, the

‡ The sulfate complexes of platinum(III) $\{\text{K}_5\text{H}_3[\text{Pt}_2\text{SO}_4(\text{HSO}_4)_8\text{O}_5]\}$, tri- and tetra-valent ruthenium $\{\text{K}_2\text{H}[\text{Ru}_2(\text{O} \cdot \text{H}_2\text{O})_2(\text{SO}_4)_3]\}$, and rhodium(II) $[\text{Cs}_4\text{Rh}_2(\text{SO}_4)_4(\text{H}_2\text{O}) \cdot 2\text{H}_2\text{O}]$, the phosphate complexes of platinum(II, IV) $\{\text{K}_2(\text{H}_3\text{O})_3[\text{Pt}_2(\text{PO}_4)_3(\text{HPO}_4)\text{H}_2\text{O}]\}$, palladium(II) $\{\text{K}_3(\text{H}_3\text{O})_3[\text{Pd}(\text{P}_2\text{O}_7)_2] \cdot 2\text{H}_2\text{O}\}$, rhodium(III) $[\text{Na}_3(\text{H}_3\text{O})_6\text{Rh}(\text{P}_2\text{O}_7)_3]$, iridium(IV) $\{\text{K}_6\text{H}_2[\text{Ir}_4\text{O}_3(\text{H}_2\text{PO}_4)_{10}(\text{OH})_8]\}$, and tri- and tetra-valent ruthenium $[\text{K}_3\text{Ru}_2(\text{H}_2\text{P}_2\text{O}_7)_5 \cdot 7\text{H}_2\text{O}]$, the acetate complexes of rhodium(II) $[\text{Rh}_2(\text{CH}_3\text{COOH})_4 \cdot 2\text{H}_2\text{O}]$ and rhodium(III) $[\text{Rh}(\text{CH}_3\text{COO})_3]$, and the hydroxynitrate complex of palladium(II) $[\text{Pd}(\text{NO}_3)_2(\text{OH})_2]$ have been obtained by members of the Institute of General and Inorganic Chemistry of the Russian Academy of Sciences.^{83–91}

selectivity of the sulfate and phosphate complexes with respect to Cu, Fe, and other transition metals as well as Rh and Ir is markedly higher compared with the chloride forms. However, the selectivity with respect to silver and mercury is higher for the chloride forms. On the other hand, from the practical point of view, it is important that conditions have been found under which platinum sulfates and phosphates are stable and retain their reactivity for a long time. The possibility of converting kinetically inert platinum chloride complexes into more reactive ones, for example the phosphate complexes, has also been demonstrated; in this case, the reaction takes place in concentrated H_3PO_4 solutions at 200 °C in the presence of perchloric acid, which decomposes the chlorides, oxidising Cl^- to Cl_2 , the aquohydroxo-complexes formed react directly with H_3PO_4 .

Palladium(II) sulfate, phosphate, hydroxonitrate, and chloride complexes interact with SCPAR under similar conditions. The spectroscopic characteristics of these complexes are close, but the kinetic reactivity of the sulfates, phosphates, and hydroxonitrates is higher than that of the chlorides. The solubilities of the products of the interaction of the sulfates, phosphates, and hydroxonitrates are higher than those of the corresponding compounds derived from the chlorides.^{8,9,54,82}

Iridium sulfate and phosphate complexes are less active in reactions with organic reagents than the chloride complexes. On prolonged heating, iridium in the form of phosphates and sulfates reacts with sulfochlorophenolazorhodanine in strongly acid media. However, these reactions are less sensitive than those involving the chloride complexes.^{8,9}

Tri- and tetra-valent ruthenium sulfate, phosphate, and chloride complexes react with sulfochlorophenolazorhodanine to form coloured compounds with similar spectrophotometric characteristics. The reactions of ruthenium sulfate and phosphate with the reagent are preceded by a stage involving the conversion of the initial forms of ruthenium into the chloride form, which has been identified as $[\text{Ru}_2\text{OCl}_{10}]^{4-}$ on the basis of absorption spectra. Regardless of the nature of the ligand and the oxidation state of ruthenium in the initial complex, the aquochlororuthenium(III) complex apparently reacts with the organic reagent. The conditions of the colour reaction (a mixture of HCl with CH_3COOH) and the reducing properties of the reagent ensure the conversion of the initial forms of ruthenium into the active form.^{53,56}

In the presence of organic solvents, for example CH_3COOH , the formation of the chloride form from the initial phosphate and sulfate forms is possible in more dilute HCl solutions, for example in 0.5–2 M solutions instead of 5–7 M solutions. In the presence of organic solvents, the degree of hydrolysis of the chloride form apparently diminishes; under these conditions, the organic solvent is a stabilising additive. Furthermore, in the presence of organic solvents, the formation of the active form — the aquochlororuthenium(III) complex — and the substitution for the organic ligand take place more readily than in the case of large amounts of HCl, which entails an increase in the sensitivity of the reaction. Acido-complexes of ruthenium do not enter into colour reactions with sulfochlorophenolazorhodanine in sulfuric and phosphoric acid solutions, which is due to the formation of unreactive hydrolysed forms under these conditions. The interaction of ruthenium with sulfochlorophenolazorhodanine results in the formation of 1:2 complexes. Under the conditions of its interaction with ruthenium, the reagent is in a neutral form¹⁶ and apparently behaves as a monodentate ligand, ruthenium being coordinated to the reagent *via* the thioxo-group of rhodanine.

Regardless of the nature of the ligand and the oxidation state of the central atom in the initial rhodium complexes — rhodium(II) and rhodium(III) sulfates, phosphates, and acetates and rhodium(III) chlorides — coloured compounds with $\lambda_{\text{max}} = 510 \text{ nm}$ are formed in the reactions with SCPAR. Similar dependences of the yields of the reaction products on the nature and concentration of the acids and the reagent are observed for the above rhodium complexes. It has been suggested that the nature of the reactive form of rhodium in the reactions with SCPAR is the

same for all the initial forms of di- and tri-valent rhodium. There are significant differences in the kinetics and sensitivities of the reactions. The dimeric rhodium(II) acetate and sulfate complexes are more reactive in the ligand substitution reaction than, for example, rhodium(III) chlorides and acetates; the highest reactivity has been noted for the dimeric acetate complex.

The rate of formation of the coloured rhodium(II) acetate complex of SCPAR is unusually high. The reaction develops at room temperature over a period of 10–20 min and is characterised by a fairly high sensitivity. The high kinetic reactivity of the dimeric rhodium(II) complexes compared with the corresponding rhodium(III) complexes is due to their ability to form ‘more readily’ the labile aquo-complexes, with participation of which many processes, including ligand substitution reactions, take place faster.

In the case of the rhodium(III) sulfate, phosphate, and chloride complexes, one may postulate that one of the intermediate stages of the overall complex formation reaction between rhodium and SCPAR is the conversion of the initial forms into the more reactive (dimeric acetate or acetate-sulfate) rhodium(II) complexes. This is confirmed by the fact that the conditions of the colour reactions of acido-complexes of rhodium with SCPAR (mixture of 7 M H_2SO_4 and 6 M CH_3COOH , heating to 60–70 °C, excess of the reducing agent) are virtually identical with those in the preparative synthesis of these complexes.^{4,8,9}

The study of the state of solutions of rhodium acetate and sulfate complexes has shown that under certain conditions they retain their reactivity in relation to SCPAR for a fairly long time. The high kinetic reactivity of the dimeric rhodium complexes [in the first place, rhodium(II) acetate] as well as the high sensitivity of their reactions with SCPAR are properties which may serve as the basis for the creation of new high-speed methods for the determination of rhodium *via* reactions of its dimeric complexes.

VI. Applications

1. Photometry

One of the main fields in which azorhodanines and azothiopropiorhodanines are used is photometry. The distinctive features and advantages of azorhodanines as photometric reagents are as follows.

Firstly, the high sensitivity of the determination of the elements, primarily the platinum metals, and, secondly, the interaction with metal ions over a wide pH range. These properties are due to the presence of several functional-analytical groups in the reagent molecules. For example, there are three regions corresponding to the interaction of silver with SCPAR — pH 2–6 and 7–10 and 1–6 M H_2SO_4 , which makes it possible to employ in practice the ‘optimum’ region of the interaction, depending on the composition and the content of the object analysed. Thus, in the determination of silver with the aid of SCPAR, for example at pH 5–7, the presence of the remaining platinum group elements (except palladium) is permissible, whereas the determination of silver in strongly acid media (for example, in 6 M H_2SO_4) permits the presence of a much greater excess of nonferrous and heavy metals.

Thirdly, the reactivity of the reagents in relation to surfactants and certain organic solvents. Under certain conditions, this leads to the formation of modified forms of the reagents, the colour reactions of which with platinum and other metals are characterised by an unusually high sensitivity [$\varepsilon = (100–600) \times 10^3$].

Fourthly, the interaction with platinum metals in the form of various acido-complexes (chlorides, phosphates, sulfates, and acetates). Such interaction is due to the fact that azorhodanines and azothiopropiorhodanines react with platinum metals in strongly acid media, where the presence of stabilising additives (CH_3COOH , HCOOH , metal salts) is permissible. All these features hinder the hydrolysis of the platinum metals, *i.e.* hinder the formation of their unreactive forms.

Fifthly, the possibility of analysing solutions containing both individual forms of platinum metals and their sum. For example, ruthenium is determined in chloride and sulfate solutions, which are used for its preparation in the course of the complex processing of copper–nickel ores. The conditions in the colour reaction of ruthenium with SCPAR (mixture of HCl with CH₃COOH) (Table 2) and the reducing properties of the reagent ensure a fairly rapid conversion of the initial forms of ruthenium into the reactive form — ruthenium(III) chloride.

Sixthly, the high selectivity of the determination. Despite the fact that azorhodanines and azothiopropiorhodanines are group reagents, a high selectivity of the determination is attained by virtue of different spectroscopic characteristics of the colour reactions with the elements (sensitivity and contrasting properties of the reactions), reaction conditions (nature and concentration of the acids, pH), reaction kinetics, the stability of the complexes formed, and, in the case of noble metals, also the different reactivities of their initial forms.

Highly sensitive methods have been developed for the determination of Pt, Pd, Rh, Ir, Ru (in the form of various acido-complexes), Au, and Ag with sulfochlorophenolazorhodanine, Pt, Pd, Au, Ag, Pb, Cd, and Cu with tyrodine, Pd, Pt, Ru, Rh, and Cu with sulfobenzeneazorhodanine derivatives, and Hg and Cu with *p*-phenolazo-3-aminorhodanine, which have found applications in the analysis of various natural and industrial objects.^{1, 2, 4–11, 13–23, 50–56, 58, 69, 72, 74, 76, 77, 82, 92–100}

2. Differential photometry

The problem of creating direct differential-photometric (DP) methods for the determination of noble metals which are no less accurate than gravimetric or titrimetric methods (or approach them in accuracy) but are greatly superior to the latter in the speed of the determination has been successfully solved by virtue of the application of azorhodanines and tyrodine. The success has been due to the ready solubility of both the reagents themselves and of their complexes with noble metals, the possibility of the direct determination of the noble metals and a series of accompanying elements in natural and industrial objects, the possibility of using various acido-complexes as the initial form in reactions with the reagent, the fairly high kinetic reactivity of some of these complexes (phosphates, sulfates, acetates), and, in the case of Pt, Rh, and Ir chloride complexes, the possibility of activation, for example with ascorbic acid or copper salts. In the differential measuring procedure, the fundamental light absorption law holds over a wide range of concentrations of the noble metal. The DF methods developed are universal and, when combined with the photometric version, make it possible to determine 0.2–250 µg ml⁻¹ of the noble metal. High-speed DF methods are used in the analysis of alloys and composite materials for the direct determination of silver (Ag–Cu, 10%–90% Ag), platinum (Pt–Rh, Pt–Ir, 10%–20% Pt), and ruthenium [lead ruthenite, bismuth ruthenite, 30% Ru; residue remaining after the combustion of the waste from the manufacture of materials for the electronic industry containing Pb and Bi (ash), 50% Ru] and also in the analysis of other objects.^{24, 58, 74, 77}

3. Sorption-photometric methods

The methods in which azorhodanines are used both for determination and detection, on the one hand, and for the separation and concentration of reagents, on the other, merit special attention. Such are the electrophoretic and chromatographic (on paper and in a thin layer of sorbent) methods as well as methods based on the use of immobilised reagents. Their principal advantages are simplicity, clarity, and high speed of execution (primarily at the level of qualitative and semiquantitative visual determinations — test methods) and the possibility of combining separation (including the procedure based on the specific effect of the reagent) and concentration from large volumes under static or dynamic conditions.

a. Chromatographic and electrophoretic method

Conditions have been found and limits have been established for the detection of toxic heavy metals such as Cu, Pb, Zn, Fe, Ni, Cd, and Hg (the organic forms are methyl-, propyl-, and phenylmercury, while the inorganic forms are Hg⁺ and Hg²⁺) on a thin layer of sorbent (sorbfil, silufol) with the aid of azorhodanine derivatives — SCPAR and PATAR.

The sensitivity of the visual determination is 0.1–0.5 µg, and for Cu 0.01 µg, of the element in the zone. The possibility of the semiquantitative estimation of the content of both individual toxic elements and their sum has been demonstrated. The selectivity of the detection is achieved as a result of the specificity of the reagents, variation of the colour reaction conditions in a thin layer (nature of the acid, pH), and selection of the separation conditions on the chromatograph.

Conditions have been developed for the separation of various forms of mercury — organic (phenyl-, methyl-, and propylmercury) and inorganic (Hg⁺, Hg²⁺).

At the same time, when SCPAR is used in an ammoniacal medium as the mobile phase, it is possible to separate methylmercury (*R_f* = 0.9) and propylmercury (*R_f* = 0.45) from phenylmercury (*R_f* = 0.0) and inorganic mercury (*R_f* = 0.0) in the form of their coloured complexes with the reagent. The separation of organic and inorganic forms of mercury and their separation from other heavy metals with subsequent detection by means of SCPAR have also been achieved using other chromatographic systems. When chromatograms are sprayed with azorhodanines, red zones appear against the yellow background of the sorbent which is due to the formation of complexes of different forms of mercury with the reagent. The colour in the zones develops over a period of 1–5 min and is maintained for between 2 h and several days. The methods for the determination of toxic elements in a thin layer of sorbents have been tested on food products.¹²

Procedures have been devised for the development of chromatographic and electrophoretic zones of both individual noble metals (except osmium) and their sum in the form of various acido-complexes. The sensitivity of the visual detection is 0.5–0.01 µg of the element in the zone. Together with high sensitivity and stability (as a function of time) of the colour, the advantage of SCPAR as the developer over other reagents consists in the fact that SCPAR develops zones corresponding to different acido-forms of the noble metal. Methods have been proposed for the electrophoretic and paper and thin-layer chromatographic separation with subsequent detection of the noble metal (in the form of chloride complexes) by means of SCPAR in the Pd–Ir, Pd–Rh, Ir–Rh, Pt–Pd–Au, Pd–Pt–Ir, Pd–Pt–Rh, Pd–Au, and Pt–Rh systems. These methods have found applications in the analysis of alloys.^{101–102}

The electrophoretic mobilities of noble metals in the form of coloured compounds with azorhodanines in buffer solutions based on formic, acetic, and oxalic acids (pH 1.5–1.7), acetic and boric acids (pH 2), and pyridine and oxalic acid (pH 5.9) have been investigated. The electrophoretic characteristics have been determined. A clear-cut separation of the zones is observed in the case of Pd–Ag, Pt–Ag, and Pd–Au in the form of their complexes with SCPAR and other reagents.¹⁰³

b. Sorption-photometric methods based on the use of immobilised reagents

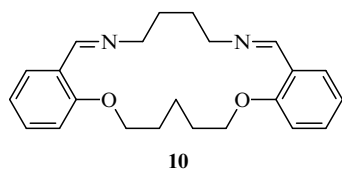
The prospects for the analytical application of the colour reactions of azorhodanines in the solid phase have been demonstrated.^{13, 73} Azorhodanines immobilised on a polymer matrix (for example, on a polyamide caprone membrane, a polyacrylonitrile fibre filled with finely disperse KU-2 cation exchanger, and a fabric with phosphate groups) retain their reactivity in relation to noble and heavy metals over a wide pH range (1–10), the reactions being fairly rapid. The similarity of the spectroscopic characteristics of the reactions of azorhodanines in solution and in the sorbent phase has been noted.

High-speed and sensitive methods for the determination of Pt, Pd, Au, Ag, Cu, and Hg with a $1-3 \mu\text{g ml}^{-1}$ detection limit have been developed with the aid of azorhodanines and azothiopropiorhodanines immobilised on polymer supports.^{22,23} A microporous polyamide material (a caprone membrane) or a polyacrylonitrile fibre filled with a finely-disperse cation exchanger (KU-2) have been used as supports. The supports are employed in the form of discs 0.8, 1, and 2 cm in diameter and with a mass of 2–10 mg. The reagents are immobilised by immersing the support disc in 10^{-5} – 10^{-6} M solutions of the reagents in a weakly acid medium (pH 2–5) for 15–30 min. Two versions of the determination have been proposed — static and dynamic. In the first case, the coloured discs (photometric elements) are lowered into a flask containing the sample (the preliminary preparation of the sample is carried out — acidification and introduction of additives activating the colour reaction and giving rise to a high rate of response) and are kept there for 5–60 min at 20–50 °C. In the second case, the coloured discs are placed in the cell of an optical sensor analyser or a vacuum pump is employed. The colour change on the discs is estimated visually (test methods) or from the change in the diffuse reflection coefficients. A high sensitivity of the determination is attained both as a result of the employment of qualitative reagents and the possibility of accumulating the element analysed from dilute solutions on the coloured support disc. The selectivity is ensured by the specificity of the immobilised forms of the reagents, the sorption conditions, and the kinetic differences between the colour reactions on the polymer matrix.

A sorption-photometric method for the determination of silver in natural waters with a detection limit of $5 \mu\text{g litre}^{-1}$ in accordance with the 'sorbent–metal–reagent' scheme has been developed. It involves the sorption of silver on discs made of polyacrylonitrile fibre filled with KU-2 cation exchanger and subsequent detection of silver in the sorbent phase with the aid of rhodazol Kh (compound **1f**) at 490 nm.²³

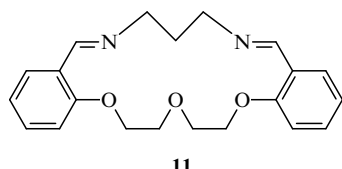
4. Extraction-photometric methods

The extraction-photometric method for the determination of silver (the 'two reagents' method) is based on the ability of silver to form mixed coloured compounds with azorhodanines or azothiopropiorhodanines and certain macrocyclic compounds (MCC) of the type



10

12,13-dibenzo-1,15-diaza-5,11-dioxacyclononadeca-1,14-diene



11

12,13-dibenzo-1,15-diaza-5,8,11-trioxacyclononadeca-1,14-diene

The MCC are used initially for the selective extraction of silver in the form of ionic associated species $[\text{Ag-MCC}]\text{Pi}$ (Pi = picrate). Then tyrodine, for example, is added to the organic layer. It interacts with the associated species to form mixed coloured compounds (reagent–Ag–MCC) characterised by an unusually high sensitivity; $\epsilon = (4-9) \times 10^5$. With the aid of the 'two reagents' method, it has been possible to reduce by more than an order of magnitude the detection limit for silver and also to increase the selectivity of the determination relative to Au, Pd, Pb, and Hg (Table 3).^{57,58} The method has been used in the determination of silver in drinking water. A somewhat greater complexity of this

Table 3. Photometric determination of silver with tyrodine by the direct method and by the 'two reagents' (MCC–tyrodine) method.

Characteristics of method	Direct determination with tyrodine ^a	'Two reagents' method, determination in extracts	
		see ^b	see ^c
Range of concentrations of compounds determined $\mu\text{g ml}^{-1}$	0.2–2.4	0.01–0.10	0.02–0.40
Detection limit $\mu\text{g ml}^{-1}$	0.04	0.015	0.008
ϵ ($\lambda_{\text{max}}/\text{nm}$)	5×10^4 (540)	4.5×10^5 (550)	9×10^5 (580)
Selectivity factor			
Zn	5×10^3	1×10^4	1×10^4
Co	1×10^3	1×10^4	7×10^4
Pb	50	—	1×10^4
Hg	1	200	200
Pd	1	1×10^3	100
Au	1	500	—
Cu	5×10^3	500	3×10^3
Cl	1	25	25

^a In 1 M H_3PO_4 + 10 M CH_3COOH solution.¹⁷ ^b Tyrodine–MCS (compound **10**) in dichloroethane.⁷⁸ ^c Tyrodine–MCC (compound **11**) in a chloroform–triphenylphosphine mixture.⁵⁷

method compared with the usual photometric version must be included among its disadvantages.

In order to increase the selectivity of the determination of silver with SCPAR in an inorganic raw material, silver was extracted (in the form of its complex with the reagent) with cyclohexanone (in the presence of tributyl phosphate) and photometric measurements on the coloured organic layer was subsequently carried out.⁵⁸

5. Automatic analytical schemes

A version of the flow-injection analysis (FIA) has been used with the aid of SCPAR for the spectrophotometric determination of noble metals.^{104,105} The difficulty of devising such methods arises from the kinetic inertness of noble metal complexes in reactions with the organic reagent.

In order to investigate the conditions under which the colour reactions of Au and Ag take place, a two-channel flow system was employed. Best results in the determination of silver were obtained with the following parameters of the FIA system: microvolume of solution containing the metal to be determined $V_0 = 200 \mu\text{l}$; length of thermostated reaction coil $l = 30 \text{ cm}$; flow rate of the support (dilute acid solution) with the metal to be determined $v_1 = 2.8 \text{ ml min}^{-1}$; flow rate of reagent solution $v_2 = 1.2 \text{ ml min}^{-1}$. The range of silver contents which can be determined is $0.3-4.5 \text{ mg litre}^{-1}$. The speed of the analysis is 180 determinations per hour. In the case of the slower reaction involving gold chloride complexes, the peak height is a maximum at $V_0 = 200-300 \mu\text{l}$, $v_1 = 1.2 \text{ ml min}^{-1}$, $v_2 = 0.8 \text{ ml min}^{-1}$, and $l = 60 \text{ cm}$. The range of gold contents which can be determined is $2-19 \text{ mg litre}^{-1}$. The speed of the analysis is 90 determinations per hour. Comparison of the conditions in the colour reactions of Au and Ag with SCPAR in the usual photometric version and in the FIA version demonstrates an appreciably lower optimum acid concentration in the latter case, which is necessary to ensure a higher rate of reaction and this is in its turn important for obtaining the narrowest and highest peaks and also attaining a higher number of determinations per unit time.

The flow-injection method for the determination of palladium with SCPAR at pH 5 is characterised by a speed of analysis of 120 determinations per hour.¹⁰⁵ The high speed of analysis in this case

is due primarily to the high rate of interaction of palladium with SCPAR in weakly acid media. The necessary selectivity of the method is achieved with the aid of masking substances. The range of concentration which can be determined is $0.045\text{--}30\text{ mg litre}^{-1}$. Thus a high number of determinations of noble metals per unit time is attained in FIA systems without loss of sensitivity and without narrowing the range of contents which can be determined compared with the static version employing the same reagent — SCPAR.

Continuous flow analysis (CFA) also belongs to the class of high-speed automatic analytical methods.¹⁰⁶ A photometric method has been proposed for the determination of silver with SCPAR in the presence of nonionic surfactants (Triton-100 X).¹⁰⁷ The introduction of the surfactant into the system stabilises the hydrodynamic flow parameters (ensures the stability of the rate and uniformity of the flow) and improves the solubility of the reagent, which has a positive effect on the reproducibility of the results. The selectivity of the determination of silver relative to Pb, Co, Ni, Cu, and Zn also increases under these conditions. The principal characteristics of the method are as follows: range of silver contents which can be determined $(0.4\text{--}0.5) \times 10^{-5}\text{ M}$; relative standard deviation 0.05; Triton-100 X content $0.3\% \text{--} 0.03\%$. The determination is carried out in 0.1 M HNO_3 .

6. Other methods

The kinetic determination of rhenium is based on the catalytic effect of tetravalent rhenium ions on the reduction of benzene-azobenzeneazorhodanine **7a** by tin(II) in an alkaline medium ($1.5\text{--}2.5\text{ M NaOH}$) and on the time variation of the optical density of the reagent solution. The calibration plot is linear in the range $0.01\text{--}0.1\text{ }\mu\text{g}$ of rhenium in 1 ml . The determination of $0.02\text{ }\mu\text{g}$ of rhenium in 1 ml is not interfered with by Mo, W, Ca, and Cu. The method has been used for the high-speed determination of the rhenium content in specimens of cupriferous sandstone.^{79–81}

In the concentration and separation of noble metals with chelating sorbents based on rhodanine, azorhodanine, and azothiopropiorhodanine, one uses, for example, cellulose, styrene–divinylbenzene copolymers, and sephadexes as the matrix. Polymeric compounds interact under approximately the same conditions as the monomers and the selectivity is also similar. The concentration and separation methods based on chelating sorbents have found extensive application in the analysis of ores, industrial solutions, and natural waters.^{108–115}

VII. Conclusion

Using azorhodanines and azothiopropiorhodanines as the reagents, it has been possible for the first time to approach the problem of the direct and high-speed determination of noble metals in a form other than the chlorides and to achieve a sensitivity of the determination which is unusually high for analytical reagents ($\varepsilon \approx 10^6$). There are diverse applications of azorhodanines and azothiopropiorhodanines, including their modified and immobilised forms, in inorganic analysis — in photometry, differential photometry, sorption photometry (primarily in methods where the reagent is used simultaneously for the concentration, extraction, separation, testing, and determination, including procedures employing sensitive photometric cells), in extraction photometry (including the 'two reagents' method), and in chromatographic and electrophoretic analytical methods. The likely usefulness of azorhodanines and azothiopropiorhodanines in automatic analytical schemes (FIA, CFA) has been demonstrated. Other applications of the reagents, including their use as intermediates in the synthesis of chelating sorbents for the concentration and separation of the elements and in kinetic analytical methods, have been noted. The methods developed using azorhodanines and azothiopropiorhodanines cover a wide range of noble and heavy metal concentrations which can be determined — $1 \times 10^{-3}\text{--}2 \times 10^2\text{ }\mu\text{g ml}^{-1}$. Reagents such as sulfo-

chlorophenolazorhodanine, tyrodine, *p*-aminophenol-3-amino-rhodanine, rhodazol Kh, and sulfo-derivatives of rhodanine and benzeneazobenzeneazorhodanine have found the greatest practical applications.

The unique properties of the reagents and, in the first place, the universality and effectiveness of their analytical activity are in many respects responsible for the interest of investigators in their further study and wider employment in inorganic chemical analysis.

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Metal ions as enzyme effectors

E P Medyantseva, M G Vertlib, G K Budnikov

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Abstract. The role of metal ions as enzyme effectors is considered. Data on inhibitory and activating effects of metal ions are summarised. The dual character of action of the effectors depending on their concentration and the nature of the enzyme is highlighted. The analytical applications of these effects are discussed. The bibliography includes 66 references.

I. Introduction

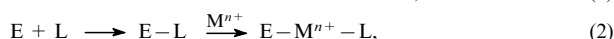
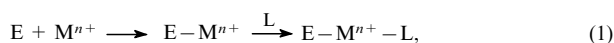
The role of metal ions in the mechanism of catalytic effects of enzymes is diverse.¹ One group of enzymes is characterised by the presence of one or several tightly bound metal ions involved in catalytic processes (metalloenzymes). Other enzymes do not contain directly bound metal ions but manifest catalytic activity only when the ions are present (metal-dependent or metal-activated enzymes). For enzymes of the third group, metals are not obligatory participants of the catalytic reaction; however, their presence in the system influences the enzyme activity (metal-independent enzymes).

Three types of metal–enzyme complexes are generally formed in enzymic catalysis:

(1) Complexes through the ligand L (substrate) as a bridge. Here, the metal ion binds only to the ligand and takes part in the catalysis not being directly bound to the enzyme (Fig. 1, pathway I). These complexes are typical of many enzymes, e.g., creatine kinase,^{2,3} and some other kinases and synthetases.^{4–6}

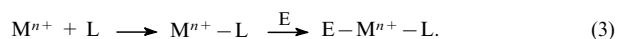
(2) Complexes in which the metal ion binds the ligand completely (Fig. 1, pathway IIa) or partly (Fig. 1, pathway IIb). The existence of enzyme–metal–ligand complexes has been demonstrated by NMR (pyruvate kinase),⁷ X-ray analysis (carboxypeptidase),⁸ and infrared spectroscopy (carbonic anhydrase).⁹

There exist at least two routes¹ for the formation of the enzyme–metal–ligand complexes with a bridge metal:¹



where L is the ligand.

A third route of enzyme–metal–ligand complex formation is also possible, where the metal ion non-bound to the enzyme manifests strong affinity for the ligand.



(3) Complexes with the enzyme as a bridge. Here, the metal ion and the ligand interact with different sites of the enzyme (Fig. 1, pathway III). This type of complex is characteristic of glutamine synthetase¹⁰ and some other synthetases.^{11, 12}

The catalytic activity of enzymes, which is their most distinctive feature, can vary widely depending on the mode of interaction of metal ions with enzymes. Therefore, the study of effects of metal ions on enzyme activity has both theoretical and practical significance.

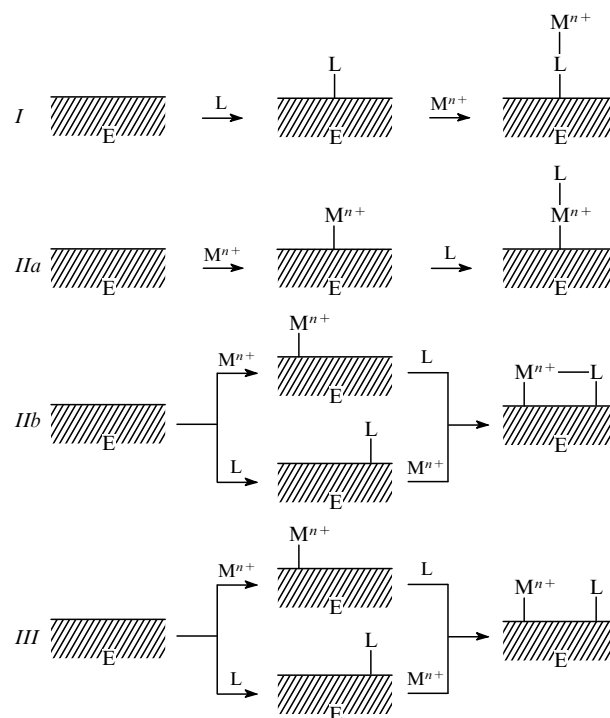


Figure 1. The pathways of interaction of the enzyme (E) with the metal ion (Mⁿ⁺) and the ligand (L). For I–III, see text.

E P Medyantseva, M G Vertlib, G K Budnikov Kazan State University, ul. Lenina 18, 420008 Kazan, Russian Federation. Fax (7-843) 238 09 94. Tel. (7-843) 231 85 46 (E P Medyantseva), (7-843) 231 84 09 (G K Budnikov)

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This review will not consider metalloenzymes and metal-dependent enzymes. The role of metals in catalytic processes involving these enzymes is the subject of special studies and presents particular interest for biochemistry and medicine (see Refs 13–15). The review summarises the papers devoted mainly to the effect of metal ions on catalytic properties of metal-independent enzymes.

II. The effect of metal ions on the catalytic activity of enzymes

During the last 10–15 years interest in biochemical methods of determination of inorganic toxic agents based on the analysis of properties of native and immobilised enzymes in the presence of metal ions has increased. And the main contribution to the development of this field has been made by Russian scientists. The same conclusion can be made from the analysis of the Proceedings of the 5th International Symposium 'Kinetics in Analytical Chemistry' held in Moscow in 1995, which shows that the chemico-analytical aspect of the effect of metal ions on the catalytic activity of enzymes was mostly covered by reports of Russian investigators.

Most commonly, the catalytic activity of enzymes in the presence of metals is evaluated as changes in the rate of the enzymic reaction. This can be done by measuring the changes in the concentration of the substrate or reaction products with time. A physicochemical parameter (most often, optical density or an ionisation potential) related to the substance concentration is used as the analytical signal.

1. The inhibitory effect of metal ions

Far greater attention has been given to the study of the inhibitory effect of metal ions on the catalytic activity of enzymes than to the activating effect. In most studies, the effect of doubly charged metal cations was examined. In particular, doubly charged ions, like Hg^{2+} , Cu^{2+} , Co^{2+} , Cd^{2+} , Zn^{2+} , Pb^{2+} , Ni^{2+} , and some others were shown to inhibit bovine ribonuclease A,¹⁶ urease,^{17–19} cholinesterases,^{20–22} and some others. The I_{50} value (*i.e.*, the inhibitor concentration causing a 50% decrease in the enzyme catalytic activity) and the value of the inhibition constant, K_i , are commonly used for the quantitative estimation of the inhibitory effect.

Thus in order to estimate the inhibitory effect of metal ions (Ag^+ , Hg^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+} , Ni^{2+} , Cd^{2+} , Co^{2+}) on *St. saprophyticus* urease, the I_{50} values were determined for each of them.¹⁷ The smaller the I_{50} value the stronger the metal inhibits the enzyme. Ag^+ ions ($I_{50} = 8 \times 10^{-6}$ mol litre⁻¹) appeared to be the most effective inhibitor of *St. saprophyticus* urease. According to the strength of their inhibitory effect, these ions can be arranged in the following series: $\text{Ag}^+ > \text{Ni}^{2+} > \text{Cd}^{2+} > \text{Co}^{2+} > \text{Hg}^{2+} > \text{Cu}^{2+} > \text{Zn}^{2+} > \text{Pb}^{2+}$. The inhibitory action of these ions begins to manifest itself at concentrations from 1×10^{-7} to 2.5×10^{-6} mol litre⁻¹. The maximum inhibitory effect (100%) is observed at the concentrations 5×10^{-4} mol litre⁻¹ (Ag^+) and 1×10^{-3} mol litre⁻¹ (Hg^{2+} , Cu^{2+} , Zn^{2+} , Pb^{2+}). In the presence of Ni^{2+} , Cd^{2+} , and Co^{2+} ions (10^{-3} mol litre⁻¹) in the reaction medium, complete suppression of the enzyme activity does not occur: urease retains up to 10%–20% of its original activity. The inhibition of urease by the ions assayed is independent of the enzyme concentration and the time of incubation with the solution of a metal salt. The inhibitory effect of all these ions is reversible and is easily eliminated by dilution or desalting of the enzyme on a Sephadex G-25 column. However, when the concentration of Pb^{2+} , Hg^{2+} , Zn^{2+} , and Ag^+ ions in the reaction medium exceeds 10^{-3} mol litre⁻¹, irreversible denaturation of the enzyme takes place. The inhibition, which precluded reactivation of the enzyme, was not observed for Cu^{2+} , Ni^{2+} , Cd^{2+} , and Co^{2+} ions in the whole range of the concentrations studied (1×10^{-7} – 1×10^{-3} mol litre⁻¹). Although the authors do not draw such a

conclusion, it may be assumed that in this particular case reversible non-specific inhibition takes place.

The values of apparent inhibition constants, K_i , for Mg^{2+} , Co^{2+} , and Mn^{2+} ions, which competitively inhibit the activity of Ca^{2+} -ATPase of skeletal muscle plasma membranes, have been determined.²³ The smaller the K_i value the stronger the effect produced by the inhibitor. It was found that according to their affinity for Ca^{2+} -ATPase, these ions can be arranged in the following order: $\text{Mg}^{2+} > \text{Co}^{2+} > \text{Mn}^{2+}$. The inhibitory effect is a maximum at a Mg^{2+} concentration of 1×10^{-4} mol litre⁻¹. A linear dependence of the degree of inhibition of the enzymic activity on the magnesium concentration in the range of 1×10^{-5} – 5×10^{-5} mol litre⁻¹ was established. Further increase in the magnesium concentration influenced the inhibition to a lesser degree, *i.e.*, it disturbed the linear dependence.

Mn^{2+} and Co^{2+} ions used at concentrations 1×10^{-5} – 1×10^{-4} mol litre⁻¹ have no effect on Ca^{2+} -ATPase. Their inhibitory effect becomes apparent only at a concentration of *ca.* 2.5×10^{-4} mol litre⁻¹; a linear dependence of the decrease in the enzyme activity on the cation concentration is observed at concentrations from 2.5×10^{-5} to $(2–3) \times 10^{-3}$ mol litre⁻¹.

The study¹⁶ deserves special mention among other studies concerned with the inhibition of the catalytic activity of enzymes by metal ions. This not only quantitated the effect observed (*i.e.*, the experimental values of inhibition coefficients defined by the author as the ratio of initial rates of substrate cleavage in the presence and in the absence of M^{2+}), but also considered the influence of some other parameters (ionisation potentials, hydration energy, ionic radii of cations) on the magnitude of the inhibitory effect. In the work cited, the effect of Ca^{2+} , Mg^{2+} , Ba^{2+} , Sr^{2+} , Mn^{2+} , Fe^{2+} , Co^{2+} , Ni^{2+} , Pb^{2+} , Cd^{2+} , Zn^{2+} , Cu^{2+} , and Hg^{2+} on the catalytic activity of bovine RNase A was studied. The inhibitory effect of these cations was found to increase in the series: $\text{Ba}^{2+} \approx \text{Sr}^{2+} \approx \text{Ca}^{2+} < \text{Mg}^{2+} < \text{Mn}^{2+} < \text{Fe}^{2+} < \text{Co}^{2+} < \text{Ni}^{2+} < \text{Pb}^{2+} < \text{Cd}^{2+} < \text{Zn}^{2+} \ll \text{Cu}^{2+} < \text{Hg}^{2+}$. It is seen that Hg^{2+} , Cu^{2+} , and Zn^{2+} cations manifest the strongest inhibitory activity; the cations of the iron subgroup (Mn^{2+} , Fe^{2+} , Co^{2+} , and Ni^{2+}) are weak inhibitors, whereas the cations Ba^{2+} , Sr^{2+} , and Ca^{2+} do not produce any inhibitory effect at all.

In the author's opinion,¹⁶ the fact that the metal cations do not possess strict selectivity, *i.e.*, that they can interact with functional groups in the enzyme active centre differing in electronic effect, a complex dependence of the mode of enzyme inhibition by the metal cations on their concentration, and their ability to form complexes both with enzymes and the substrates preclude the estimation of the inhibitory activity of metal cations from the inhibition constants.

In order to evaluate the inhibitory strength of cations the author introduces a parameter W , which is equal to the sum of the electrostatic (Z^2/r) and the reduced covalent ($E - \Delta H$) characteristics:

$$W = \frac{Z^2}{r} + (E - \Delta H),$$

where Z is the ionic charge, r is the ionic radius, E is the sum of the ionisation potentials for the first and second electrons, and ΔH is the energy of cation hydration.

The higher inhibitory activity of Zn^{2+} , Cu^{2+} , and Hg^{2+} is largely determined by the reduced covalent characteristics. In the cations of the iron subgroup (Mn^{2+} , Fe^{2+} , Co^{2+} , and Ni^{2+}), the electrostatic characteristics are comparable with those of Zn^{2+} , Cu^{2+} , and Hg^{2+} , while the values of the reduced covalent characteristics are 2–3 times as low. These cations manifest only weak inhibitory activity. For Ba^{2+} , Ca^{2+} , Mg^{2+} , and Sr^{2+} cations, the values of electrostatic and, particularly, reduced covalent characteristics are smaller than those for Zn^{2+} , Cu^{2+} , and Hg^{2+} . It has been shown experimentally that these cations do not inhibit RNase at the concentrations from 1×10^{-4} to 1×10^{-2} mol litre⁻¹.

The effect of rare-earth elements (REE) (Pr, Nb, Sm, Eu, Tb, Er, Tu, Yb) on the catalytic activity of inorganic pyrophosphatases from bakers yeast and *E. coli* has been studied.²⁴ Analysis of the dependence of the rate of the indicator reaction on the concentration of REE over the range of 10^{-5} – 10^{-1} $\mu\text{g ml}^{-1}$ revealed that all these ions inhibited both enzymes; the inhibitory effect of different REE was manifested in different concentration ranges. Praseodymium (Pr^{3+}) appeared to be the most effective inhibitor of pyrophosphatases. The inhibitory effect decreased on going from praseodymium to ytterbium, *i.e.*, with a decrease in the ionic radius of REE. The mechanism of inorganic phosphatase inhibition by praseodymium is consistent with complete competitive inhibition. The value of the inhibition constant, which reflects the stability of the enzyme–inhibitor complex, demonstrates that Pr^{3+} ions form a catalytically inactive complex with pyrophosphatase, which is more stable than that with Eu^{3+} ions.

In other studies,^{24–32} only qualitative aspects of the effect of metal ions on the catalytic activity of enzymes have been considered with a mere statement of the existence of the corresponding effect and indicating the range of concentrations where it is manifested.

Cu^{2+} ions decrease the catalytic activity of glutamate dehydrogenase from bovine liver²⁵ ($I_{50} = 2 \times 10^{-6}$ mol litre⁻¹). At concentrations of Cu^{2+} equal to 1×10^{-5} mol litre⁻¹ and higher, the residual activity makes up 8%–10% of the original. This effect is a result of the direct interaction of the copper cations with glutamate dehydrogenase (the difference absorption spectrum of glutamate dehydrogenase in the presence of Cu^{2+} suggests the formation of an enzyme–metal complex). This inhibition is allosteric. Zn^{2+} ions also inhibit this enzyme. Spectral data point to identical conformational changes in the substrate-binding site induced by Cu^{2+} and Zn^{2+} cations.²⁵

Zn^{2+} cations also inhibit poly(ADP-ribose)polymerase from rat brain. At a Zn^{2+} concentration equal to 1.25×10^{-4} mol litre⁻¹, the enzyme is fully suppressed. The changes in the enzyme activity are due to the binding of Zn^{2+} ions with the sulfhydryl groups of polymerase. The inhibitory effect is reversible, since dithiothreitol neutralises the effect of this cation on the polymerase activity.²⁶

Pb^{2+} and Cd^{2+} ions (10^{-3} – 10^{-2} $\mu\text{g ml}^{-1}$) inhibit alkaline phosphatase from chicken intestine in the hydrolysis of *p*-nitrophenyl phosphate.^{23,27} The decrease in the activity is a maximum at Cd^{2+} concentrations of 1–10 $\mu\text{g ml}^{-1}$ (Ref. 23). Cd^{2+} ions (1×10^{-4} $\mu\text{g ml}^{-1}$) also inhibit horseradish peroxidase.²⁷ The catalytic activity of peroxidase is also inhibited by Hg^{2+} cations (5×10^{-13} – 5×10^{-8} mol litre⁻¹).^{28–30} A drop in peroxidase activity is also observed in the presence of Bi^{3+} [$(2\text{--}10) \times 10^{-4}$ $\mu\text{g ml}^{-1}$]. At higher Bi^{3+} concentrations, the rate of this reaction remains virtually unchanged.³¹

Protein disulfide reductase from bovine liver catalyses the thiol–disulfide exchange between glutathione and insulin and reactivates randomly oxidised ribonuclease. The activity of this enzyme is inhibited by Cu^{2+} and Hg^{2+} ions.²⁹

The effects of Zn^{2+} , Cu^{2+} , Mn^{2+} , Fe^{2+} , Co^{2+} , and Ni^{2+} ions on the activity of acetylcholinesterase (AChE) of human erythrocytes have been studied over a broad range of salt concentrations.^{20,33} It was found that all the salts in question (with the exception of MnCl_2 , which has no effect on the AChE activity) are reversible competitive inhibitors of AChE. To a first approximation, the inhibitory effect is directly proportional to the concentration of the corresponding metal. From the pH dependence of the AChE inhibition by the salts it was concluded that the AChE activity is inhibited by hydroxo complexes of the MOH^+ type.

Cu^{2+} and Cd^{2+} ions suppress the catalytic activity of cholinesterase (ChE) isolated from pea sprouts.²² Co^{2+} and Al^{3+} ions also manifest inhibitory activity. According to another report,²¹ Ca^{2+} and Mn^{2+} used at concentrations of 1×10^{-3} – 1×10^{-2} mol litre⁻¹ inhibit ChE from kidney bean roots, whereas Mg^{2+} has no effect on the enzyme.

Calcium occupies a special position among metals, since it manifests an activating rather than inhibitory effect.³⁴ However, it can also inhibit certain enzymes, *e.g.*, yeast hexokinase³⁰ and alkaline phosphatase.²⁷

It has been established that calcium ions taken at a 10–100-fold excess over praseodymium enhance the inhibitory effect of the latter. The inhibitory action of calcium²⁴ is ascribed to the fact that its ionic radius is similar to those of REE and thus it can exert a similar effect on the enzyme.

Ca^{2+} cations markedly decrease the activity of hexokinase.³⁵ The catalytic activity of alkaline phosphatase from chicken intestine is also decreased in the presence of calcium ions (10^{-3} – 1 $\mu\text{g ml}^{-1}$). It should be noted that the inhibitory effect of calcium on the enzyme decreases with an increase in the ion concentration.²⁷

Recently, some papers have been published, which deal with the study of the catalytic activity and properties of immobilised enzymes.^{18,19,36–38} Naturally, metal cations also change the catalytic activity of immobilised enzymes.

Urease immobilised on a solid carrier (a microporous styrene–divinylbenzene copolymer) is inhibited by ions of toxic metals. The inhibitory effect of Fe^{2+} manifests itself even at a concentration of 10^{-10} – 10^{-9} mol litre⁻¹, whereas that of most ions, at 10^{-8} mol litre⁻¹. With respect to the strength of their inhibitory action, the metal ions can be arranged in the following series:^{18,19} $\text{Ag}^+ > \text{Hg}^{2+} > \text{Fe}^{2+} > \text{Cu}^{2+} > \text{Ni}^{2+} > \text{Co}^{2+} > \text{Al}^{3+} > \text{Mg}^{2+} > \text{Cd}^{2+} > \text{Pb}^{2+}$. As noted above, Ag^+ is the strongest and Pb^{2+} is the weakest inhibitor of native urease.¹⁷ At the same time, the series of other metals for the native urease (see above) differs from that for the immobilised enzyme due to the changes caused by enzyme immobilisation.

A number of papers have been devoted to the effects of Zn^{2+} , Fe^{2+} , Ni^{2+} , Hg^{2+} , Pb^{2+} , Ti^+ , Bi^{3+} , Cd^{2+} , Cu^{2+} , Cr^{3+} , Hf^{4+} , Ti^{4+} , and Zr^{4+} ions on the catalytic activity of cholinesterase immobilised by incorporation into cellulose nitrate films.^{36–38} All these metals inhibit the immobilised enzyme. The greatest inactivating effect is produced by Cu^{2+} . The minimum Cu^{2+} concentration (c_{min}), which causes a statistically significant decrease in the catalytic activity of immobilised ChE, is 4×10^{-10} mol litre⁻¹. A similar change in the catalytic activity in the presence of other ions is observed at the following concentrations:^{36–38}

Ion	Zr (IV)	Ti (IV)	Nb (V)	Hf (V)	Ta (V)
c /mol litre ⁻¹	5×10^{-10}	8×10^{-10}	2×10^{-9}	3×10^{-9}	5×10^{-9}
Ion	Cr (III)	Pb (II)	Fe (III)	Cd (II)	
c /mol litre ⁻¹	5×10^{-8}	5×10^{-7}	1×10^{-6}	1×10^{-5}	

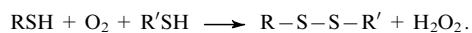
The inhibitory effect also depends on the catalytic activity of the enzyme itself. Thus, for ChE immobilised in a cellulose nitrate matrix with a specific activity of 1.12 ± 0.04 $\mu\text{mol min}^{-1} \text{cm}^{-2}$, c_{min} for Cu^{2+} is 4×10^{-10} mol litre⁻¹, whereas for the samples with a threefold lower specific activity (0.33 ± 0.02 $\mu\text{mol min}^{-1} \text{cm}^{-2}$), it is equal to 1×10^{-9} mol litre⁻¹ (Ref. 38).

Solutions of cysteine and EDTA restore completely the catalytic activity of immobilised ChE after the action of heavy metal ions. However, only 70% of totally inhibited ChE is observed in the case of Pb^{2+} . This is probably due to the interaction of Pb^{2+} with the histidine residue of the active centre of ChE, especially in the presence of high ($\sim 10^{-4}$ mol litre⁻¹) concentrations of Pb^{2+} (Ref. 36).

The mechanism of the inhibitory effect of metal ions on the catalytic activity of enzymes is rather difficult to establish. The metal can compete with the substrate for the binding sites in the active centre, it can also interact with different groups in the protein molecule outside the active centre but influencing the catalytic functions of the enzyme,³⁹ *i.e.*, it can bind to the allosteric centre of the enzyme.

It is believed that the effect of metal ions on the enzyme molecule can be due to the formation of thiolates with both

cysteine, which is a constituent of the enzyme, and products of cleavage of disulfide bridges.⁴⁰ If the cysteine residue is incorporated into the active centre of the enzyme or is responsible for the maintenance of the appropriate conformation of the protein molecule, the modification of its thiol group inactivates the enzyme. In addition, heavy metal ions can catalyse the oxidation of thiols to disulfides:⁴¹



Most commonly, the inhibitory effect of metal ions is ascribed to their ability to form coordinate bonds.⁴¹ As is known,⁴² the nucleophilic residues of some amino acids incorporated into the active centres of enzymes, can form coordinate bonds with heavy metal ions. For example, histidine, which is a constituent of the esterase region of the active centre of ChE, can interact with metal ions.³⁶ Some authors explain the difference in the inhibitory action of various metal ions by the difference in the ionic radii of cations.^{16, 29, 36}

2. The activating effect of metal cations

Metals can not only inhibit but also enhance the catalytic activity of enzymes. Most often, the activating effect is produced by ions of rare-earth metals. It should be noted that the processes related to the activation of enzymes with metal ions have been documented in far fewer publications than those on the inhibition processes. Unfortunately, in the case of studies of the inhibitory effect, most authors give only a qualitative outline of the activation process,^{43–56} without quantitative estimates, which makes it difficult to compare the published data.

The activating effect of Ca^{2+} cations on mitochondrial glycerol-3-phosphate dehydrogenase has been studied.⁴³ Ca^{2+} cations are not selective activators. They interact with both electron-donor amino acid residues and those nitrogen atoms of the peptide bonds that are not necessarily incorporated into the enzyme active centre. It thus follows that not all Ca^{2+} cations that interact with the enzyme play the same role in the maintenance of its activity. Some of them that interact with the amino acid residues remote from the enzyme active centre not only are devoid of the activation effect, but, conversely, produce an inhibitory effect.

Analysis of literature data reveals that the simultaneous presence of several metal cations, even of the same nature (Ca, Mg), has an ambiguous effect on the activity of the enzyme under study: one of the ions can either enhance the effect of the other ion (synergism) or attenuate it.

Most often, the synergistic effect is produced by Ca^{2+} and Mg^{2+} ions.³⁴ For example, even a short-term preincubation of phosphorylase kinase with these ions caused a sevenfold increase in the catalytic activity. It is believed that the simultaneous presence of Ca^{2+} and Mg^{2+} favours the interaction of phosphorylase kinase with glycogen.³⁴

Ca^{2+} and Mg^{2+} ions also activate myofibrillar creatine kinase from rat skeletal and cardiac muscles. Calcium activates the enzyme to a lesser degree than magnesium. In the presence of Mg^{2+} ions, calcium inhibits creatine kinase. Presumably, creatine kinase has different binding sites for Ca^{2+} and Mg^{2+} ions, since the latter does not eliminate the inhibitory effect of calcium even when used in a 100-fold excess.⁴⁴

Ca^{2+} and Mg^{2+} ions activate myometrium actomyosin ATPase. As the Ca^{2+} concentration is increased ($0.01–5 \times 10^{-3}$ mol litre⁻¹ in a Mg^{2+} -free medium or after addition of Mg^{2+} (1×10^{-3} mol litre⁻¹), the ATPase activity is noticeably increased and then reaches a plateau.³⁹

A change in the Mg^{2+} concentration from 1×10^{-5} to 5×10^{-3} mol litre⁻¹ in a Ca^{2+} -free medium increases the activity of ATPase in the region of low concentrations after which it reaches a plateau. Significant induction of the ATP-hydrolase reaction is observed after addition of the physiological concentration of Ca^{2+} (1×10^{-3} mol litre⁻¹) to the incubation medium. Ca^{2+} ions are more effective activators of the reaction of ATP hydrolysis.⁴⁶

The effect of cations of alkaline and alkaline-earth metals on the activity of native ChE^{21, 46} and immobilised butyrylcholinesterase³⁶ has been studied. Na^+ , K^+ , and Mg^{2+} ions stimulate the cholinesterase activity in pea sprouts by 30%–60%.^{21, 22} The catalytic activity of immobilised ChE increases in the presence of Na^+ , Mg^{2+} , and Mn^{2+} ions in the concentration range of $8 \times 10^{-4}–2 \times 10^{-2}$ mol litre⁻¹.³⁶ Presumably, this is due to the presence of an anionic group near the active centre of ChE, which prevents the interaction of the enzyme with the substrate. Introduction of these metal salts results in binding of this group by ions of ChE-activator metals, which creates the most favourable conditions for the formation of the Michaelis complex. It was found that the larger the radius and the charge on the activator metal the lower the concentration of this metal ion needed to block the anionic group of ChE.

Ca^{2+} cations activate butyrylcholinesterase.^{47–49} The maximum rate of the reaction is increased in the presence of Ca^{2+} , whereas the Michaelis constant remains practically unchanged. Apparently, Ca^{2+} ions do not compete with the substrate for the binding sites, since the activation cannot be eliminated by an excess of acetylcholine. It is believed that Ca^{2+} exerts an allosteric effect as it binds with specific sites.^{50, 51} Co^{2+} , Ni^{2+} , and Mn^{2+} ions do not influence the acetylcholine hydrolysis.⁴⁷

Immobilised ChE is activated by microquantities of heavy metals, such as Pb, Hg, Cd, and Tl used generally at concentrations below $10^{-7}–10^{-6}$ mol litre⁻¹.^{52, 53} Some platinum metals (Pt^{2+} , Rh^{3+}) also activate the immobilised ChE.^{54, 55}

It should be noted that the inhibitory effect correlates linearly with the concentration of the effector.^{27–31, 37, 38} As to the activation, this process demonstrates a more complex dependence on the concentration of metal ions.^{35, 36} First of all, an increase in the catalytic activity is observed over a small range of concentrations that differ usually by not more than a factor of 10–15 (Fig. 2). The maximum catalytic activity is manifested sometimes only at a definite concentration of the effector (Fig. 2b). In some cases, a small plateau is observed (Fig. 2a). A deviation from the optimum concentration results in a decrease of the enzyme catalytic activity towards the control level.

Among studies concerned with enzyme activation, that dealing with the mechanism of the activating effects of Mg^{2+} and Co^{2+} ions on glucose isomerase of *Actinomyces olivocinereus* 154 stands separately.⁵⁷ In this study, the main kinetic constants have been calculated and quantitative estimates of the activating capacity of these cations (the activation constants) have been given. It was found that the activating effect of Mg^{2+} ions is much stronger than that of Co^{2+} . The maximum activating effect of Mg^{2+} ions is observed at a concentration $(2.0–2.5) \times 10^{-2}$ mol litre⁻¹, that of Co^{2+} ions, at $(2.5–5) \times 10^{-4}$ mol litre⁻¹. Further increase in the concentrations of Mg^{2+} and Co^{2+} ions leads to the inhibition of glucose isomerase; for Co^{2+} ions, this phenomenon is more strongly pronounced and manifests itself even at a concentration of 1.25×10^{-3} mol litre⁻¹.

Studies of the activating effect of Mg^{2+} and Co^{2+} ions added to the reaction mixture simultaneously revealed a complex dependence of the enzyme activation on both the absolute concentrations of these metal ions and their ratio. The maximum activity was observed at a Mg^{2+} ion concentration of 2×10^{-5} mol litre⁻¹ and that of Co^{2+} at 5×10^{-3} mol litre⁻¹. It should be noted that for Mg^{2+} the optimum concentrations of this activator ion used in a mixture were slightly lower than when it was added separately, whereas for Co^{2+} ions, they were tenfold higher.

Mg^{2+} and Co^{2+} ions bind to different sites on glucose isomerase and influence its activity differently.⁵⁷ Therefore, the mechanism of activation of the glucose isomerisation reaction by these ions is also different. The activation with Mg^{2+} ions is non-competitive, while that with Co^{2+} ions is synergistic; when Mg^{2+} and Co^{2+} ions are used simultaneously, the activation is of a mixed type. In the non-competitive activation, glucose and Mg^{2+} ions bind to the enzyme independently of each other to form an

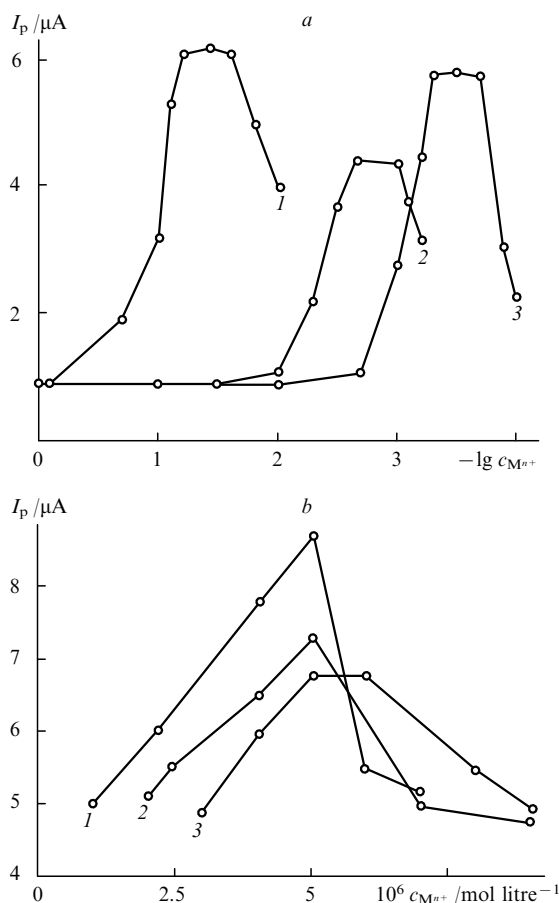


Figure 2. Dependence of the analytical signal (electric current at a potential of -0.55 V) on the concentration of metal ions (pH 9.05; the concentration of butyrylthiocholine iodide, 0.6 mg ml^{-1}). Specific activity of immobilised ChE is $0.35 \mu\text{mol min}^{-1} \text{ cm}^{-2}$ (a) and $1.17 \mu\text{mol min}^{-1} \text{ cm}^{-2}$ (b).

(a): (1) — Mn (II), (2) — Mg, (3) — Na; (b): (1) — Ca, (2) — Sr, (3) — Ba.

active bridge-like ternary complex (Fig. 1, pathway II). The value of the activation constant is very low (0.002), which points to a high stability of an active ternary complex ($\text{Mg}^{2+} - \text{E} - \text{S}$) and the activated enzyme ($\text{Mg}^{2+} - \text{E}$) and to a small rate constant for their dissociation into the original enzyme and the enzyme–substrate complex (ES). Thus, in the activation of glucose isomerase with Mg^{2+} , the major part of the enzyme is bound into the ternary complex $\text{Mg}^{2+} - \text{E} - \text{S}$. As has been mentioned above, the activation with Co^{2+} ions is synergistic. Co^{2+} ions bind to the glucose isomerase molecule and increase the enzyme affinity for glucose. In addition, the ES complex interacts with Co^{2+} ions much faster than the free enzyme. The authors suggest that the main role of Co^{2+} ions consists in conferring a conformation that is resistant to thermal inactivation on the enzyme quaternary structure rather than in the activation of the enzyme. Moreover, this conformation facilitates the attachment of glucose even in the absence of Mg^{2+} ions and accelerates the formation of a bridge-like ternary complex in their presence, as a result of which the rate of isomerisation increases. This is corroborated by experiments with simultaneous addition of Mg^{2+} and Co^{2+} ions to the reaction mixture.⁵⁷

Attempts have been undertaken^{56,58} to characterise quantitatively the processes of activation of immobilised ChE in the presence of alkaline-earth metal ions on the basis of voltammetric measurements. The results of these studies indicate that the activation is controlled by many factors, such as substrate concentration, pH, activity of the immobilised enzyme (*i.e.*, the type of immobilisation), activator concentration, incubation time, and the order in which the substrate and the effector act on

immobilised ChE. The maximum activating effect was observed at pH 8.95–9.05. The lower the catalytic activity of immobilised ChE the higher the concentration of metal ions needed for the manifestation of their activating effect. Thus immobilisation according to Nikolskaya³³ in which incorporation of the enzyme into a cellulose nitrate matrix was performed together with treatment with a bifunctional reagent (glutaraldehyde) gave immobilised ChE with a catalytic activity about 3–4 times lower than that obtained by immobilisation of the enzyme followed by treatment with a bifunctional reagent. In order to increase the catalytic activity of these samples, it is necessary to use high concentrations of the activators (6×10^{-3} – $6 \times 10^{-4} \text{ mol litre}^{-1} \text{ Ca}^{2+}$).³⁷ To verify these effects, the authors carried out a radiochemical analysis with ^{85}Sr . The results of this study suggest that under optimum conditions (pH 9.05, $5 \times 10^{-6} \text{ mol litre}^{-1} \text{ Sr}^{2+}$, substrate concentration, $2 \times 10^{-3} \text{ mol litre}^{-1}$) alkaline-earth metal ions change the catalytic activity of immobilised ChE in the order: $\text{Ca}^{2+} > \text{Sr}^{2+} > \text{Ba}^{2+}$, which is consistent with their ionic radii. Similar correlation between the ion radii and their activating effect was observed earlier for alkali metal ions.³⁶ As the substrate concentration is increased from 2×10^{-3} to $4 \times 10^{-3} \text{ mol litre}^{-1}$, the type of activation changed from associative to pseudo- and then to two-parametrically disbalanced activation. The activation constants for Ca^{2+} ions are $(3.7 \pm 0.3) \times 10^{-6} \text{ mol litre}^{-1}$ at low $[(1.5\text{--}3) \times 10^{-3} \text{ mol litre}^{-1}]$ and $(1.8 \pm 0.2) \times 10^{-8} \text{ mol litre}^{-1}$ at higher ($4 \times 10^{-3} \text{ mol litre}^{-1}$) substrate concentrations; that for Ba^{2+} ions is $(8.40 \pm 0.3) \times 10^{-6} \text{ mol litre}^{-1}$. The experimental values of the activation constants correlate with a stronger activating effect of Ca^{2+} ions (the catalytic activity of immobilised ChE is increased more strongly in the presence of Ca^{2+}).

3. The dependence of the mode of action of metal ions on their concentration

It is well known that the same metals can increase or decrease the catalytic activity of enzymes depending on their concentration.

Thus Cu^{2+} ions used in low concentrations stimulate the activity of purified poly(ADP-ribose)polymerase. At a Cu^{2+} concentration of $5 \times 10^{-6} \text{ mol litre}^{-1}$, the polymerase activity is increased 1.4-fold. Further increase in the Cu^{2+} concentration inhibits the enzyme activity and with $5 \times 10^{-5} \text{ mol litre}^{-1} \text{ Cu}^{2+}$ the polymerase activity drops down to zero. Poly(ADP-ribose)-polymerase contains sites with different affinity for Cu^{2+} cations. At low Cu^{2+} concentrations, the binding of these ions to the high-affinity sites of the enzyme increases the polymerase activity, whereas at high Cu^{2+} concentrations, the binding may also occur to sites with a lower affinity for the metal, which results in the inhibition of the enzyme activity.²⁶

Mg^{2+} ions (10^{-3} – $1 \mu\text{g ml}^{-1}$) inhibit alkaline phosphatase from chicken intestine. They strongly activate the enzyme over the concentration range 1 – $100 \mu\text{g ml}^{-1}$. Aluminium ions slightly inhibit the enzyme when used at the concentrations of 10^{-3} – $1 \mu\text{g ml}^{-1}$ but strongly activate it at the concentrations of 1 – $10 \mu\text{g ml}^{-1}$ (Ref. 27).

Low concentrations of Mn^{2+} , Ni^{2+} , and Co^{2+} ions activate muscle pyruvate kinase, whereas higher concentrations inhibit the enzyme. Ca^{2+} ions (4×10^{-4} – $2 \times 10^{-4} \text{ mol litre}^{-1}$) inhibit liver glutamate dehydrogenase and activate it at concentrations above $4 \times 10^{-4} \text{ mol litre}^{-1}$. At the same time, Mg^{2+} ions inhibit glutamate dehydrogenase only in the concentration range of $(2\text{--}4) \times 10^{-4} \text{ mol litre}^{-1}$. Higher and lower concentrations of Mg^{2+} activate this enzyme. Some phosphatases are activated by low concentrations of Mg^{2+} (up to $5 \times 10^{-3} \text{ mol litre}^{-1}$), whereas higher concentrations of this ion cause their inhibition.³⁴

The changes in the properties of enzymes in the presence of some metal ions are summarised in Table 1.

Almost all investigators emphasise that the effect of metal ions on the activity of ChE is of dual character: activation at small concentrations and inhibition at high concentrations.⁴⁷ Even such cations as Na^+ , Mg^{2+} , Ca^{2+} , Sr^{2+} , and Ba^{2+} do not increase the catalytic activity of ChE when used at high concentrations.⁵⁶

Table 1. The effect of some metal ions on the catalytic activity of enzymes.

Enzyme	Metal ion	Effect	c_{eff}^a /mol litre ⁻¹	Ref.
Ca ²⁺ -ATPase EC 3.6.1.3.	Mg ²⁺ , Co ²⁺	inhibitor	$1 \times 10^{-5} - 1 \times 10^{-3}$	23
	Mn ²⁺	"	$1 \times 10^{-5} - 1 \times 10^{-3}$	23
ATPase EC 3.6.1.8.	Ca ²⁺ ,	activator	$1 \times 10^{-5} - 5 \times 10^{-3}$	45
	Mg ²⁺	"	$1 \times 10^{-5} - 5 \times 10^{-3}$	45
Hexokinase EC 2.7.1.1.	Ca ²⁺	inhibitor	$1 \times 10^{-3} - 5 \times 10^{-2}$	35
Glycerol-3-phosphate dehydrogenase EC 1.1.1.8	Ca ²⁺	activator	$1 \times 10^{-6} - 1 \times 10^{-5}$	43
Glutamate dehydrogenase EC 1.4.1.4.	Cu ²⁺ ,	inhibitor	$1 \times 10^{-6} - 1 \times 10^{-4}$	25
	Zn ²⁺	"	$1 \times 10^{-6} - 1 \times 10^{-4}$	25
Glucose isomerase EC 5.3.1.18.	Mg ²⁺ ,	activator	$1 \times 10^{-3} - 9 \times 10^{-1}$	57
	Co ²⁺	"	$1 \times 10^{-3} - 9 \times 10^{-1}$	57
Creatine kinase EC 2.7.3.2.	Ca ²⁺ ,	"	$1 \times 10^{-3} - 1 \times 10^{-2}$	44
	Mg ²⁺	"	$1 \times 10^{-3} - 1 \times 10^{-2}$	44
Inorganic pyrophosphatase EC 3.6.1.1.	Pr, Nb, Sm	inhibitor	$1 \times 10^{-5} - 1 \times 10^{-1}$	24
	Eu, Tb, Er	"	$1 \times 10^{-5} - 1 \times 10^{-1}$	24
	Tu, Yb	"	$1 \times 10^{-5} - 1 \times 10^{-1}$	24
Peroxidase EC 1.11.1.7.	Hg ²⁺	"	$5 \times 10^{-13} - 5 \times 10^{-8}$	28
	Bi ³⁺	"	$1 \times 10^{-5} - 2 \times 10^{-4}$	31
Poly(ADP- ribose)poly- merase EC 2.4.2.30	Zn ²⁺	"	$2 \times 10^{-5} - 2 \times 10^{-4}$	26
	Cu ²⁺	"	$1 \times 10^{-5} - 5 \times 10^{-5}$	26
	Cu ²⁺	activator	$1 \times 10^{-6} - 1 \times 10^{-5}$	26
Ribonuclease EC 3.1.4.8.	Ba ²⁺ , Sr ²⁺	no influence	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
	Ca ²⁺	"	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
	Hg ²⁺ , Cu ²⁺	inhibitor	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
	Zn ²⁺ , Mn ²⁺	"	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
	Fe ²⁺ , Co ²⁺	"	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
	Ni ²⁺	"	$1 \times 10^{-4} - 1 \times 10^{-2}$	16
Urease EC 3.5.1.5.	Ag ⁺ , Hg ²⁺	"	$1 \times 10^{-7} - 1 \times 10^{-3}$	17
	Cu ²⁺ , Zn ²⁺	"	$1 \times 10^{-7} - 1 \times 10^{-3}$	17
	Pb ²⁺ , Ni ²⁺	"	$1 \times 10^{-7} - 1 \times 10^{-3}$	17
	Cd ²⁺ , Co ²⁺	"	$1 \times 10^{-7} - 1 \times 10^{-3}$	17
Cholinesterase EC 3.1.1.8.	Pb ²⁺	"	$5 \times 10^{-7} - 1 \times 10^{-3}$	36
	Pb ²⁺	activator	$1 \times 10^{-9} - 1 \times 10^{-7}$	53
	Cd ²⁺	inhibitor	$1 \times 10^{-6} - 1 \times 10^{-3}$	37
	Cd ²⁺	activator	$5 \times 10^{-9} - 8 \times 10^{-7}$	53
	Hg ²⁺	inhibitor	$5 \times 10^{-5} - 1 \times 10^{-3}$	36
	Hg ²⁺	activator	$1 \times 10^{-12} - 1 \times 10^{-6}$	53
	Tl ⁺	inhibitor	$5 \times 10^{-5} - 1 \times 10^{-3}$	37
	Tl ⁺	activator	$1 \times 10^{-11} - 1 \times 10^{-5}$	53
	Ca ²⁺ , Sr ²⁺	"	$1 \times 10^{-6} - 1 \times 10^{-5}$	56
	Ba ²⁺	"	$1 \times 10^{-6} - 1 \times 10^{-5}$	56
Alkaline phosphatase EC 3.1.3.1.	Ca ²⁺	inhibitor	$2 \times 10^{-8} - 3 \times 10^{-5}$	27
	Ba ²⁺	"	$7 \times 10^{-9} - 7 \times 10^{-7}$	27
	Cd ²⁺	"	$9 \times 10^{-9} - 9 \times 10^{-4}$	27
	Pb ²⁺	"	$5 \times 10^{-9} - 5 \times 10^{-4}$	27
	Mg ²⁺	"	$4 \times 10^{-8} - 4 \times 10^{-5}$	27
	Mg ²⁺	activator	$4 \times 10^{-5} - 4 \times 10^{-3}$	27

^a c_{eff} is the concentration range where the effect is observed.

Pb²⁺, Hg²⁺, Cd²⁺, and Tl⁺ ions activate ChE at concentrations below $10^{-7} - 10^{-6}$ mol litre⁻¹ and inhibit the enzyme at higher concentrations.^{36, 37, 52, 53} Most authors attribute the activating

effect of cations to the possible formation of the ternary complex E–M–S (Fig. 1, pathway II),^{1, 58} which provides conformationally more favourable conditions for the enzymic reaction. The inhibitory effect of high concentrations of metal ions is assigned to the competitive reaction between metal and substrate cations (if the substrate bears a positive charge) for the active centre of the enzyme. At high salt concentrations, the active centre of the molecule can be occupied by metal ions, thus being inaccessible to the substrate cations. As a result, the catalytic activity of both native and immobilised ChE may decrease.^{36, 59} According to other authors,⁶⁰ the effect of metal ions on the enzyme activity is due to changes in the substrate solubility at high salt concentrations.

Obviously, the effect of metal ions on enzymes depends on many factors. It is therefore difficult and usually impossible to identify the determining factor. In particular, the effect of metals on the catalytic activity of enzymes depends on the nature of the metal, its size, charge, ionisation potential, the nature of the enzyme, its state (native or immobilised), conditions of the enzymic reaction, *etc.* Most commonly, the effect of metal ions on the enzyme activity is associated with their ability to form enzyme–substrate complexes, which may participate in the catalytic process by facilitating the transfer of electrons, to stabilise the active conformation of the enzyme or association of its subunits, and to act as an ‘anchor’ group without being directly involved in the catalytic act. These and other effects may also occur in combination. Unfortunately, the majority of authors give only qualitative characteristics of changes in the enzymic activity, which naturally hampers comparative analysis of the experimental data, and only very few try to estimate these effects quantitatively and get an insight into the mechanism of action of metal ions. These studies have received the greatest attention in the present review.

III. Changes in the catalytic activity of enzymes in the presence of metal ions: an analytical aspect

Over a long period of time, investigators have merely noted the effects of metal ions on the catalytic activity of enzymes, but these effects did not find practical application. As the bulk of experimental data have been accumulated, the analytical application of these effects became possible. The studies on this subject covering the period of 1949–1979 have been summarised in a review.⁶¹

One of the first studies by Russian authors on the application of the effects of metals on enzymes for analytical purposes was that by Dolmanova *et al.*²⁸ in which the authors offered a highly selective procedure for the quantitation of mercury, which was based on the inhibitory effect of mercury on horseradish peroxidase [the detection limit is $(1.0 \pm 0.5) \times 10^{-5}$ µg ml⁻¹]. Further investigations²⁹ in this field were directed to the use of various substrates and the optimisation of conditions for enzymic reactions, which made it possible to lower the detection limit to 3.0×10^{-7} µg ml⁻¹. Bismuth and cadmium ions interfere with the determination. A procedure for quantitation of mercury was proposed³⁰ (in which the lower limit of concentrations is 1×10^{-5} µg ml⁻¹), which differed from the standard ones by being time-saving (the analysis lasted for 30 minutes instead of 4 hours) and which permitted determination of mercury in the presence of relatively high (≥ 1 µg ml⁻¹) concentrations of Fe³⁺. Iron is masked by tartaric acid, which has no effect on the catalytic activity of peroxidase under the given experimental conditions and at selected concentrations. Quantitation of mercury in natural water is carried out using the method of additives, which makes it possible to estimate the effect of other components of the matrix (particularly that of Fe³⁺) without masking.

The inhibitory effect of Bi³⁺ on the catalytic activity of horseradish peroxidase was used as the basis for the kinetic method used for its quantitation. The lower limit of concentrations that can be determined is 2×10^{-4} µg ml⁻¹. This assay is not hampered by a 1000-fold excess of Ca, Mg, Zn, Ni, and Al, by

100-fold excess of Pb and Ag, and by a 10-fold excess of Cd. The presence of comparable amounts of Hg^{2+} interferes with the analysis.^{31, 62}

A highly sensitive ($c_{\min} = 8 \times 10^{-6} - 4 \times 10^{-4} \mu\text{g ml}^{-1}$), selective enzymic method²⁴ for the quantitation of REE is based on their inhibitory effect on the catalytic activity of bakers yeast and *E. coli* pyrophosphatases. The interference of Co^{2+} , Ni^{2+} , and Mn^{2+} ions was neutralised by introducing an excess of magnesium into the indicator reaction. The addition of $5 \times 10^{-3} \text{ mol litre}^{-1}$ of magnesium in the presence of $5 \times 10^{-5} \mu\text{g ml}^{-1}$ of praseodymium and of $5 \times 10^{-5} - 5 \times 10^{-3} \mu\text{g ml}^{-1}$ of manganese, cobalt, and nickel to the system eliminates their interference; this magnesium concentration has no effect on the inhibitory effect of praseodymium. The interference of calcium ions was eliminated by masking it with tartrate.

The high sensitivity of enzymic methods makes it possible to determine many components of various waters in small samples and without preliminary concentration at the maximum permissible concentration (MPC) level. For example, metal ions like Cu, Co, Ni, Fe, Mn, Cr, Hg, Cd, Bi, Pb, and Zn can be detected at concentrations of $1 - 100 \text{ pg ml}^{-1}$ on the basis of their inhibitory effect on horseradish peroxidase and alkaline phosphatase.⁶³

It was proposed to use enzymic methods in the study of formation of hydroxo complexes. The stability constants of hydroxo complexes, K_{MOH^+} , have been calculated for zinc, copper, iron, cobalt, and nickel.²⁰ Analytical methods based on the use of enzymes also permit measurement of the equilibrium concentrations of hydroxide ions and of ions of some *d*-block elements in complex heterogeneous systems and the study of salt hydrolysis with a high degree of sensitivity and selectivity unattainable by the majority of other methods.³⁴

The use of native enzymes for some specific assays has a number of disadvantages, such as the instability of enzymes on storage and under the influence of various factors (*e.g.*, heat treatment) and the impossibility to separate enzymes from the reagents and the reaction products. A contemporary approach to the solution of this task consists in the wide use of immobilised enzymes. Immobilisation favours the stabilisation of enzymes on long-term storage and increases their resistance to external factors. The possibility of multiple use of enzymes reduces considerably the cost of analysis.

The use of immobilised enzymes in metal ion assays has been reviewed.⁶⁴ Immobilisation of enzymes for determination of metal ions entails their incorporation into various membranes or binding to glass beads. Polymeric films with immobilised enzymes incorporated in them are now often used as membranes for biochemical sensors.

Thus an amperometric biochemical sensor for determination of metal ions has been constructed on the basis of ChE immobilised by incorporation into cellulose nitrate films.³⁶⁻³⁸ A method for assaying Cr^{3+} , Ti^{4+} , Zr^{4+} , and Hf^{4+} ($1 \times 10^{-10} - 1 \times 10^{-5} \text{ mol litre}^{-1}$) has been developed, which is based on the inhibitory effect of heavy metal ions on the catalytic activity of immobilised cholinesterase.³⁸

It was suggested⁶⁵ that Cu^{2+} be determined using an enzymic electrode containing glucose oxidase; it is based on the inhibitory effect of these cations on the enzyme in the concentration range of $2.5 \times 10^{-4} - 5 \times 10^{-3} \text{ mol litre}^{-1}$.

Recently, much attention has been paid to semiquantitative test-methods, which allow rapid, simple, and reliable determination of concentrations of toxic substances at the MPC level. The use of immobilised enzymes for the elaboration of these methods is also very promising.

A test-method for the determination of Hg^{2+} using peroxidase immobilised as a solid solution in chitosan has been described.⁶⁶ The assay is based on the inhibitory effect of mercury on the oxidation of *o*-dianisidine, *o*-phenylenediamine, and 3,3',5,5'-tetramethylbenzidine with hydrogen peroxide in the presence of thiourea catalysed by immobilised peroxidase. The change in the colour of the reaction solution due to the formation of red or

orange products of enzymic oxidation allows visual monitoring of the reaction rate. The lower limits of mercury concentrations that can be determined in these reactions are 1×10^{-5} , 5×10^{-5} , and $1 \times 10^{-7} \mu\text{g ml}^{-1}$, respectively. This method is noted for selectivity (the assays are hampered only by a 10^5 -fold excess of cadmium and bismuth), rapidity (the analysis is completed within 15 minutes), simplicity, and low cost.

Enzymic methods for assaying metal ions are characterised by high sensitivity and in some cases, high selectivity.²⁷ However, most of these assays are not sufficiently selective. A combination of high sensitivity of biochemical sensors based on immobilised enzymes with traditional methods of masking makes it possible to solve complex analytical problems. Thus, enzymes act as a new generation of analytical reagents. The use of biosensors for quantitation of metal ions is also a promising approach because it exploits the conditions modelling individual functions of a living organism. The elaboration of novel measuring tools including biosensors, especially those based on highly sensitive methods of registration, considerably extends the possibilities of evaluation of the effects of metal ions on the catalytic activity of enzymes. It may be assumed that in many cases the concentration range of inhibition or activation for a definite 'metal-enzyme' pair could not be determined because of the limited potentialities of the recording systems. In addition, in the case of specific assays, allowance should be made for the ionic composition of the medium and the composition of the buffer solutions used for each assay. Buffer solutions must be selected in such a way that their ionic composition ensures the maximum catalytic activity of the enzyme. This provides the conditions for the generation of a maximum analytical signal, which in turn extends the analytical capabilities of enzymic assays of various effectors including metal ions.^{37, 57}

IV. Conclusion

The above analysis of literature data shows that the effect of metal ions on the catalytic activity of enzymes is still a timely problem. At the same time, special mention should be made of some recent specific features of these studies. Thus in the 1960-70's interest in these studies was mostly biological or medical, while in the last decade interest has been shifted towards the chemical aspects of the problem. This is primarily due to the pollution of the biosphere with various metals above the permissible level and secondly, due to the possibility of their estimation with the help of enzyme preparations possessing higher sensitivity and, in some cases, selectivity. Two main trends in these studies can be isolated: quantitative assay of inhibitors or activators from the magnitude of the induced effect and the use of the activating effect of metal ions for increasing the sensitivity of assays for a wide range of compounds of various natures.

An overview of current literature demonstrates that it is difficult to predict *a priori* how one or another metal will influence the enzyme. This depends not only on the nature of the metal and the enzyme, but also on other specific conditions. The most important of those are the ionic radius and the concentration of the metal. One should not consider the problem of interaction of metal ions with the enzyme separately from the pH of the solution and the presence or the absence of the substrate. The activating or inhibitory effect of metal ions must be considered only with allowance for these factors.

Unfortunately, the majority of authors restrict themselves currently to the qualitative description of effects of metal ions on the catalytic activity of enzymes, while very few papers deal with quantitative estimates and analysis of the mechanism of interaction between metals and enzymes. It may be supposed, however, that the number of such publications will be increasing with the development of highly sensitive methods of registration.

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Phase transitions in polymer solutions induced by mechanical fields

S A Vshivkov, S G Kulichikhin (deceased), E V Rusinova

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Abstract. The review summarises and analyses recent results of studies into phase transitions in polymer solutions induced by mechanical fields. Processes of dynamic structure formation preceding phase transitions in shearing and longitudinal fields are described. The effect of molecular weight, chain flexibility, and concentration of the polymer, shear stress (rate), and surface energies of components on the phase separation of polymer solutions in a mechanical field is considered. The theoretical concepts of phase transitions in polymer solutions under mechanical stress are analysed. The bibliography includes 186 references.

I. Introduction

The study of phase transitions in polymer systems is a task of current interest, since phase transitions largely govern the structure, and hence, the properties of systems.

Processes leading to the formation of new phases play an important role in polymerisation and polycondensation, microencapsulation, adsorption from solution, and in the production of fibres, films, and membranes. Studies of phase equilibria are necessary for the development of the solution theory and for experimental verification of the existing theoretical assumptions. It is therefore natural that phase equilibria draw much attention.^{1–8}

Polymeric systems are exposed to various mechanical effects (shearing, stretching, compressing, and other deformations) during exploitation and processing. Directed mechanical stress is the main method for the orientation of polymers aimed at enhancement of their mechanical properties. For example, molecular orientation implemented by deformation of melts or solutions and arrested by a phase transition (crystallisation) has opened the possibility of manufacturing high-module fibres.

A considerable number of publications on the effect of mechanical stress on the phase transitions in polymer systems have appeared over recent years; some have been reviewed.^{9,10} Undoubtedly, mechanical stress can play a role of an independent thermodynamic factor determining the positions of the boundary curves, viz., binodals and liquidus curves, on phase diagrams.

According to Frenkel,⁸ mechanical stress should lead to a shift of these boundary curves. However, the theory of phase transitions in polymeric systems induced by mechanical fields[†] is still under development.

The accumulated body of data on the effect of a mechanical field on the liquid and crystalline phase separation, as well as on the gel formation in polymer solutions are summarised and analysed in this work. Phase transitions in polymer mixtures are not considered.

II. Dynamic structure formation in polymer solutions

Changes in viscosity, optical, thermodynamic, and other properties are observed in polymer solutions well below phase separation temperatures (T_{ph}) (on approaching T_{ph}).^{7,11–15} This implies a continuous reorganisation of the solutions: concentration fluctuations increase abruptly, and the size of light-scattering particles, which are nuclei of the new phase, increases.

In addition to temperature, concentration, and chemical structure of the components, the structure of polymer solutions is much affected by the external mechanical field. Its action can cause uncoiling of macromolecules, their orientation resulting in the formation of supramolecular structures, and decomposition of the structures already present.

Polymer flow can be caused by both stretching and shearing deformations. The shearing field causes the rotation of macromolecules, and the direction of deformation is reversed before a high degree of stretching is attained. Under uniaxial stretching conditions, the component of rotational movement is absent, and molecule stretching is determined by the $\varepsilon\tau$ product, where ε is the deformation rate and τ is the maximum time of molecule relaxation in which it returns to the coil conformation. Since τ is proportional to the molecular weight ($M^{1.5–2.0}$), considerable stretching of a macromolecule with high M can be reached even at very low polymer concentrations ($c \approx 10^{-2}$ g dl⁻¹).¹⁶ A small fraction of molecules with molecular weight 15 times higher than the average are deformed 100 times more strongly.¹⁷ For this reason, at moderate stretching stress in a flux, the majority of short molecules only move, while long molecules present in small quantities stretch almost completely and can form nuclei of a new phase.

The transition from a coil to a stretched chain was considered theoretically in a series of papers.^{18–25} It was shown within the

S A Vshivkov, E V Rusinova Ural State University, prosp. Lenina 51, 620083 Ekaterinburg, Russian Federation. Fax (7-343) 255 74 01. Tel. (7-343) 261 60 46. E-mail sergey.vshivkov@usu.ru (S A Vshivkov)
S G Kulichikhin Join Stock Company G S Petrov Plastics Institute, Perovskii pr. 35, 111024 Moscow, Russian Federation

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[†] Mechanical field signifies a field of vectors of stresses (forces) that appear in a system when it is deformed.

scope of nonequilibrium thermodynamics¹⁹ that in a longitudinal hydrodynamic field (under uniaxial stretching), full uncoiling of macromolecules occurs, which is accompanied by an increase in energy dissipation by the flowing solution. It was shown¹⁹ that in the case of unpermeable macromolecular coils, the transition of chains to the stretched state on changing the velocity gradient occurs as a first-order phase transition and is accompanied by an abrupt change in the conformational entropy of the chain. When the molecular weight of a polymer decreases, the transition behaviour becomes uniform.

The theoretical conclusions are confirmed by the experimental data for dilute solutions of carboxymethylcellulose, methylcellulose, nitrocellulose and a number of other polymers.¹⁹ The fact that a transition of polystyrene molecules in xylene solutions from coiled to strongly stretched state does occur was confirmed experimentally.^{26, 27} The transition, detected by the appearance of strong birefringence, was observed at shear rates ($\dot{\gamma}$) above a certain critical value ($\dot{\gamma}_{cr}$). The correlation $\dot{\gamma}_{cr} \propto N^n$, where N is the degree of polymerisation and $n = 1.47 \pm 0.08$, has been established for the polystyrene–toluene system.²⁸ The phenomenon of chain uncoiling was also observed in polymer melts. It was found²⁹ that the mean stretching of polyethylene molecules under shear deformations can be as high as 50%.

A number of papers^{20–26} present a theoretical consideration of macromolecule uncoiling in a longitudinal hydrodynamic field and analyse the changes in the friction coefficient of macro-

molecules and in the chain conformational microstructure under stretching. These processes change the environment of macromolecules to anisotropic.³⁰ Such induced anisotropy is determined by the orientation of macromolecules and manifests itself as experimentally observed birefringence of solutions, Weissenberg effect, flow swelling, *etc.*^{16, 31}

The degree of macromolecule uncoiling in a shearing field is much smaller than that in a stretching field.³² For example, 100% uncoiling of polyethylene molecules requires a *ca.* 10^3 times higher deformation rate in the shearing field than in the stretching field. Uncoiling and orientation of macromolecules leading to their association have been observed for solutions of poly(ethylene oxide) and polyacrylamide (PAA),³³ polyacrylic acid,³⁴ and poly(octyl methacrylate).³⁵

The increase in concentration fluctuations in the course of flowing has been observed for polystyrene solutions.^{36–38} The formation of supramolecular particles in such processes was considered in Refs 39 and 40. It was shown that, depending on $\dot{\gamma}$, a sharp increase in concentration fluctuations can lead to the phase separation of the system. In solutions of polymer mixtures, the dependence of the magnitude of concentration fluctuations on the shearing rate passes through a maximum at medium $\dot{\gamma}$ values. The micellar structure formation in aqueous surfactant solutions depends on $\dot{\gamma}$ in a similar way.^{41, 42}

It was found for the poly(vinyl alcohol)–water,^{41–46} poly(ethylene oxide)–water,^{47, 48} polyethylene–xylene,^{49, 50} and poly-

Table 1. Effect of mechanical field on the properties of polymer solutions.

System	Shear rate, s ⁻¹	Type of deformation	Result of exposure	Ref.
Polymethacrylic acid–water	10	shear	irreversible structure formation	60
PAA–water	1000	"	formation of gel-like particles	61
PMMA–chlorinated biphenyl	20	"	irreversible structure formation	62
PVAL–water	1000	"	formation of molecular aggregates	63
PS–dioctyl phthalate	20	stretching field	orientation solidification	64
PS–chlorinated biphenyl	150	shear	formation of gel-like particles	61
PS–cyclohexanone	400	"	reversible structure formation	66
PS–dioctyl phthalate	100	"	reversible phase separation	67
PS–decalin	100	"	the same	67
PS– <i>tert</i> -butyl acetate		"	"	68
PS–dioctyl phthalate		"	"	69
PE–xylene	–	"	structure formation	70
PVAL–water	200	"	crystallisation	71, 72
		"	irreversible structure formation	73
		"	irreversible phase separation	74
		stirring	structure formation	46, 75
Tobacco mosaic virus–water	14 400	shear	irreversible structure formation	76
Albumin–water	290	"	reversible structure formation	76
Polyesters and epoxide resins in toluene and ethylbenzene		"	abrupt viscosity change	77
PE–xylene	150 rpm	"	irreversible separation	78
	2000	stretching flow	crystallisation	79
PE–diphenyl ether	2000	the same	"	79
PE–octadecane		shear	"	51
PEO–chlorinated biphenyl	100	"	irreversible structure formation	80
PEO–water	1000–10 000	"	the same	47
		turbulent flow	structure formation	81, 82
Polycaproatamide–caprolactam		shear	crystallisation	83
PAA–water		stirring	irreversible structure formation	52
		stretching flow	structure formation	54

ethylene–octadecane⁵¹ systems that structure formation resulting in phase separation occurs in the solutions exposed to mechanical stress (stirring, flowing). Analogous effects were observed for polyacrylamide–water,^{52–54} polystyrene (PS)–dioctyl phthalate,⁵⁵ poly(methyl methacrylate)–chlorinated biphenyl,⁵⁶ polystyrene–decalin⁵⁷ and polystyrene–cyclohexane⁵⁸ systems. It was found that dynamic structure formation is most pronounced in solutions of medium concentration.⁵⁹ Table 1 displays data on the effect of mechanical field on the properties of a number of polymeric systems.

Structure formation occurs in rheometer parts of various shapes: cone–plane, coaxial cylinders, capillary. The effect of deformation on solubility does not depend on the type of deformation. For example, similar results were obtained⁶⁹ in a study of changes in T_{ph} of solutions for a laminar Poiseuille-type flow through a capillary and for a torsion flow geometry in a gap between a cone and a plate. This is a common phenomenon for solutions of polar and nonpolar polymers with high molecular weight in a wide range of concentrations at any temperatures and in any solvents.

Thus, a study of the structure of polymer solutions showed that, first, uncoiling of macromolecules, their orientation and association leading to phase separation occur in a hydrodynamic field; second, depending on the shear rate and the polymer concentration, the effect of a mechanical field on the solution structure has a dependence passing through an extremum; third, as the molecular weight of a polymer and concentration increase, structure formation starts at lower shear rates; and fourth, a solid phase with new morphology, which is completely stable with respect to re-dissolution, is sometimes isolated from the solution.

III. Phase transitions in polymer solutions induced by mechanical fields

1. Systems with crystalline phase separation

The effect of mechanical field on crystallisation has been studied most thoroughly for polymer melts.^{84–98} The phenomenon of stress-induced crystallisation was discovered in 1805 by Gough.⁸⁷ Later, this problem was studied by Katz,⁸⁸ Flory,⁸⁹ Krigbaum and Roe,⁹⁰ Vinogradov and Malkin,⁹¹ Haas and Maxwell,⁹² Southern and Porter,⁹³ Fritzsche and Price,⁹⁴ Baranov,⁹⁵ Hoffman,⁹⁶ and Lindenmeyer.⁹⁷ This phenomenon has been covered in detail in a monograph⁹ and in a review.⁹⁸

Crystallisation of polymers from solutions and melts induced by mechanical stress has been observed in a number of studies.^{99–121} For example, crystallisation of *cis*-1,4-polyisoprene, *trans*-1,4-polybutadiene, poly(ethylene terephthalate), poly(vinylcarbazole), and poly(vinyl chloride) due to stretching has been observed by birefringence and small-angle light-scattering methods.⁹⁹ The formation of rod-shaped crystalline structures upon shearing and stretching has been found for melts^{100,101} and solutions¹⁰² of poly(ethylene terephthalate) in *m*-cresol and diphenyl ether. The crystallisation of isotactic polystyrene,¹¹⁹ polyethylene,^{95,122} and poly(ethylene oxide)^{96,114,123} melts in a shearing field has been studied.

It has been found for melts that mechanical stress (stretching or shearing deformation) increases the degree of orientation of macromolecular chains so that the induction period of crystallisation decreases, the crystallisation temperature increases (by tens of degrees), the rate of nuclei growth increases by two to four orders of magnitude, the nucleation rate increases by one to two orders of magnitude, and the critical size of the new phase nuclei decreases.

An increase in the crystallisation temperature has also been found for polymer solutions. It was shown¹⁰² that crystallisation of poly(ethylene terephthalate) under flowing conditions occurs at a temperature 10 K higher than that on cooling under static conditions. The polymer that formed consisted of elongated crystals, which were more thermally stable than the spherulites obtained upon phase separation of unperturbed solutions.

Pennings *et al.*^{78,108,116} have carried out systematic studies of polyethylene crystallisation from flowing solutions. They found that flowing causes a 15–20 K increase in the crystallisation temperature, while the crystallisation rate increases by a factor of several thousand. Similar dependences for polymer solutions were observed in other studies.^{103–107,111} It should be noted that experimental data are in good agreement with those calculated using the theory of polymer crystallisation from melts under deformation.^{103,108} Acceleration of crystallisation under flow conditions has been found in solutions of polypropylene, poly(ethylene oxide),¹⁰⁴ and poly(*p*-phenylene terephthalamide).¹⁰⁴

In a study of polycapramide crystallisation in caprolactam,^{123,124} it was found that an increase in shear rate to 50 s^{−1} decreases the induction period of crystallisation, but starting from 130 s^{−1}, the flow slows down the crystallisation, *i.e.* inversion occurs. It is assumed^{95,123,124} that this phenomenon is caused by the destruction of crystallisation nuclei at high shear rates.

Thus, it has been shown experimentally that uncoiling of macromolecules in the flow and orientation of chains favour the formation of nuclei of a new phase and phase separation. A detailed study of the effect of shear stress on the position of the boundary curve in the crystal separation of phases has been first carried out by Malkin and Kulichikhin.¹²⁴ They have shown that the mechanical field causes the boundary curve to shift to higher temperatures. This shift depends on the shear rate and is caused by a decrease in the entropy of the system due to processes of uncoiling and orientation of molecules in the flow.

Later, the T_{ph} of solutions and the melting points (m.p.) of polyethylene under static and dynamic conditions (Fig. 1) were determined by Vshivkov *et al.*^{48,125,126} It was found that application of a mechanical field results not only in an increase in T_{ph} and m.p., but also in a change in the boundary curve shape. It was only in the case of dilute solutions ($c < 1$ mass %) that no change in T_{ph} within the γ range studied was observed. In concentrated solutions, an increase in the shear rate results in a 10–30 K increase in T_{ph} . For solutions with $c = 30$ mass % and 40 mass %, the T_{ph} – γ function is a curve with a maximum; this indicates that the dependence of the crystallisation rate on the rate of the solution deformation has an extremal form. A similar correlation was observed by other authors.¹²³ These data and the data given below prove that this phenomenon is of general character and results from two oppositely directed processes, namely, uncoiling of macromolecules, their orientation in the flow, and destruction of nuclei of a new phase by the mechanical field at high γ values. The first process favours the crystallisation and the second one impedes phase separation.

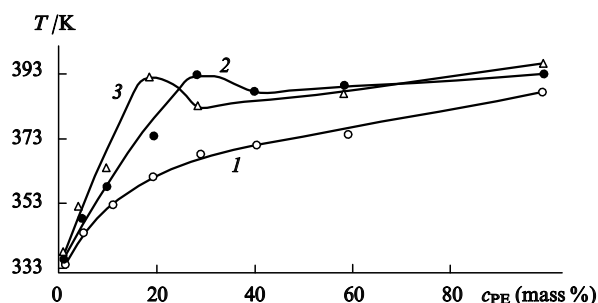


Figure 1. Boundary curves for the PE ($\bar{M}_n = 2.3 \times 10^5$)–xylene system. γ / s^{−1}: (1) 0, (2) 47, (3) 246.

From analysis of data on crystallisation of polyethylene from flowing solutions it was assumed¹²⁷ that the formation of amorphous gel-like phases precedes the formation of polyethylene fibrils. It was concluded that the phase diagram of solutions of a polymer that undergoes crystallisation can be changed both quantitatively and qualitatively under flowing conditions. In

fact, a shearing field can cause a qualitative change in the boundary curve (see Fig. 1). A maximum appears, the position of which is shifted towards low concentrations of the polymer on increasing the shear rate. Such curves are typical of systems where both liquid and crystal phase separation occurs simultaneously. However, we did not observe liquid phase separation in this system; the shearing field caused only a decrease in the degree of crystallinity of polyethylene precipitated from solutions.

2. Systems with liquid–liquid phase separation

Winsor¹²⁸ was the first to mention the effect of mechanical stress on stratification of liquids. He found that turbid systems, such as water–cyclohexanol–alkyl ethers of poly(ethylene glycol), lauryl alcohol–sulfodiethyl succinate–benzene–ethylene glycol and others, become transparent on vigorous shaking and return to the original state after a few minutes of rest.

Silberberg and Kuhn^{129–131} studied a polystyrene–ethylcellulose–benzene ternary system, which became turbid on cooling. They showed that the solution was turbid under quiescent conditions but became transparent on flowing at a certain critical shear rate and stratified again at a lower temperature, *i.e.*, the solubility of the components increased on flowing. In this case, the difference in phase separation temperatures under dynamic and static conditions (ΔT) was defined by the equation $\Delta T = -(\gamma_{cr}/\alpha)$, where $\alpha = 3.6 \times 10^6 \text{ mol}^{-1} \text{ litre}$. As can be seen from this equation, significant changes in T_{ph} under flow should occur for polymers with high molecular weight (10^6 – 10^7).

The enhancement of miscibility in the flow has also been observed for other ternary systems, such as polystyrene–polypropylene–decalin,¹³² polystyrene–polypropylene–toluene,¹³³ legumin–sodium chloride–water¹³⁴ and polystyrene–polybutadiene–dioctyl phthalate.^{135, 136}

The observed phenomenon was explained^{129–131} by the fact that the mechanical field destroys drops of a new phase. This is possible if the interfacial surface energy is low ($\sigma \approx 10^{-6} \text{ J m}^{-2}$). In this case, the energy of the hydrodynamic field may be sufficient to compensate the free energy gain due to the destruction of drops. The drops are destroyed until their volume reaches V

$$V = \left(\frac{0.74\sigma}{\eta\gamma} \right)^3,$$

where η is the viscosity of the medium.¹³⁷

Homogenisation in the flow of a polystyrene–polybutadiene–dioctyl phthalate ternary system, which stratifies on cooling, was studied using small-angle light scattering.^{136–138} It was found that the decrease in T_{ph} depends on the shear rate within its 6–1300 s^{-1} range according to the equation

$$\frac{\Delta T_{cr}}{T_{cr}} = (2.6 \pm 0.6) \times 10^{-3} \gamma^{0.50 + 0.02}.$$

The enhancement of solubility of the components is explained by the fact that a mechanical field suppresses the concentration fluctuations and destroys the nuclei of a new phase. Similar results were obtained using low-angle scattering of neutrons.¹³⁷

In a study of the optical properties of a polystyrene–toluene system, a decrease in the miscibility of components in the flow was observed.¹³⁹ A beam of light was passed parallel to the capillary walls, and it was found that the layer of the solution which scatters light decreased on flowing.

The effect of changes in mutual solubility of components in the flow on the shape of the phase diagram was first studied by Ver Strate and Philippoff.⁶⁷ They showed that T_{ph} for solutions of polystyrene in dioctyl phthalate and decalin increases in the flow from 284 to 313 K and from 289 to 302 K, respectively.

Later, the shift of boundary curves in shearing field was observed for polystyrene–cyclohexane, poly(methyl methacrylate)–butanol and poly(ethylene oxide)–water⁴⁷ systems. The observed increase in the higher critical solution temperature (UCST) and decrease in the lower critical solution temperature

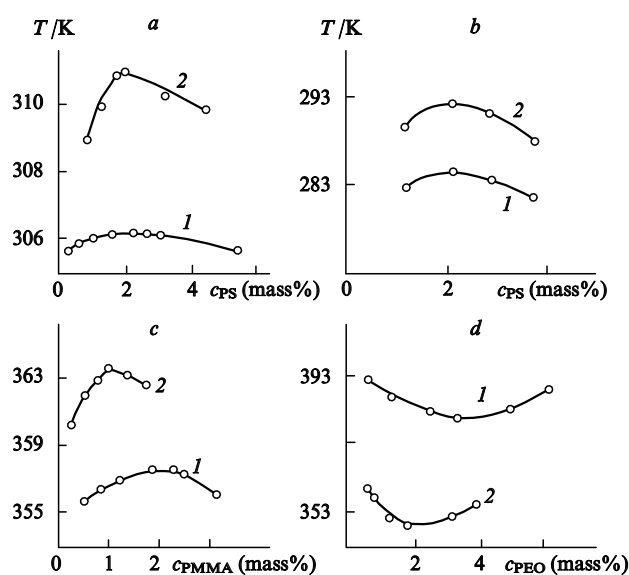


Figure 2. Boundary curves for PS–cyclohexane (a), PS–di(2-ethylhexyl) phthalate (b), PMMA–butanol (c), and PEO–water (d) systems under static (1) and dynamic (2) conditions.

(LCST) (Fig. 2) means a decrease in solubility of the components and formation of stable associates of polymer macromolecules in solution at temperatures at which none are formed under static conditions. The observed phenomenon is explained^{47, 67} by uncoiling of macromolecular coils in the mechanical field and by the orientation of chains along the flow, which increases the number of contacts between the macromolecules, *i.e.* increases the degree of association. This assumption has been confirmed experimentally.^{54, 58, 70, 84, 140, 141}

The decrease in the solubility of components, which manifests itself as changes in the T_{ph} of flowing solutions, has also been observed for poly(vinyl acetate)–ethanol,¹⁴² poly(methyl methacrylate)–dimethylformamide,¹⁴³ polystyrene–cyclohexanone–ethanol,¹⁴⁴ polybutadiene–toluene–ethanol,¹⁴⁴ and poly-(dimethylsiloxane)–ethyl methyl ketone¹⁴⁵ systems.

It was shown¹⁴⁵ for the poly(propylene glycol)–water, polyacrylic acid–dioxane, and poly-*p*-chlorostyrene–isobutyl acetate systems¹⁴⁵ that mechanical stress does not necessarily result in shifting of the boundary curves if uncoiling of macromolecular coils and the orientation of chains in the flow are hindered. In this case, insignificant uncoiling of macromolecules is explained by the low molecular weight of poly(propylene glycol) (1000) and by the high stability of polyacrylic acid globules near T_{ph} due to intramolecular hydrogen bonds.¹⁴⁶ The orientation of poly-*p*-chlorostyrene molecules is hindered by thermal motion (LCST = 423 K). Thus, the orientation effects in all the three systems are small and can be compensated by the destruction of nuclei of new phases in the mechanical field; as a result, the position of the boundary curves remains unchanged.¹⁴⁷

Wolf *et al.*^{148–154} have systematically studied the liquid phase separation of polymer solutions initiated by mechanical field. Using solutions of polystyrene in decalin, *tert*-butyl acetate, and dioctyl phthalate, they showed that both stratification and homogenisation of a system in the flow can be expected, depending on the concentration and the molecular weight of the polymer and the γ value. For example, for polystyrene with $M = 10^5$, mechanical field does not affect the T_{ph} of the solutions; for the sample with $M = 6 \times 10^5$, flowing results in an increase in miscibility, which manifests itself as a decrease in T_{ph} ; for the sample with $M = 2 \times 10^6$, flowing decreases the solubility. For solutions with $M = 1.2 \times 10^6$, $\Delta T = 0$ at low shear rates, T_{ph} becomes negative (the solubility increases) with an increase in γ , and $\Delta T > 0$ at high shear rates ($\gamma = 3000 \text{ s}^{-1}$).

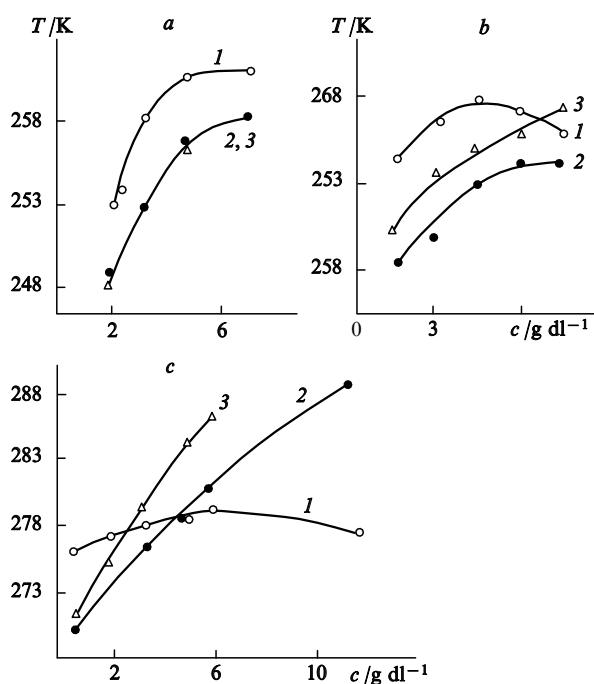


Figure 3. Boundary curves for a PS–di(2-ethylhexyl) phthalate system. $\bar{M}_\eta = 5.7 \times 10^4$ (a), 1.6×10^5 (b), 2.5×10^5 (c); γ/s^{-1} : (1) 0, (2) 24, (3) 118.

A different dependence was found for a polystyrene–cyclohexanone–ethanol system.¹⁴⁴ For the polystyrene samples with $M < 10^4$, the mechanical field did not affect T_{ph} , whereas at $M \approx 10^6$, the ΔT – γ dependence was described by a curve with a maximum. This is explained by the effect of two opposite processes occurring in the system, *viz.*, the orientation of macromolecules due to flowing and the destruction of new phase nuclei by the mechanical field. The first process favours phase separation and the second one prevents it. It was shown that the decrease in miscibility in the flow in the case of solutions of polystyrene, poly(vinyl acetate), and polybutadiene can be described by one curve in the ΔT – τ coordinates (where τ is the shear stress). The enhancement of solubility of the components (decrease in ΔT) starts from different τ for each polymer.

A systematic study of the effect of the polymer molecular weight and concentration on liquid phase separation under the action of mechanical field has been carried out for a polystyrene–di(2-ethylhexyl) phthalate system (Figs 2–4).^{155, 156} An increase in γ leads to a shift of the boundary curve towards higher temperatures, *i.e.* to a decrease in the solubility of a high-molecular polystyrene sample. A more complicated effect of mechanical field was observed for solutions of polystyrene with lower molecular weight. An increase in the solubility of the components, which manifested itself in a decrease in T_{ph} , was observed for a sample with $\bar{M}_\eta = 5.7 \times 10^4$. These data indicate an inversion of the effect of the mechanical field on liquid phase separation: the mutual solubility of the components increases in the flow in dilute and moderately concentrated solutions ($\Delta T < 0$) and decreases in concentrated solutions ($\Delta T > 0$). The higher the molecular weight of the polymer and the higher γ , the lower the concentration of the inversion point (c_i). It should be noted that c_i is close to the concentration c^* at which macromolecular coils begin to overlap. According to Debye, it equals $c^* = [\eta]^{-1}$, where $[\eta]$ is the characteristic viscosity. One may assume that in solutions with $c < c^*$, the shear field can destroy associates of fluctuation origin that form macromolecular coils in solution upon decrease in the quality of the solvent. The dependences of ΔT on the molecular weight of polystyrene for equiconcentrated solutions are described by curves with minima. In this case, the critical

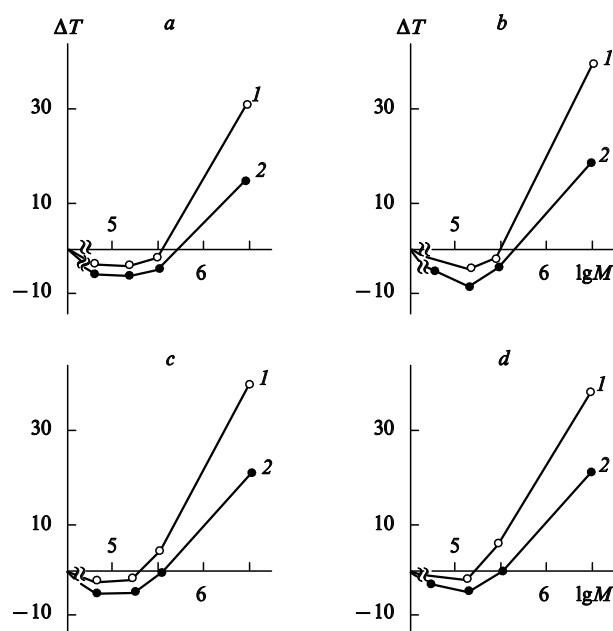


Figure 4. Dependence of ΔT on $\lg M$ for the PS–di(2-ethylhexyl) phthalate system. $c/\text{g dl}^{-1}$: (a) 1.51, (b) 3.06, (c) 4.26, (d) 5.00; γ/dl^{-1} : (1) 118, (2) 24.

molecular weight (M_{cr}), which marks the limit where ΔT becomes positive, decreases with an increase in the polymer concentration and shear rate. The mutual solubility of the components in the shear field increases for solutions of polystyrene with $M < M_{\text{cr}}$.

In the opinion of Barham and Keller,¹⁴³ flowing of solutions results in adsorption of macromolecules on the capillary walls. They classify the adsorption-entanglement layers according to their thickness: (1) layers several microns thick formed upon adsorption from solutions in good solvents at small γ (the existence of such layers has been discussed in a monograph¹⁵⁷); (2) layers formed in poor solvents at large γ that can be several millimetres thick and block the capillary, which increases τ . In these cases, the formation of gel-like particles is referred to. An attempt was made¹⁵⁸ to distinguish processes of liquid phase separation and the formation of adsorption-entanglement layers using oscillating flow. Periodic changes in the flow direction hinder the growth of adsorption layers but do not prevent liquid phase separation, which is determined by the magnitude of shear stress rather than by its direction. Four types of flow behaviour of solutions of poly(methyl methacrylate) in dimethyl phthalate were found: (1) usual flowing, which is not disturbed either by adsorption or by phase separation, at small rates of rotor oscillation (less than $2 \times 10^{-5} \text{ rad s}^{-1}$); (2) flowing where τ increases with time to a constant value (at $2 \times 10^{-5} - 10^{-2} \text{ rad s}^{-1}$), which is related to the formation of adsorption-entanglement layers of interpenetrating chains; (3) flowing where τ increases continuously (at $10^{-2} - 2 \text{ rad s}^{-1}$) due to the formation of adsorption-entanglement layers followed by liquid phase separation according to the nucleation and growth mechanism in which the role of nuclei is played by adsorption layers; (4) flowing characterised by large unstable τ oscillations. At rates above 3 rad s^{-1} , solutions become turbid due to liquid phase separation according to the spinodal mechanism. Thus, transition from behaviour type 3 to type 4 corresponds to crossing a spinodal, while transition from behaviour type 2 to type 3 corresponds to crossing a binodal. Using these rheological criteria, Barham and Keller¹⁵⁸ have determined the binodals and spinodals and showed that boundary curves and UCST shift to higher temperatures as τ increases. The results of the analysis performed by these and other authors are presented in Table 2.

Table 2. Polymer–solvent systems displaying anomalies on flowing.

System	Geometry of the measuring cell	Type of behaviour	Ref.
PS–toluene	capillary	formation of adsorption layers	56, 62, 158
PS–decalin	"	the same	158, 159
PS–chloroform	"	"	160
PS–dimethyl phthalate	cone–plane	spinodal separation	161
PS–dioctyl phthalate	coaxial cylinders	phase separation according to nucleation-growth mechanism or spinodal separation	67
	capillary	phase separation according to nucleation-growth mechanism	67
PE–xylene	coaxial cylinders	the same	162
PE–decalin	the same	spinodal separation	163
	capillary	phase separation according to nucleation-growth mechanism	164
PAA–water	"	formation of adsorption layers	165
Proteins–water	oscillating plate	spinodal separation	166
PVAL–water	coaxial cylinders	the same	162
PMMA–dimethyl phthalate	cone–plane	phase separation according to nucleation-growth mechanism or spinodal separation	161
	coaxial cylinders	phase separation according to nucleation-growth mechanism	62
	capillary	the same	62
PMMA–chloronaphthalene	cone–plane	"	167
	coaxial cylinders	"	62
PMMA–xylene	the same	"	62

The effect of mechanical field on phase transitions in solutions in which both liquid and crystal phase separation occurs was first studied for the polyethylene glycol (PEG)–poly(propylene glycol) (PPG) and PEG–glycerol–water systems.^{168–170} In the former system, a combination of liquid phase separation and crystal phase separation on cooling is observed; in the latter, liquid phase separation on heating and crystal phase separation on cooling occur. In the PEG–PPG system, the shearing field considerably increases the crystallisation temperatures ($\Delta T \simeq 10–16$ K) and almost does not affect liquid phase separation. The absence of a noticeable effect of the hydrodynamic field on the liquid phase separation of PEG solutions is caused by the low molecular weight of PEG. A similar dependence was found for the PEG–glycerol–water system: the change in crystallisation temperatures in the flow was an order of magnitude greater than the change in liquid phase separation temperatures. In both systems, the solubility of the components decreases under flowing conditions.

3. Gel-forming systems

It was found¹⁷¹ for a polymethacrylic acid–water system that gel formation leading to a sharp increase in viscosity is observed in the shearing field. The time dependence of viscosity (at $\gamma = \text{const}$) is described by a curve with a maximum the position of which shifts to smaller times with increasing γ . The decrease in viscosity is explained by macroscopic destruction of the gel that formed. It is assumed that the aggregation of polymethacrylic acid molecules

results from the deformation and orientation of the polymer chains.

It was shown¹⁶⁹ that the increase in viscosity upon shear can be described by the Avrami equation, which is generally used for the description of polymer crystallisation. Gel formation under flowing conditions has been found for aqueous solutions of poly(vinyl alcohol),¹⁷² gelatine,¹²⁶ hydroxypropylguar,¹⁷³ and for a poly(dimethylsiloxane)–ethyl methyl ketone system.¹⁷⁴

An opposite phenomenon has been observed for a cellulose diacetate–acetone–water system, which forms a gel on cooling;^{125,170} applying mechanical field results in a decrease in gelation temperatures, *i.e.* widening of the homogeneous region. This phenomenon is probably caused by the fact that cellulose diacetate has high kinetic rigidity, thus no considerable additional uncoiling of macromolecules should be observed in the flow. Hence, the role of the hydrodynamic field is reduced mainly to the destruction of nuclei of a new phase, which enhances the mutual solubility of the components. It was found that under deformation with $\gamma \simeq 10^2 \text{ s}^{-1}$, solutions containing a 1.4–2 times higher concentration of the polymer can exist than in the absence of flow.

IV. Theoretical background of the phase separation of solutions exposed to mechanical fields

1. Liquid separation

At present, several approaches to the description of the effect of mechanical field on the miscibility of components in polymeric systems are known. For example, Di Marcio and Guttman¹⁷⁵ assume that the polymolecular nature of polymers is the reason for the stratification of the flowing solutions. Since the distance between the mass centres of particles and the capillary walls cannot be smaller than the radii of the particles, larger molecules will be closer to the capillary centre and will thus move at a higher velocity, which results in phase separation. However, this concept has not been developed further, as it did not explain the shift of boundary curves for monomolecular polymer solutions and low-molecular-weight compounds.

Other scientists^{67, 126, 127, 149, 154} suggest that the free energy of solution mixing in mechanical field (ΔG_γ) should be represented by a sum of the free energies of solution mixing under static conditions (ΔG) and the energy the solution can store while it flows (G_s),

$$\Delta G_\gamma = \Delta G + G_s.$$

The free energy of solution mixing under static conditions is calculated according to the Flory–Huggins theory

$$\Delta G = RT(n_1 \ln \varphi_1 + n_2 \ln \varphi_2 + \chi n_1 \varphi_2),$$

where n and φ with indices 1 and 2 are the mole number and the volume fraction of the solvent (1) and the polymer (2), respectively, and χ is the parameter describing the interaction of the solvent (1) with the polymer (2). The free energy G_s accumulated by the flowing solution due to uncoiling and orientation of macromolecules can be determined according to the equation^{67, 148}

$$G_s = \tau^2 I,$$

where τ is the shear stress and I is the compliance caused by the first difference of normal stresses, which equals

$$I = 0.4 \frac{M_2}{c_2 RT} \left(1 - \frac{\eta_0}{\eta} \right)^2$$

for Newtonian solutions, where M_2 is the molecular weight of the polymer, c_2 is the polymer concentration, and η_0 and η are the solvent and solution viscosities, respectively.

The first calculations of the stored energy at temperatures near T_{ph} were performed by Ver Strate and Philippoff⁶⁷ for the polystyrene–decalin system. It was shown that at $\Delta T \approx 5$ K, $\tau = 3 \times 10^3$ dyn s⁻¹, $I \approx 10^{-3}$ cm³ dyn⁻¹, $\chi = 0.5$, and $\phi_2 = 0.03$, the stored energy G_s is 2×10^{-4} cal cm⁻³. The magnitude of G_s is of the same order as the change in the energy of mixing ($\Delta G'$) required for the given change in the solution T_{ph} ($\Delta G' \approx 5 \times 10^{-4}$ cal cm⁻³). The concentration dependences of G_s and $\Delta G'$ corresponding to the change in T_{ph} in a polystyrene–di(2-ethylhexyl) phthalate system in the flow were calculated.¹⁵⁵ The calculated values coincided. Hence, the change in the solubility of components in a mechanical field can actually be caused by the energy stored by solutions in the flow.

It was found for a polystyrene–dioctyl phthalate system⁶⁹ that the dependence of normal stress, which determines G_s , on the polymer concentration at a constant τ is described by a curve containing a maximum. The pure solvent behaves as a Newtonian liquid, hence the normal stresses are equal to zero. The addition of the polymer imparts elastic properties to the solution, leading to the development of normal strains upon shear deformations. At high polymer concentrations, the fluctuation entanglement network hinders the elastic deformation of chains in the shearing field, which results in a decrease in normal stresses. It is the extremal character of the G_s – c dependence that explains the extremum observed on the ΔT – c dependence.⁶⁹

Using the Marrucci and Sarti relationship¹⁷⁶ between the solution elasticity and G_s , an equation relating the system parameters for the critical point in a shearing field was found⁶⁹

$$-\frac{1}{(1-\phi_2)^2} + 2\chi - \frac{a\bar{V}_1}{RT} = 0,$$

where a is a coefficient relating G_s to the volume fraction of the polymer and $\bar{V}_1$ is the partial molar volume of the solvent.

By comparing this equation with the known equation for $\gamma = 0$

$$-\frac{1}{(1-\phi_2)^2} + 2\chi_0 = 0,$$

it is possible to find a parameter of interaction between the components in a flowing solution

$$\chi = \chi_0 + \frac{a\bar{V}_1}{2RT}.$$

Presumably, the polymer concentration in the critical point of a system is not changed in the flow,⁶⁹ but the interaction parameter is 'shifted' by $\Delta\chi = a\bar{V}_1/2RT$. Hence, boundary curves for a system under mechanical stress should be shifted along the χ (or T) axis and remain parallel to the boundary curves for the undisturbed system. The ΔT values determined experimentally for solutions of polystyrene in dioctyl phthalate at 3–28 K coincided with those predicted⁶⁹ to within ± 3 K. However, it should be noted that experimental boundary curves are shifted along the T axis with an increase in τ but are not parallel to those for the undisturbed system.

The concept of stored energy was used^{149,154} to calculate a series of boundary curves. It was shown that in the general case, both an increase and a decrease in the solubility of components can be expected in a mechanical field. The overall pattern is determined by the relative behaviour of the concentration dependences of ΔG_γ , ΔG , and G_s (Fig. 5). For solutions of polymers with low molecular weight, a concentration higher than the critical concentration ϕ_2^{cr} corresponds to the maximum G_s , and in this case the contribution of G_s to ΔG of the system can result in the system homogenisation in the flow and hence in a change in the shape of the ΔG – ϕ_2 curve. For solutions of polymers with high molecular weights, the concentration at the maximum G_s and ϕ_2^{cr} are comparable. In this case, a homogeneous system whose ΔG – ϕ_2 curve is concave (which corresponds to the thermodynamically stable state) separates into two phases in mechanical

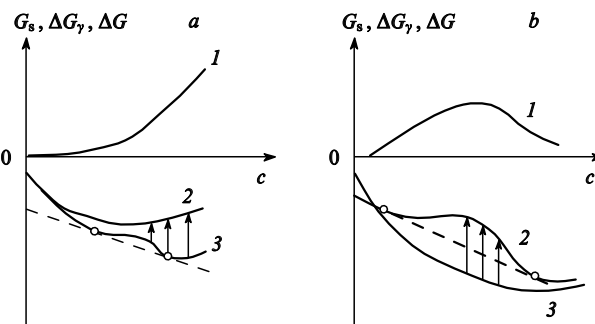


Figure 5. Concentration dependences of the stored free energy (G_s) and the free energy of solution formation under dynamic (ΔG_γ) and static (ΔG) conditions.¹⁵²

(a) shear-dissolution; (b) shear-demixing; (1) G_s , $\gamma = \text{const}$; (2) ΔG_γ ; (3) ΔG ; c is the polymer concentration.

field, and extremums appear on the ΔG_γ – ϕ_2 curve. According to the calculations,^{149,154} polymer solutions can separate into three coexisting phases at certain τ values. An eulytic point was introduced, where two binodals, which appear upon deformation from one original binodal corresponding to the undisturbed system, intersect.

The change in the free energy of mixing due to flow is related^{127,177} to a decrease in chain flexibility on deformation. The Flory equation¹⁷⁸ for f , i.e. the fraction of flexible chains in a macromolecule, was supplemented by parameter A , which describes the work of an external mechanical field required for stretching a macromolecule,

$$f = \frac{(z-2) \exp(-\varepsilon/kT - A)}{1 + (z-2) \exp(-\varepsilon/kT - A)}, \quad (1)$$

where z is the coordination number in the quasi-lattice model, ε is the difference between the free energies of the flexible and rigid macromolecule conformations, and $A = Fl/kT$ (F is the stretching force applied to a segment of length l). It was shown¹⁷⁷ that an isotropic solution can become anisotropic on imposing a mechanical field. This approach does not take into account the enhancement of the miscibility of components in the flow observed experimentally.

The authors of Ref. 127 analysed the latter two approximations. They used Eqn (1) under the condition that Fl is an increase in the free energy due to the translation of macromolecular segments with characteristic length l . In this case, the free energy of a system of semi-flexible chains in a flowing solution containing n_2 polymeric molecules and n_1 solvent molecules was written as:

$$\begin{aligned} \Delta G = kTn_2 \left\{ (x-1) - \ln\left(\frac{xz}{2}\right) + (x-2)[f \ln f + \right. \\ \left. + (1-f) \ln(1-f) - f \ln(z-2)] \right\} + n_2 \{ f(x-2)(\varepsilon + Fl) \} + \\ + kT(n_1 \ln \phi_1 + n_2 \ln \phi_2 + \chi n_2 \phi_1), \end{aligned} \quad (2)$$

where x is the number of segments of length l in the macromolecule. From Eqns (1) and (2), an equation was obtained for the free energy of mixing, ΔG . Using this equation, the chemical potentials of the components and the change in the free energy per mol of the polymer under flowing conditions were calculated

$$\Delta G_f = RT(x-2) \ln[(1-f)(z-1)]. \quad (3)$$

It was shown¹²⁷ that Eqn (3) for the calculation of a binodal can be solved only if, after phase separation, the chains in the concentrated phase are straightened to a larger extent than in the dilute phase. The approximation for accumulated energy was

analysed and the following expression for the energy of mixing of a flowing solution was obtained:

$$\Delta G_{\gamma} = RT \left\{ N_1 \ln \varphi_1 + N_2 \ln \varphi_2 + \chi x N_2 \varphi_1 - N_2 \left[\ln \frac{x}{2} + \ln \frac{z}{z-1} + (x-1) \ln \left(\frac{z-1}{e} \right) \right] \right\} + N_2 G_s,$$

where N_1 and N_2 are the mole numbers of the solvent and the polymer, respectively, G_s describes the free energy change due to stretching of one mole of macromolecules, and 'e' is the base of natural logarithms. It should be noted that the expressions for G_s presented in Ref. 127 were derived with account of the properties of the solution rather than of separate macromolecules. At $G'_s = G_s$ (the prime mark corresponds to the more concentrated phase), no displacement of the binodal should occur. It follows from the equation obtained in the same work

$$G'_s - G_s = RT(x-2) \ln \left(\frac{1-f'}{1-f} \right),$$

that the approximation of chain flexibility decrease is identical with the approximation of accumulated energy if G_s is interpreted as the free energy of the coil–stretched chain transition. In this case, the two-phase region broadens as the rigidity of macromolecules in the concentrated phase increases, and the binodal is shifted to higher temperatures with an increase in $(1-f)/(1-f')$; the critical concentration decreases in the flow, which is in accord with the experimental data.

The liquid phase separation of polymer solutions in a mechanical field has also been analysed theoretically in other papers.^{143, 179–181}

2. Crystalline phase separation

One of the first studies dealing with crystallisation of polymers under deformation was carried out by Flory,⁸⁹ who derived the dependence between the melting point and the degree of stretching of a loosely cross-linked polymer

$$\frac{1}{T_m^0} - \frac{1}{T_m} = \frac{R}{\Delta H_m} \left[\left(\frac{6}{\pi m} \right)^{1/2} \lambda - \frac{\lambda^2}{2m} - \frac{1}{\lambda m} \right], \quad (4)$$

where T_m^0 is the equilibrium melting point of non-deformed polymer, ΔH_m is the heat of melting of one mole of statistical segments, m is the number of statistical segments between cross-linking points, and λ is the stretching ratio. At small λ , Eqn (4) gives overestimated melting point values, since it was derived with the assumption that crystals grow only along the direction of stretching.

Krigbaum and Roe⁹⁰ suggested the following relationship between the deformation and the melting point:

$$\frac{1}{T_m^0} - \frac{1}{T_m} = \left(\frac{R}{2\Delta H_m} \right) m \left[\lambda^2 + \frac{2}{\lambda} - 3 \right].$$

This equation makes it possible to obtain equilibrium melting points for non-deformed specimens as well. However, as the authors themselves admit,⁹⁰ Eqn (4) gives a better fit of the experimental data over a broad range of λ values.

Flory⁸⁹ explains the increase in the melting point on stretching by a decrease in the polymer entropy by a value of the orientation entropy S_{or} . According to Yeh *et al.*,^{85, 86} the increase in the rate and temperature of crystallisation in the flow occurs for the same reason. They compared the following equations:

(1) for the melting point

$$T_m = \frac{\Delta H_m}{\Delta S_m} \text{ (under static conditions); } T_m = \frac{\Delta H_m}{\Delta S_m - |\Delta S_{or}|}$$

(under shearing conditions), where ΔH_m and ΔS_m are the specific enthalpy and entropy of melting and ΔS_{or} is the change in entropy caused by molecular orientation.

(2) for the nucleation rate N

$$\frac{N_{\gamma>0}}{N_{\gamma=0}} = \exp \left[-\frac{B}{RT} \left(\frac{1}{\Delta g} - \frac{1}{\Delta g + T|\Delta S_{or}|} \right) \right],$$

where Δg the free energy of nucleation and B is a constant.

It follows from the equations that an increase in the shearing rate, and hence $|\Delta S_{or}|$, increases the nucleation rate and the melting point. The decrease in polymer entropy due to the orientation of macromolecules in the flow has been calculated¹²⁶ for the polyethylene–xylene system according to the equation

$$|\Delta S_{or}| = \frac{\Delta S_m}{1 + T_m/\Delta T}.$$

The values of ΔS_{or} obtained are of the same order of magnitude as those reported for the polycaproatamide–caprolactam system.¹²⁴ The dependence of S_{or} on the concentration has a maximum, which indicates that the dependence of the coefficient of molecular extension on the concentration, which depends on S_{or} according to the equation⁸⁴

$$\alpha = 1 + A|\Delta S_{or}|,$$

where A is a constant for a particular system, also has an extremum. In fact, polymeric chains in dilute solutions are isolated and can change their conformations in the flow almost without interacting with each other, hence one should not expect a considerable effect of mechanical field on the phase behaviour of the system. As the polymer concentration increases, a fluctuation entanglement network, which does not yet hinder the orientation processes, is formed in solution. In this case, the interaction between the macromolecules is strong, which results in an increase in viscosity, and hydrodynamic field affects considerably the phase transition temperature. As the concentration is increased further, the network density increases, thus hindering the orientation processes. This diminishes the effect of mechanical field on phase transitions. The decrease in the molecular orientation due to the formation of a spatial network has been reported⁹⁶ for a polyethylene melt. The higher the shear rate, the lower concentration is required for the formation of a fluctuation entanglement network. Therefore, the maximum ΔS_{or} is reached at lower polymer concentrations.

V. Conclusion

Mechanical deformations (shearing, stretching) of polymer solutions lead to changes of the macromolecule conformations, their aggregation, and eventually to the phase separation of the systems. In some cases, on the contrary, the hydrodynamic field enhances the mutual solubility of the components. This is observed as a shift of boundary curves and depends largely on the difference in the surface energies of the components, σ_{12} . At $\sigma_{12} > 10^{-2} \text{ J m}^{-2}$, the miscibility of the components decreased in the flow and increased at $\sigma_{12} < 10^{-4} \text{ J m}^{-2}$ (Table 3), because the energy of the mechanical field is sufficient for the destruction of the new phase nuclei at low σ_{12} .

For systems with crystalline phase separation, no enhancement of the solubility of the components under flowing conditions was observed. Mechanical stress leads only to an increase in the polymer melting point in melts and solutions. The increase in the melting point is caused by a decrease in the entropy of the system due to the uncoiling and orientation of the macromolecules. Systems with crystalline phase separation are more sensitive to mechanical stress than systems with liquid phase separation. Mechanical field even affects the crystallisation of low-molecular-weight compounds with molecular weights of *ca.* 10^2 , and this effect becomes stronger as the molecular weight of the solute

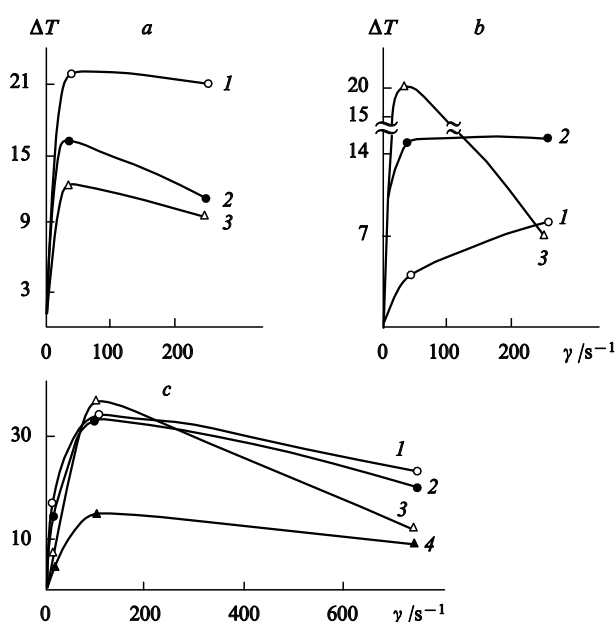
Table 3. Values of σ_{12} and effect of shearing deformation on the mutual solubility of components.

System	$10^3 \sigma_{12} / \text{J m}^{-2}$ (293 K)	Solubility in mechanical field
PS–dioctyl phthalate	12.6	decreases
PS–decalin	15.3	"
PS–cyclohexane	20.2	"
PMMA–butanol	30.5	"
PEO–water	32.0 (363 K)	"
DAC ^a –acetone–water	0.3	increases
PS–ethylcellulose– benzene	10^{-2}	"
PDMS ^b –ethyl methyl ketone	0.2	"

^a DAC is cellulose diacetate; ^b PDMS is polydimethylsiloxane.

increases. In systems with liquid phase separation, the shearing field manifests itself as a change in the T_{ph} of solutions of polymers with molecular weights above 10^5 .

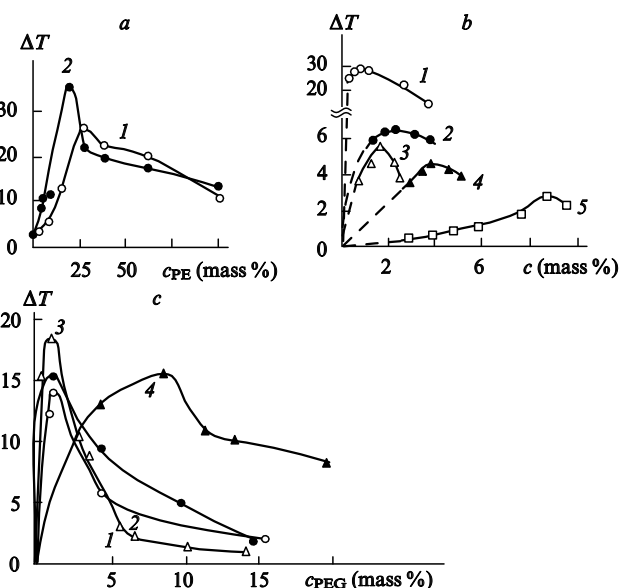
The dependences of ΔT on shear rate (stress) contain maxima. This does not depend on the type of phase separation and is caused by the existence of two oppositely directed processes in the system: uncoiling of macromolecules and their orientation in the flow (which favours phase separation) and destruction of new phase nuclei by the mechanical field at high shear rates (which hinders phase separation). Fig. 6 gives examples of dependences of ΔT on γ for different systems.

**Figure 6.** Dependence of ΔT on γ for various systems.

(a) PEG ($\bar{M}_\eta = 800$)–PPG ($\bar{M}_\eta = 3100$): $c_{PEG}/\text{mass \%}$: 1.1 (1), 3.51 (2), 5.42 (3); (b) PE ($\bar{M}_\eta = 2.3 \times 10^5$)–xylene: $c_{PE}/\text{mass \%}$: 10.0 (1), 30.0 (2), 40.0 (3); (c) PS ($\bar{M}_\eta = 3.3 \times 10^6$)–di(2-ethylhexyl) phthalate: $c_{PS}/\text{g dl}^{-1}$: 7.01 (1), 4.60 (2), 2.83 (3), 1.00 (4).

The concentration dependence of the effect of hydrodynamic field on ΔT has an extremum (Fig. 7). The maximum effect is observed in moderately concentrated solutions. This is valid for liquid and crystalline phase separation as well as for gel formation and is a result of the extremal concentration dependence of normal stresses that appear in the flow.

An inversion of the effect of the mechanical field on the mutual solubility of the components as a function of the polymer concentration and molecular weight and the shearing rate has

**Figure 7.** Concentration dependences of ΔT for different systems.

(a) PE ($\bar{M}_\eta = 2.3 \times 10^5$)–xylene, $\gamma = 47$ (1) and 246 s^{-1} (2); (b) (1) PEO ($\bar{M}_\eta = 4.0 \times 10^4$)–water, $\gamma = 9.5 \times 10^3 \text{ s}^{-1}$; (2) PS ($\bar{M}_\eta = 3.3 \times 10^6$)–di(2-ethylhexyl) phthalate, $\gamma = 246 \text{ s}^{-1}$; (3) PMMA ($\bar{M}_\eta = 9.9 \times 10^4$)–butanol, $\gamma = 3 \times 10^4 \text{ s}^{-1}$; (4) PS ($\bar{M}_\eta = 3.3 \times 10^6$)–cyclohexane, $\gamma = 2.1 \times 10^4 \text{ s}^{-1}$; (5) cellulose acetate ($\bar{M}_\eta = 6.9 \times 10^4$)–acetone/water (1.6/1.0), $\gamma = 170 \text{ s}^{-1}$; (c) PEG ($\bar{M}_\eta = 800$)–PPG ($\bar{M}_\eta = 3100$), $\gamma = 248$ (1) and 47 s^{-1} (2); PEG ($\bar{M}_\eta = 3.3 \times 10^4$)–glycerol/water (80/20), $\gamma = 248 \text{ s}^{-1}$ (3); PEG ($\bar{M}_\eta = 1.8 \times 10^3$)–glycerol/water (90/10), $\gamma = 248 \text{ s}^{-1}$ (4).

been observed for a number of systems with liquid phase separation.

These data make it possible to suggest the following mechanism for the effect of shearing field on the phase separation of polymer solutions. In dilute solutions, polymeric chains are isolated and can change their conformations in the flow almost without interactions. When the thermodynamic quality of the solvent gets worse (due to temperature changes), macromolecules can form associates. However, these structures are unstable and are easily destroyed by a mechanical field, which leads to enhancement of the mutual solubility of the components in the flow, *i.e.* to the displacement of the binodal ($\Delta T < 0$ for systems with upper critical solution temperatures). As the polymer concentration is increased, a fluctuation entanglement network, which does not yet hinder orientation processes, is formed in solution. In this case, the interaction between the macromolecules is strong, the hydrodynamic field affects the temperature of phase separation, and $\Delta T > 0$. As the concentration is increased further, the network density increases, thus hindering the orientation processes. This diminishes the effect of mechanical field on phase transitions, hence ΔT decreases. An increase in the polymer molecular weight favours the formation of a fluctuation network, therefore the concentration at the inversion point c_i and the concentration at the maximum ΔT decrease as these parameters increase.

This review does not deal with the destruction of macromolecules that occurs in polymer solutions at very high deformation rate and stress, as this phenomenon has been analysed in sufficient detail elsewhere.^{182–186}

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Double-helical nucleic acids with cross-linked strands: synthesis and applications in molecular biology

S I Antsylovich, T S Oretskaya

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Abstract. Data on the methods employed for cross-linking of DNA strands and for the synthesis of oligonucleotide duplexes with cross-links between strands are summarised. Existing methods are systematised; their advantages and drawbacks are discussed. The examples of applications of DNA duplexes with covalently cross-linked chains for the study of protein–nucleic acid recognition and mechanisms of action of nucleic acid-binding proteins for gaining information about the spatial structure of nucleic acids, and for the solution of other problems of molecular biology are given. The bibliography includes 131 references.

I. Introduction

Studies of fine details of cellular processes related to the expression and processing of genetic information require that a new generation of modified oligonucleotide derivatives be created that can be used as tools in these studies.

Therefore, in recent years the chemical approach employing modified oligonucleotides for the study of mechanisms of interaction of proteins with nucleic acids has been widely used in combination with physicochemical methods, such as X-ray structural analysis and NMR spectroscopy. The direct modifications of the nucleic acid chemical structure in protein–nucleic acid complexes and the analysis of properties of such synthetic systems has made it possible to gain information about the spatial structure of these complexes and the nature of protein–nucleic acid contacts. Directed modification allows useful properties to be conferred on oligonucleotides, such as resistance against nuclease degradation, enhanced thermodynamic stability of the duplexes formed by them, low toxicity, and the ability to penetrate cellular membranes. It also favours selective recognition and site-specific (including covalent) binding of DNA with proteins.^{1–9}

Oligonucleotides and their reactive derivatives are important tools for the study of protein–nucleic acid interactions in transcription, translation, replication, repair, recombination, and modification of nucleic acids. Until fairly recently, it was mainly derivatives of single-stranded oligonucleotides that were used to this end. Meanwhile, a great variety of processes, such as repair, recombination, initiation of transcription by the corresponding factors, *etc.*, occur with the involvement of double-stranded nucleic acids. Consequently, it is the double-stranded structures that should be used as models and affinity reagents in studies of these processes.

Modified nucleic acid duplexes have found use in elucidating the mechanisms of action of enzymes that interact with nucleic acids and in establishing the features of protein–nucleic acid recognition. The method based on the use of cross-linked nucleic acid duplexes is one of the most promising and popular procedures for investigation of protein–nucleic acid interactions. DNA duplexes with covalently cross-linked strands can be used as models for the study of the majority of the aforementioned cell-mediated processes and for the construction of affinity reagents and ‘decoys’ for proteins binding double-stranded DNA.^{10–16}

For example, if the mechanism of action of an enzyme includes the unwinding of the double helix of DNA, covalent cross-links between the strands will prevent this process and thus strongly suppress the action of the enzyme. Duplexes stabilised by cross-linking can be potential inhibitors of nucleic acid-binding proteins.^{10, 13} Duplexes with covalently cross-linked chains are promising for the isolation of proteins by affinity chromatography. Covalent cross-links formed in specific positions can stabilise thermodynamically unstable DNA structures.^{15, 17}

Two main methods exist for the synthesis of this type of compound. Historically, the first of them consists in non-specific treatment of sufficiently long DNA molecules with bifunctional alkylating agents, such as derivatives of psoralen, pyrroles, and some other compounds.^{1–5, 18} The second method, which leads to the formation of DNA duplexes with covalently cross-linked chains, is based on the use of derivatives of modified oligonucleotides containing chemically reactive groups.

One of the first to begin the study of reactions between the strands of DNA duplexes more than 30 years ago was a group of Russian investigators from the Siberian Branch of the Russian Academy of Sciences directed by Academician D G Knorre.^{1–3, 19–23} These studies have ushered in the method

S I Antsylovich, T S Oretskaya Department of Chemistry,
M V Lomonosov Moscow State University, Leninskie Gory,
119899 Moscow, Russian Federation. Fax (7-095) 939 31 81.
Tel. (7-095) 939 31 48

of 'targeted chemical modification' which has been used in the structural analysis of nucleic acids. Conceptually, this method is related to the construction of synthetic analogues of nucleases specific for a definite type of DNA base. Later, this method gave way to the method of 'complementarily targeted modification'.^{1–3, 24–31} The latter consists in the introduction of a reactive alkylating group into an oligonucleotide. After hybridisation, this group interacts site-specifically with the target DNA, *i.e.*, it alkylates the target at a predetermined position.

Thus, the majority of studies connected with the use of alkylating reagents aimed at the modification of nucleic acids dealt with the synthesis of highly reactive derivatives, which reacted with the target nucleic acid resulting in labilisation of the glycosidic bond in one of the nucleosides and, as a consequence, in the cleavage of the phosphodiester bonds of the oligonucleotide.^{1–3} Irrespective of the nature of the alkylating reagent, double-stranded complexes with covalently cross-linked chains formed were unstable and underwent spontaneous hydrolysis in aqueous solutions. These investigations gave information about the reactions between the chains of double-stranded nucleic acids; however, the synthesis of DNA duplexes with covalently cross-linked chains was not the aim of these studies, and for this reason they are not considered in detail in the present review.

This review encompasses studies devoted predominantly to the preparation of synthetic oligonucleotide duplexes with covalently cross-linked chains and to the methods of nonspecific cross-linking of DNA chains. It does not consider covalently closed structures of nucleic acids, such as cyclic oligonucleotides and dumbbell-like structures, since this is an independent trend of research, which is also being developed in recent years.

II. The main methods for the synthesis of cross-linked DNA duplexes

It is known that bifunctional alkylating reagents that can form cross-links between the chains (such as 2-chloroethylnitrosourea, *etc.*) can also inhibit nucleic acid biosynthesis. In many cases, such reagents are efficient antitumour drugs.^{5, 6, 32–34} This is due to the fact that nonspecific cross-linking of DNA chains is highly toxic for the cell,^{5, 34} since it prevents expression of the genetic material. The ability to form cross-links in double-stranded DNA is the reason for the cytotoxicity of many compounds employed in clinical practice.

A great number of compounds that can cross-link nucleic acid chains have been described. Psoralen^{7, 11, 12, 18, 35–64} and pyrrole^{34, 65–71} derivatives are the most popular to this end. Other compounds used for the formation of interchain cross-links in double-stranded nucleic acids include aziridinolbenzoquinones (2,5-bisaziridino-1,4-benzoquinone^{72, 73} or alkylaziridino-1,4-benzoquinones),⁷⁴ aziridinonitrobenzamides (5-aziridino-2-nitro-4-nitrosobenzamide and 5-aziridino-4-hydroxylamino-2-nitrobenzamide⁷⁵), anthracyclines (daunomycin,⁷⁶ adriamycin,⁷⁷ anthramycin,^{78, 79} mitomycin C^{80–83} and its analogues⁸⁴), melamine derivatives, *e.g.*, trishydroxymethyl(trimethyl)melamine,⁸⁵ acridine derivatives, *e.g.*, 1-nitro-9-(3-*N,N*-dimethylaminopropyl)aminoacridine,⁸⁶ chloroambucyl,^{87, 88} 4-hydroperoxycyclophosphamide,⁸⁹ tris(2-chloroethyl)amine,^{90, 91} 1,3-bis(2-chloro-ethyl)-1-nitrosourea,⁹² 2-aminomethylpyrrolidine(cyclo-butane-1,1-dicarboxy)platinum(II),⁹³ cisplatin,^{34, 80, 92, 94} and *cis*-diamminedichloroplatinum(II).⁹⁵

Synthetic cross-linked oligonucleotide duplexes are the most convenient tools for the study of gene structure and functions. Their application has a number of salient advantages over non-specific alkylation of nucleic acids. The presently known bifunctional electrophilic reagents usually recognise those sequences in nucleic acids the length of which does not exceed two nucleotide residues. As a rule, the reactions with the participation of these reagents yield mixtures of monoadducts and products of intra-strand cross-links. Heterogeneity of the reaction mixture resulting from the alkylation of DNA with non-specific bifunctional

reagents¹⁸ is often an obstacle in the studies of effects of individual interstrand cross-links on DNA processing.

At present, the synthesis of oligonucleotide duplexes cross-linked at the predetermined positions of the double helix is complicated because the cross-links between the chains are either unstable⁹⁶ or endow significant disturbances in the secondary structure of DNA.^{35, 36} New approaches to the synthesis of DNA duplexes with interstrand cross-links have recently appeared, which permit cross-links to be created at any predetermined site of the DNA duplex and to introduce several cross-links into the same duplex.

The main requirements for the methods of synthesis of modified oligonucleotides that are used in the preparation of duplexes with covalently cross-linked chains can be formulated as follows: (1) the possibility of targeted incorporation of modified units into any predetermined position of the oligonucleotide chain; (2) the applicability of standard procedures of oligonucleotide synthesis, and (3) the possibility of incorporation of several modified units into the same oligonucleotide for subsequent synthesis of an oligonucleotide duplex with several cross-links between the chains.

III. Methods for the synthesis of modified oligonucleotides

Generally, an oligonucleotide can be modified at heterocyclic bases, phosphate groups (internucleotide or terminal), or carbohydrate residues. The potentialities of modern chemical synthesis of nucleic acid fragments allow targeted incorporation of one or several modified units (identical or different) into the oligonucleotide.

Compounds carrying primary aliphatic amino groups as well as aldehyde, carboxy, sulfhydryl, and phosphate groups are used for the cross-linking of the duplex chains. The general requirement for the formation of a cross-link is the localisation of the reactive group at the end of a spacer (a cross-linking arm). The length of the spacer can vary widely depending on the mutual arrangement of the reactive groups within the duplex. Thus in the case of psoralens, a relatively short, two-carbon-atoms-long spacer is sufficient for the interaction with the opposite chain.^{37, 38}

A functional group can be incorporated into the oligonucleotide by the following methods:⁸

(a) using a modified nucleotide component carrying the corresponding functional group in the chemical oligonucleotide synthesis;

(b) incorporating a precursor compound into the oligomeric chain followed by treatment with the corresponding reagents that give the target-modified unit either in the course of the oligonucleotide synthesis or after its completion;

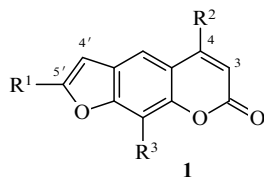
(c) post-synthetic modification of an oligonucleotide.

The potentialities of the latter approach are limited. It can be used only for preparing oligonucleotide analogues carrying numerous statistically modified units (*e.g.*, units with identical heterocyclic bases undergoing modification). In the former two methods, modification is envisaged in the very pattern of the chemical synthesis of oligonucleotides.

The first method is the most versatile. It consists in preliminary formation of modified units and their subsequent incorporation into the oligonucleotide in the process of synthesis. This method does not constrain either the number or the chemical nature of the units to be introduced into the oligonucleotide chain. Moreover, it significantly simplifies isolation of the target product. Side reactions in the process of oligonucleotide synthesis are minimised because all chemically reactive functional groups of the oligonucleotide have been preliminarily protected. The initial modification of the nucleoside to be inserted is usually carried out in non-aqueous media, which permits the use of a broad spectrum of modifying reagents, whereas post-synthetic modifications are usually performed in aqueous solutions.

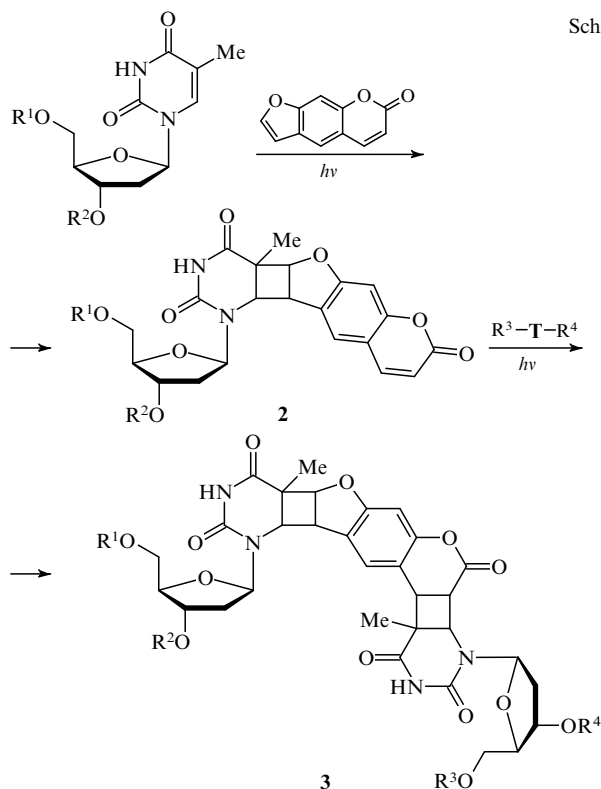
IV. The use of psoralens for the synthesis of covalently linked DNA duplexes

Psoralens {7*H*-furo[3,2-*g*][1]benzopyran-7-ones}[†] are polycyclic aromatic compounds of the general formula **1**; they have a planar structure and are capable of intercalating between the base pairs of the double helix.^{36, 39–41}



$R^1, R^2, R^3 = \text{H, Alk.}$

These compounds are specific to the thymidine and uridine residues. On UV irradiation of DNA duplexes at λ 320–360 nm, psoralen incorporates into the double helix and binds covalently with the pyrimidine bases of DNA, preferentially with thymine, at positions 5 and 6 to form four-membered rings (Scheme 1).^{37, 42, 43}



$R^1 - R^4$ are fragments of oligonucleotide chains.

Psoralens can enter into photoaddition reactions with cytidine. However, this reaction occurs 15 times more slowly than with thymidine.⁴⁴ In DNA, psoralens predominantly bind with the 5'-d(TpA) sequence.^{40, 43, 45, 46} The efficiency of psoralen photoaddition to this sequence is at least one order of magnitude higher than that to thymidine in any another environment. The same regularities hold for the synthesis of cross-linked RNA duplexes.^{11, 12, 47, 48}

Since psoralen is a bifunctional reagent, the photo-induced reaction can lead either to the monoadduct of the type **2**, when the psoralen molecule is added to only one chain of nucleic acid, or to the bisadduct of the general formula **3**. In the latter case, a duplex with covalently cross-linked chains is formed. The formation of the bisadduct **3** requires the absorption of two photons⁴⁹ and

occurs in two steps (Scheme 1).^{7, 11, 45} If the pyrone ring of psoralen enters into the reaction at the first stage, the bisadduct is not formed, since the furan ring of the monoadduct becomes incapable of absorbing UV light.¹¹

Intercalation of psoralen into the double helix, which usually increases the thermodynamic stability of the duplex, is a prerequisite for the reaction between the chains. The formation of adducts can be accompanied by photoinactivation of psoralen, which consists in photochemical degradation of the pyrone ring.³⁸ The adducts of nucleic acids with psoralen are decomposed into the original components on irradiation with UV light with a wavelength that depends on the structure of the psoralen derivative,^{39, 40, 42, 45} as a rule, it is equal to 254 nm. Thus, the cross-linking of DNA chains with psoralen is reversible.

In the absence of UV irradiation, psoralens are non-toxic. The ability of these compounds to form cross-links between DNA chains makes possible their application in *in vitro* and *in vivo* studies of the DNA structure. Psoralens are used both in medicine for photochemotherapy of some diseases^{39, 40, 50, 51} and in investigations of some molecular-biological processes. Psoralen has been used for the analysis of the secondary structure of RNA^{35, 47, 48, 50–52} and the structure of the DNA–RNA-polymerase transcription complex.^{12, 53–55} Currently, psoralen derivatives are used for the study of the secondary and tertiary structure of nucleic acids as well as for the analysis of mechanisms of DNA repair.^{56–58}

Methods of targeted incorporation of psoralen into oligonucleotides (directly in oligonucleotide synthesis or after its completion and removal of protective groups) are of prime interest. The monoadduct of psoralen with the oligonucleotide can be produced post-synthetically using an activating reagent.^{12, 59, 60} Such a monoadduct was obtained in the reaction of a 5'-phosphorylated self-complementary oligonucleotide with 4'-aminoalkyl-4,5',8-trimethylpsoralen in the presence of 1-ethyl-3-(3-dimethylamino)propylcarbodiimide hydrochloride, EtN=C=N(CH₂)₃-NMe₂·HCl (water-soluble carbodiimide, CDI). Hybridisation and irradiation yield a DNA duplex, which is cross-linked at the both ends.

The second method consists normally in the addition of psoralen to the 5'-end of the oligonucleotide in the oligonucleotide synthesis. Phosphoramidite derivatives of psoralen are used at the last stage of the synthesis.^{37, 38} A typical synthetic scheme for the incorporation of psoralen into oligonucleotides is described in Ref. 38: 4,5',8-trimethylpsoralen (**4**) was converted into the phosphoramidite **6** (Scheme 2) and the latter was used for the oligonucleotide synthesis.

4,5',8-Trimethylpsoralen **4** was added to the 5'-end of an 18-membered oligonucleotide; the resulting oligonucleotide **7** was introduced into the cross-linking reaction of DNA duplex chains (Scheme 3). 4,5',8-Trimethylpsoralen **4** was shown³⁸ to be stable both under conditions of synthesis and post-synthetic treatments of the oligonucleotide. It is noteworthy that psoralen-containing oligonucleotides of the type **7** are characterised by higher hydrophobicity, which is manifested in the increased retention time (in comparison with non-modified analogues) on HPLC.³⁸

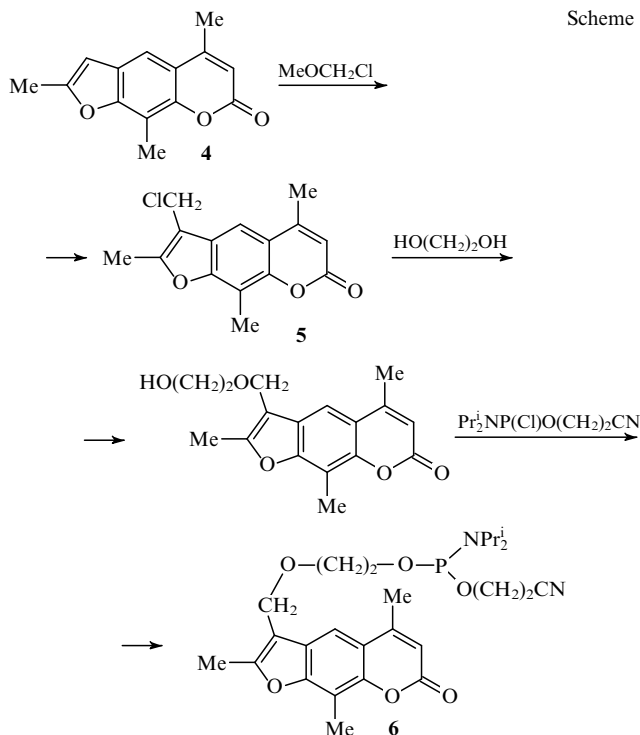
In this case, the nucleotide sequence of the oligonucleotides constituting the duplex was selected so that psoralen **4** intercalated into a double helix and reacted with thymidine in the 5'-d(TpA)/3'-d(ApT) sequence.⁶¹ It was found that the maximum yield of the DNA duplex **8** could be obtained when the CH₂-O-CH₂CH₂ group was used as the spacer for the addition of psoralen to the oligonucleotide (Scheme 3).

As a rule, the yield of the product **8** increases within the first 10–30 min after the beginning of irradiation (360 nm, 20 °C) and reaches 70%–80% after 60 min. A quantitative yield could not be attained even with a 100-fold excess of the modified oligonucleotide **7** with respect to the DNA matrix³⁸ due to partial inactivation of psoralen in the irradiation.

The 5'-d(TpA)/3'-d(ApT) motif is present in signal sequences of many genes. They represent potential targets for psoralen-

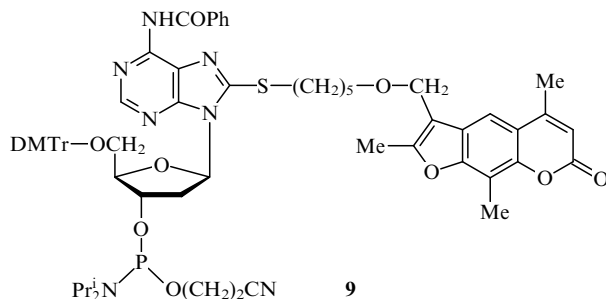
[†] Henceforth, the nomenclature accepted in the original publication is used.

Scheme 2



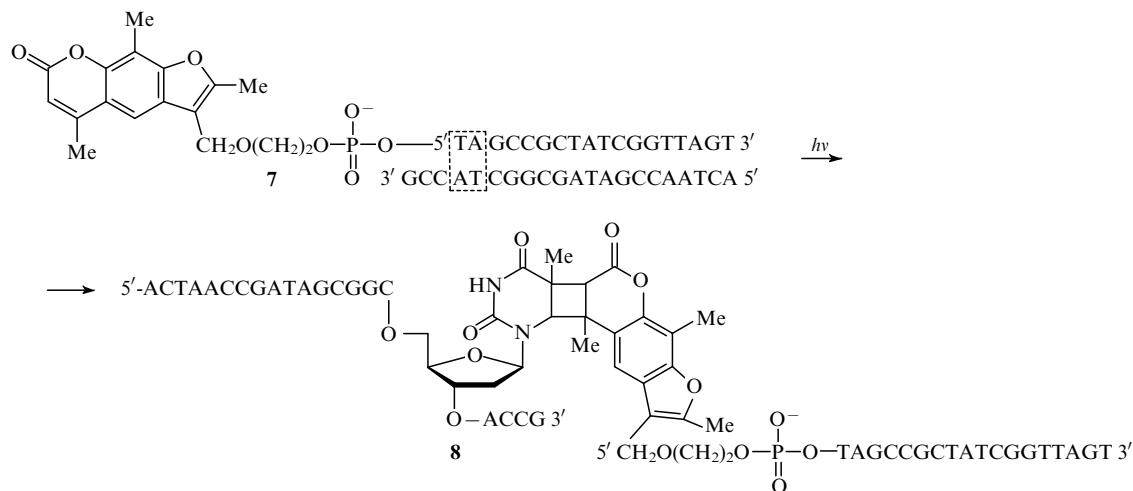
modified oligonucleotides of the type 7. Thus oligonucleotides of this type can serve as convenient probes for the study of gene expression.

A method for the synthesis of psoralen-containing oligonucleotides using a modified deoxyadenosine[‡] phosphoramidite **9** has been proposed.³⁷



DMTr = (4-MeOC₆H₄)₂PhC.

[‡] Hereinafter, the term 'deoxynucleosides' will refer to 2'-deoxyribonucleosides.



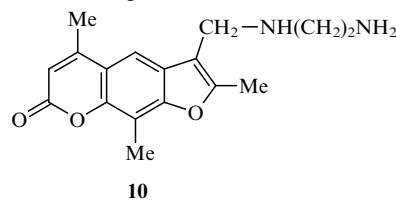
Scheme 3

4,5',8-Trimethylpsoralen **4** was attached to the C(8) atom of deoxyadenosine through the sulfur atom and the pentamethylene spacer. Subsequent phosphitylation afforded compound **9**. To achieve the maximum yield (90%) in the coupling of the phosphoramidite **9** with an oligonucleotide, 5-(4-nitrophenyl)-1*H*-tetrazole was used instead of tetrazide; the duration of condensation was 8 min.

The optimum length of the spacer was established by molecular modelling. In this particular case, the optimum length of the spacer needed for the psoralen intercalation into the 5'-d(TA)/3'-d(AT) site is five carbon atoms. An analogous derivative of deoxyadenosine of the type **9** but with a two-carbon-atoms-long spacer manifested a very weak cross-linking capacity. The efficiency of photoaddition to the complementary matrix chain exceeded 90% after 1-hr UV irradiation at λ 345 nm. This resulted in the formation of several products, which correspond to different possibilities of psoralen incorporation into the double helix. It was noted that psoralen was effectively incorporated both into the 5'-d(TA)/3'-d(AT) and the 5'-d(AT)/3'-d(TA) sequences, where it reacted both with the thymidine unit in the opposite chain and the adjacent one.

Owing to the fact that the ends of DNA duplexes of the type **8** with covalently cross-linked chains remain free, various labels (radioactive, fluorescent, or any other) can be easily attached to these ends. In addition, such duplexes can be incorporated into more extended DNA structures.³⁷

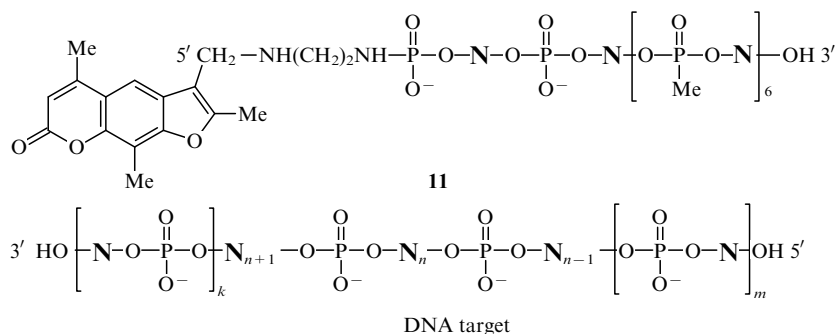
The reaction of oligonucleotide methylphosphonates (OMP) bearing the psoralen derivative, 4'-[*N*-(2-aminoethyl)amino-methyl]-4,5',8-trimethylpsoralen **10** (PS-OMP) attached to their 5'-ends with single- and double-stranded DNA, has been studied.



Compound **10** was coupled with the 5'-end of OMP carrying a phosphate group to give compound **11** (Scheme 4). Water-soluble CDI was used for the activation of the phosphate group. It was shown that the P–N bond is resistant to nucleases; however, it is cleaved in an acidic medium to give the original 5'-phosphorylated OMP.

On irradiation, PS-OMP specifically reacted with the template. The presence in the duplex of less stable nucleotide pairs (e.g., G·T or G·A) reduced the yields of the duplex with covalently cross-linked chains.¹² This is due to the decrease in thermal stability of the original duplex. The formation of by-products that result from the interaction between the chains in

Scheme 4



N denotes deoxynucleoside residues, $m \geq 6$, $k \geq 0$.

non-canonical duplexes depends on temperature: by-products are formed at 20 °C and are absent at 40 °C. This can be explained by dissociation of less stable non-canonical duplexes with an increase in temperature. In the case of a canonical duplex, the temperature dependence of the yield of the covalently cross-linked duplex is not observed below its melting point. At higher temperatures, the yield of the target product drops drastically. The efficiency of the reaction between the chains of a DNA duplex is also influenced by the ratio of the rate of this reaction to the rate of psoralen photoinactivation. The yield of the cross-linked DNA duplex increases with increasing PS-OMP concentration. However, if the PS-OMP concentration is twice as high as that of the matrix, the latter becomes saturated and the yield of the target product does not further increase.¹²

The efficiency of the interaction of various oligonucleotides with the target under identical conditions differs markedly,¹² although the differences in the nucleotide sequences should not be manifested at 4 °C. Molecular simulation has shown¹² that psoralen can be inserted between the nucleotides of the target in two modes: either between the terminal nucleosides $N_{(n+1)}$ and $N_{(n)}$ or between the nucleosides $N_{(n)}$ and $N_{(n-1)}$, where $N_{(n+1)}$ is the 3'-terminal nucleoside of the target and $N_{(n)}$ is the nucleoside that is complementary to the 5'-terminal nucleoside of PS-OMP (Scheme 4). In the former case, the spatial structure of the reaction centre is the most favourable for the photoaddition of psoralen. The reaction between the chains is the most effective, when thymidine occupies position $(n+1)$ of the template and position $(n-1)$ in OMP, which precedes the psoralen-modified unit, and adenosine is in the positions n . In this case, the reaction occurs with two possible sites and the yield of the duplex with covalently cross-linked chains reaches 95%.

Oligonucleotides of the type **11** were used for the analysis of the secondary structure of nucleic acids.¹² It was shown, in particular, that the cross-linking with the single-stranded region of DNA occurs 10–30 times more efficiently than with the double-stranded one. Since OMP are characterised by enhanced resistance in the cell, these oligonucleotide derivatives can be used in *in vivo* studies.¹²

A series of PS-OMP that are complementary to the template and non-template strands of a 57-membered DNA duplex containing a 17-membered T7 promotor of RNA-polymerase were synthesised.¹² The effects of PS-OMP on *in vitro* transcription were investigated. It was shown that PS-OMP, which is covalently cross-linked with the encoding region of DNA, effectively suppressed transcription, whereas the oligonucleotide cross-linked with the non-coding region had little inhibitory effect. Thus, the oligonucleotide that is covalently cross-linked to the template in the promotor region prevents binding of polymerase with the double helix of DNA either directly or by changing its conformation in the promotor region.

Being an agent that can directly react with DNA, psoralen can induce various mutations.¹¹ Study of mutagenesis is necessary for the understanding of regularities of the origin of cancer, hereditary diseases, and evolutionary processes.^{11, 56, 57} It remained

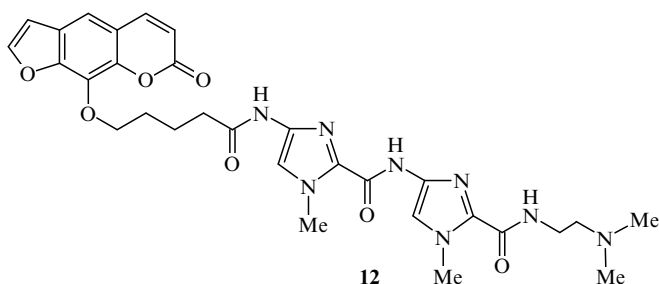
unclear which of the psoralen-induced mutations were generated by the monoadduct and which resulted from the presence of cross-links between the chains.

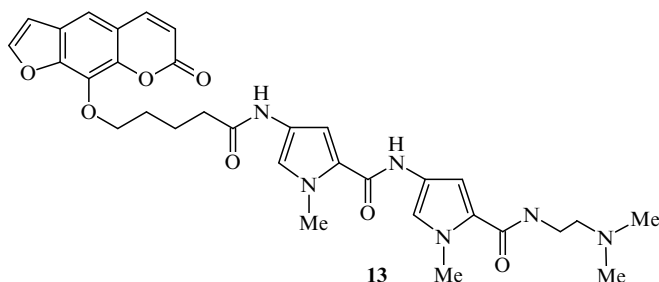
The use of a plasmid containing a single, definite damaged site has made it possible to relate the initial damage of DNA induced by psoralen to the origin of subsequent mutations.¹¹ The use of statistically modified DNA did not allow a correlation between the nature of mutations and the type of the adduct. The cyclic closed double-stranded plasmid containing the site-specifically incorporated psoralen as a mono- or bis-adduct (in the latter case, the cross-link is formed between the strands of the plasmid), has been synthesised *in vitro* and incorporated into the cells of *E. coli*. The recombinant DNA contained only one site with thymine in the form of a monoadduct with psoralen. Synthesis of the psoralen-containing plasmid was carried out using T4-DNA-polymerase and an oligonucleotide with psoralen at the 3'-end as the primer. In this case psoralen did not influence either the elongation of the chain or its subsequent ligation. The monoadduct was converted into the bisadduct by UV irradiation; the plasmid with covalently cross-linked chains was isolated taking advantage of its acquired ability to undergo reversible thermal denaturing. In contrast to the plasmid with cross-linked chains, denaturing of an ordinary plasmid is irreversible. The type and frequency of mutations was followed using two different DNA molecules. It was found that both types of psoralen-induced damages (the formation of the both monoadduct and the cross-links between the chains) can lead to severe genotoxic effects.¹¹ This finding is consistent with the results obtained by other authors.^{58, 62, 63}

The mutation induced by the formation of the monoadduct was eliminated by the repair mechanism of the cell. In the case of the bisadduct, a great number of secondary mutations (deletions, substitutions, inversions) evolved. The activity of DNA with cross-linked chains was 1.6% of the native one.¹¹

Thus, it was shown that it is by bisadducts that the toxicity of psoralen is determined, and their formation results in severe damage to DNA. Treatment of nucleic acids with psoralen was shown to prevent replication and transcription processes.¹¹

It was proposed⁶⁴ to couple psoralen with distamycin-like imidazole **12** and pyrrole **13** derivatives in order to promote the delivery of psoralen to specific sequences of DNA. Like the oligopeptide distamycin, these compounds bind with DNA in the region of the small groove.



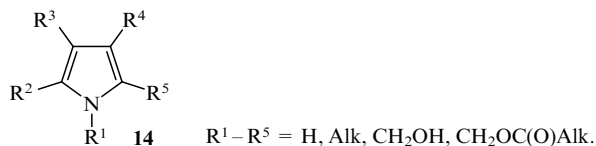


The use of oligonucleotides for the delivery of psoralen to specific sequences of DNA has posed a number of problems. They are connected with the low ability of the oligonucleotides to penetrate through hydrophobic cellular membranes and their susceptibility to nuclease hydrolysis. This circumstance restricts the application of such compounds.

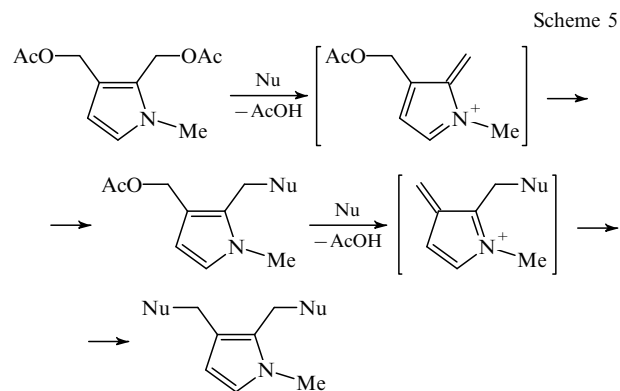
The derivatives **12** and **13** are devoid of these drawbacks and can deliver psoralen to both GC-rich (imidazole analogues of distamycin, **12**) and AT-rich (pyrrole analogues, **13**) regions of DNA. It was found that the derivatives **12** and **13** modify DNA 10 and 1000 times more efficiently than psoralen. Compound **13** is 100 times more efficient than compound **12**. Hence, psoralen, being attached to reagents that possess affinity with respect to DNA, manifests enhanced efficiency in the formation of multiple cross-links between the chains of extended DNA.

V. Cross-linked nucleic acid duplexes synthesised using pyrrole derivatives

Bifunctional pyrrole derivatives **14**, together with psoralen derivatives, are widely used for cross-linking of chains of double-stranded nucleic acids.^{34, 65–71} Only bifunctional pyrrole derivatives can cross-link the nucleic acid chains.



Cross-linking with pyrrole derivatives **14** involves exocyclic amino groups of heterocyclic bases of DNA (usually, deoxyguanosine) and those functional groups of pyrrole derivatives that can undergo nucleophilic attack. Hence, pyrrole derivatives are alkylating agents. A hypothetical mechanism of this reaction has been proposed (Scheme 5).⁶⁵

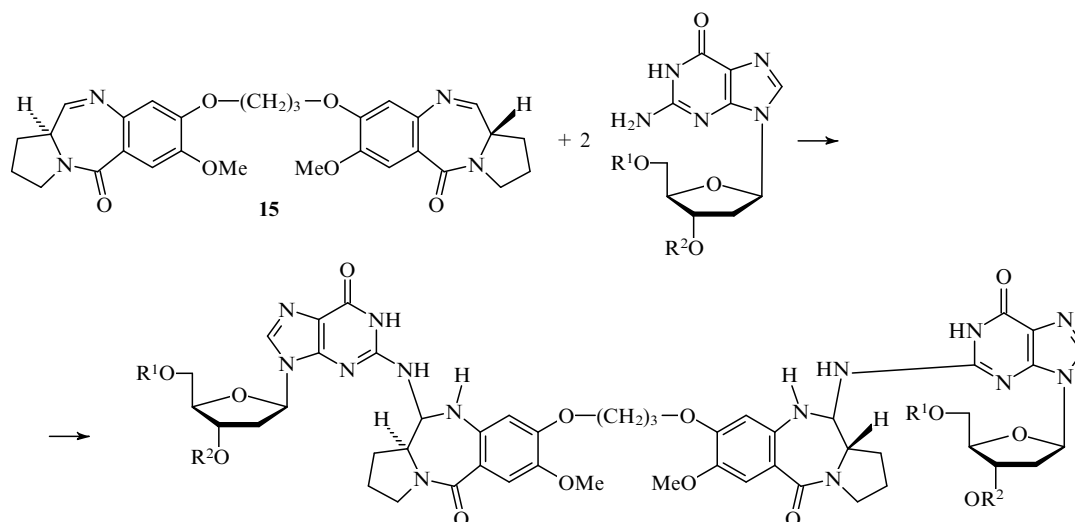


Nu is the exocyclic amino group of guanine.

Pyrrole derivatives as such are not specific reagents and can react with many reaction centres of DNA. Therefore, treatment of DNA with bifunctional pyrrole derivatives of the type **14** cannot be used to introduce cross-links at predetermined positions of DNA. The main drawback of pyrrole derivatives as antitumour agents is their low selectivity (*i.e.*, the affinity for sequences with the length of no more than two nucleotides). Such limited selectivity of pyrrole derivatives is due to the high probability of occurrence of certain short repeated nucleotide sequences in the genome.

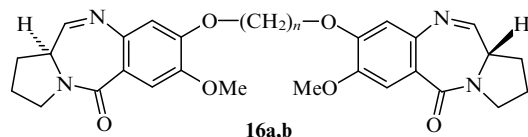
Enhancement of selectivity of bifunctional pyrrole derivatives is an important problem, particularly as regards their application as therapeutic agents. This can be achieved through a more targeted delivery of pyrrole derivatives to a definite genome region, *i.e.*, to a more rare nucleotide sequence. However, the solution of this task demands that the affinity of such agents for nucleic acids be increased.^{2, 34, 65–71} As a rule, it is sufficient to achieve selective interaction of the cross-linking reagent with sequences more extended than four nucleotide pairs. The main route for attacking the selectivity problem is the addition of a bifunctional alkylating agent (which has little or no affinity for nucleic acids) to compounds manifesting high affinity for definite sequences of DNA, *e.g.*, to oligopeptides.^{34, 65–70}

Synthesis of a new irreversible reagent **15** has been described.⁶⁶ Compound **15** belongs to the group of pyrrolobenzodiazepine dimers (PBD dimers). It binds with DNA through the small groove and reacts with the amino group of guanine (Scheme 6). The preferential sequence for the binding of this compound is the Pu-G-Pu triplet, where Pu is the purine nucleotide (A or G). The yield of the interstrand reaction product is about 50%.



R^1, R^2 are fragments of oligonucleotide chains.

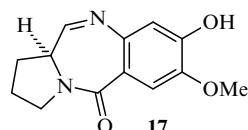
The synthesis of C(8)-linked PBD dimers of the type **16**, which are homologous to compound **15**, has been described by the same authors,⁶⁷ and their relatively high affinity for DNA has been demonstrated. The highest efficiency of the interchain reaction was achieved with compounds **15** and **16b** (three- and five-carbon-atoms-linking groups, respectively).



$n = 4(\mathbf{a}), 5(\mathbf{b})$.

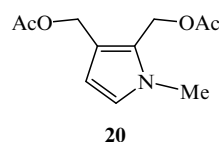
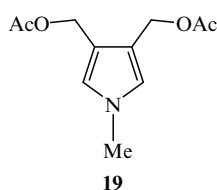
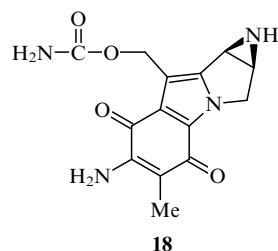
Treatment of double-stranded DNA with any PBD dimers increases the melting point of the duplexes.⁶⁷ The presence of cross-links in the linear double-stranded DNA prepared from the ring plasmid accounts for its rapid renaturation into a double-stranded form as the temperature decreases following thermal denaturing.⁶⁷ The ability of extended DNA to undergo rapid renaturation is a sign of cross-linking between the chains. Thus, PBD dimers can stabilise double-stranded DNA.

The cytotoxicity data⁶⁷ correlate with the yields of duplexes with covalently cross-linked chains. The PBD dimer ($n = 3$), *i.e.*, compound **15**, possesses the highest toxicity. On the other hand, the monomer of the type **17** hardly exerts any noticeable effect on the stability of DNA duplexes and is non-toxic.

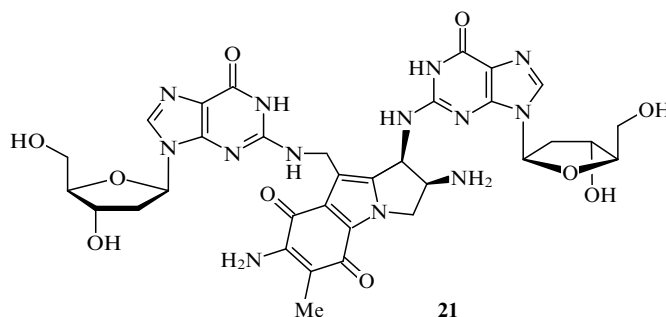


Thus a possibility exists for the application of these compounds for the treatment of tumours. Their main shortcoming is relatively low affinity for DNA.

The mechanism of cross-linking of the DNA chains by bifunctional pyrrole derivatives was investigated.⁶⁵ It was found that all the pyrrole derivatives including natural (*e.g.*, the antitumour antibiotic mitomycin C **18**), and synthetic pyrroles **19** and **20** react with DNA by the same mechanism, they are directed to a common binding site and an alkylation site. Mitomycin C is converted into a bifunctional alkylating agent following reduction with specific enzymes. A binding site in DNA molecules, which is common for all the pyrrole derivatives in question, has been identified.



The exocyclic amino group of deoxyguanosine in the 5'-d(CG)/3'-d(GC) sequence is the common target site in DNA for all the alkylating pyrrole derivatives.⁶⁵ The formation of a cross-linked duplex requires the reaction of exocyclic amino groups of both deoxyguanosines with pyrrole derivatives. The structure of the adduct **21**, the reaction product of two molecules of deoxyguanosine and mitomycin C, is given below.

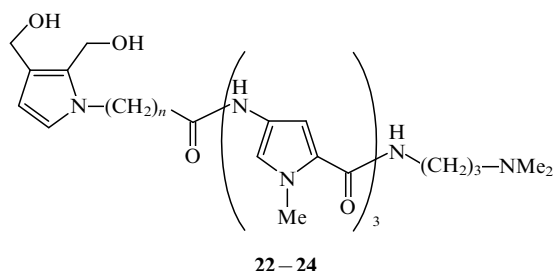


DNA duplexes containing only adenine and thymidine residues have been studied by Wou *et al.*⁶⁵ These duplexes differed in the nature of nucleosides in several nucleotide pairs. To obtain evidence for the involvement of the exocyclic amino group of guanine in the reaction between the chains, deoxyguanosine was substituted by inosine. This gave the duplexes containing the 5'-d(ACGT)/3'-d(TICA) and 5'-d(ACIT)/3'-d(TICA) fragments. When even one deoxyguanosine was substituted by inosine, the interchain cross-linking product disappeared completely. It was also shown⁶⁵ that the reaction in the 5'-d(CG)/3'-d(GC) sequence occurs at least ten times more efficiently than in any other sequence.

The structure of compounds thus obtained was established by an analysis of the products of total enzymic hydrolysis of the cross-linked duplexes and by mass spectroscopy. It is by this method that the structure of compound **21** has been established.⁶⁵ The same method has been used for structural elucidation of the adducts of the synthetic pyrrole derivatives **19** and **20**. It should be emphasised that computer simulation of a cross-linked DNA duplex revealed a relatively significant distortion of the native B-form of the DNA helix irrespective of the nature of the pyrrole derivatives, which is associated with the torsional rearrangement of the DNA structure.

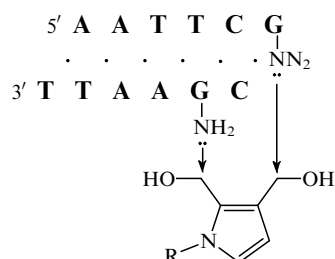
Unfortunately, the attempts to rationalise the reason for such specificity failed. The reaction between the chains is a multistage process, which includes the formation of a mono- and then of a bis-adduct. Each of these stages can be responsible for the specificity. Since both the synthetic pyrrole derivatives **19** and **20** and natural compounds having a more complicated structure manifest identical specificity, it was concluded⁶⁵ that the specificity of pyrrole derivatives is inherent in the common elements of their structure. On the other hand, the significant differences in the efficiency of pyrrole derivatives as the reagents that cross-link DNA chains point to the important role of individual structural features of pyrrole derivatives.

Recent developments in this area^{68,69} have been mainly focussed on the enhancement of the selectivity of pyrrole derivatives. In order to increase the efficiency of affinity binding of the alkylating reagent with the nucleic acid target, it was proposed^{68,69} to prepare its conjugate with an oligopeptide that can specifically recognise the small groove of the double helix. The affinity reagent **22** containing the oligopeptide distamycin, which recognises the 5'-d(AATT) sequence (through the small groove), and pyrrole derivative, which recognises the 5'-d(CG) sequence, was obtained.^{68,69}



$n = 2(\mathbf{22}), 3(\mathbf{23}), 4(\mathbf{24})$.

Thus, the affinity reagent **22** selectively recognises the nucleotide sequence 5'-d(CGAATT)/3'-d(GCTTAA) and produces a cross-link between the chains. The activity of this reagent was tested both with a synthetic duplex and a linearised plasmid. It was found that the derivative **22** is three orders of magnitude more efficient as a cross-linking reagent than a pyrrole derivative non-bound with the peptide. After thermal denaturation and cooling, the plasmid treated with this reagent underwent rapid renaturation into a double-stranded form, which can be explained by the presence of cross-links between the chains.



R is an oligopeptide.

The effect of compound **22** on DNA samples with different nucleotide sequences was studied. It was found that only the DNA containing the 5'-d(CGAATTCG)/3'-d(GCTTAAGC) sequence efficiently reacted with compound **22** (the yield of the cross-linked product is about 70% with respect to DNA). This sequence contains both 5'-d(AATT), the binding site for distamycin, and 5'-d(CG), the consensus binding site for pyrrole derivative. By-products were formed in all the cases studied as a result of the reaction of compound **22** with two deoxyguanosine residues of the same DNA chain.

The synthesis of a series of bifunctional reagents that are homologous to compound **22** has been described.⁶⁹ In these reagents (**23**, **24**), 2,3-bis(hydroxymethyl)pyrrole is also linked to the oligopeptide distamycin. They differ from compound **22** only in the length of the linker connecting pyrrole derivative with the oligopeptide. Compounds **22–24** are three orders of magnitude more efficient and more selective than ordinary pyrrole derivatives. They can form both intrachain and interchain cross-links in DNA depending on the nucleotide sequence in the cross-linking site of pyrrole derivatives. The interchain cross-link is formed in the duplex containing the 5'-d(CGAATT)/3'-d(GCTTAA) sequence, while the intrachain cross-link is formed in the case of the 5'-d(GGAATT)/3'-d(CCTTAA) sequence.

The structures of nucleosides linked through pyrrole derivatives and isolated following total enzymic hydrolysis of internucleotide bonds are identical for both the interchain and intrachain reaction products. Comparison of binding efficiency of various substrates with each of compounds **22–24** revealed that both binding sites [5'-d(CG)/3'-d(GC) (pyrrole derivative) and 5'-d(AATT)/3'-d(TTAA) (distamycin)] play an important role. Nucleotide substitution in any of these sites (CG for GC or A·T for G·C) sharply decreased the efficiency of the reaction. Thus, the 5'-d(CGAATTCG)/3'-d(GCTTAAGC) sequence was found to be the consensus sequence.⁶⁹

Compounds **22–24** were brought into reaction with a linearised plasmid containing twenty seven 5'-d(AATT)/3'-d(TTAA) sites conjugated with 5'-d(GC)/3'-d(CG).⁶⁹ The efficiency of the interchain reaction was estimated according to Hartley.^{5,70,71} This method is based on the ability of DNA with covalently cross-linked chains to undergo rapid renaturation into a double-stranded form after thermal denaturation. The efficiency of this reaction increased⁶⁹ with an increase in the reagent:DNA ratio up to 5:1 (these conditions favour saturation of the peptide-binding sites). The highest yield (80%) was observed on treatment of the oligonucleotide duplexes containing the 5'-d(CGAATTCG)/3'-d(GCTTAAGC) sequence with the compound **22**. For the 5'-d(CGAAAACG)/3'-d(GCTTTTGC) sequence, the yield of the cross-linked product was about 50%,

whereas that for the 5'-d(GC...)/3'-d(CG...) sequences was no more than 10%. In the case of compound **23**, the yield for the 5'-d(CGAATTCG)/3'-d(GCTTAAGC) sequence was 40%. Sigurdsson and Hopkins⁶⁹ could not rationalise the decreased efficiency of this reaction with an increase in the linker length. Probably, this is due to the geometrical disorientation of pyrrole derivative in the reaction centre.

The structures of compounds thus obtained were analysed by studying the composition of products of total enzymic hydrolysis of duplexes with covalently cross-linked chains. Even prolonged hydrolysis of DNA with covalently cross-linked chains by a mixture of snake venom phosphodiesterase and alkaline phosphatase did not result in its complete disintegration into nucleosides. Increased amounts of snake venom phosphodiesterase in combination with endonucleases (DNAase I and DNAase II) were used for complete hydrolysis of the phosphodiester bonds of the duplex. The cytotoxicity of the compounds in question was relatively low and comparable with that of natural pyrrole derivatives.

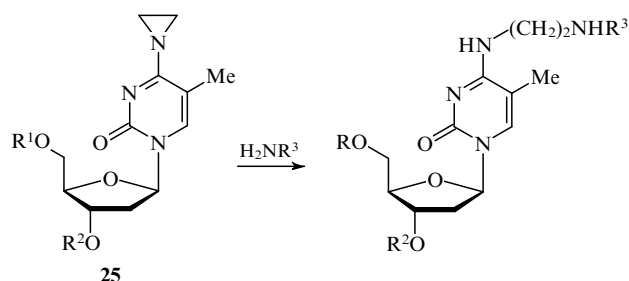
The use of compounds of the type **22–24** for cross-linking of DNA chains has a number of advantages over psoralen derivatives. Psoralen recognises the large groove of DNA and binds thymidine residues in 5'-d(TA)/3'-d(AT) sequences through intercalation into the double helix. In contrast, pyrrole derivatives coupled with peptides (compounds **22–24**) recognise the small groove. It is noteworthy that a more extended (six nucleotides) sequence is recognised in this case, and the reagent itself remains outside the double helix of DNA without causing its destabilisation. However, the use of such targeted-action agents is now limited due to the lack of the general concept of the design of oligopeptides that bind to a predetermined nucleic acid sequence.³⁴

Thus, a series of compounds capable of cross-linking nucleic acid chains has been described.^{11, 12, 18, 34–95} Each of them binds with the duplex at a definite site and produces covalent cross-links with two nucleotides from the opposite chains. However, the majority of compounds described in the literature have a number of disadvantages. They are devoid of high binding specificity with a unique site in nucleic acids. This results, as a rule, in the formation of multiple interchain and intrachain cross-links. These reagents are not versatile, because they cannot form cross-links at predetermined positions between nucleic acid chains, but interact only with definite heterocyclic bases. In some cases, they destabilise the double helix at the cross-linking region, which results in disturbances in the geometry of the canonical spatial structure of nucleic acids. Psoralens, pyrrole derivatives, and other compounds mentioned above have found use both in clinical practice (as antitumour agents) and in the study of mechanisms of functioning of some molecular-biological systems. Nevertheless, it is a new generation of chemically designed synthetic systems devoid of the above drawbacks that will be helpful for the study of peculiarities of structural organisation and mechanisms of functioning of intracellular structures at the molecular level.

VI. The main methods for the synthesis of nucleic acid duplexes with cross-links in predetermined positions of the double helix

The use of nucleic acid duplexes with cross-links at predetermined positions of the double helix is the most promising for the study of protein–nucleic acid recognition and mechanisms of action of enzymes. As a rule, synthesis of such duplexes requires the use of reactive oligonucleotide derivatives containing modified nucleosides. The use of these derivatives has a number of advantages over the above-described methods. In particular, they provide a full control over the localisation of cross-links to be incorporated between the chains and the completion of the synthetic process. Various types of reactive derivatives have been proposed.

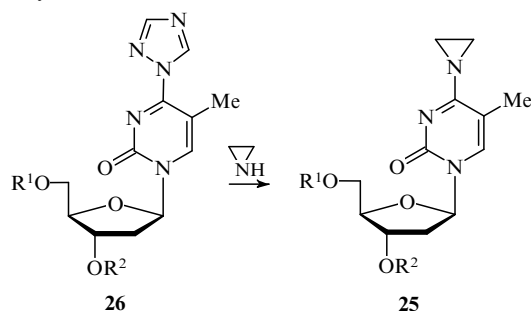
The synthesis of a series of oligonucleotides **25** containing N^4,N^4 -ethano-5-methyldeoxycytidine dC^e has been described.^{97–99} These oligonucleotides interact with the complementary chain of DNA, and N^4,N^4 -ethano-5-methyldeoxycytidine reacts with the oppositely located nucleotide immediately after hybridisation with the complementary target oligonucleotide under mild conditions and without treatment with activating reagents.⁹⁷ This method was named ‘hybridisation-triggered alkylation’.



$R^1 - R^3$ are fragments of oligonucleotide chains.

A phosphoramidite derivative of 5-methyldeoxycytidine carrying a triazole residue at position 4 was used in the synthesis of oligonucleotides of the type **25**. Oligonucleotides **26** containing this residue are stable under the conditions of the phosphoramidite procedure of oligonucleotide synthesis.

Treatment of the oligonucleotide **26** with ethyleneimine converts it into the oligonucleotide **25** in quantitative yield.⁹⁷ This makes it possible to incorporate a reactive acid-labile group into the oligonucleotide following all acidic treatments needed for the removal of the dimethoxytrityl group in the process of oligonucleotide synthesis.



R^1 and R^2 are fragments of oligonucleotide chains.

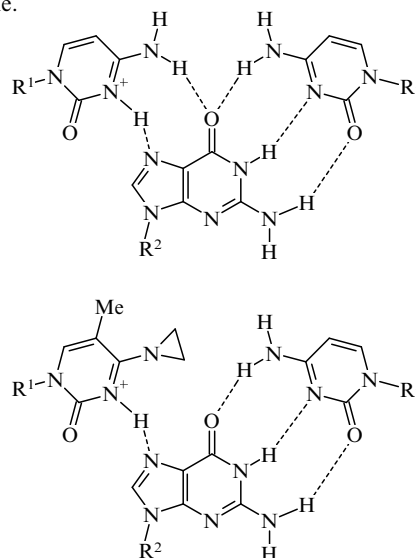
N^4,N^4 -Ethano-5-methyldeoxycytidine is unstable under conditions of standard treatment of oligonucleotides with ammonia (5 h, 55 °C, concentrated NH_4OH). Therefore, the 9-fluorenylmethoxycarbonyl group⁹⁷ (Fmoc) was used to protect the exocyclic amino groups of the nucleosides; this protective group is removed faster and under milder conditions of β -elimination than the benzoyl group routinely used for this purpose. Fmoc-protected deoxyadenosine and deoxycytidine phosphoramidites were synthesised. Attempts to obtain a Fmoc-derivative of deoxyguanosine in satisfactory yield failed. Conditions have been selected for removal of the protective groups with retention of the ethyleneimine ring of compound **25**.

The reaction with the oligonucleotide template is carried out for several days (the semi-conversion period is about 30 h at 24 °C).⁹⁸ The efficiency of the reaction between the chains substantially depends on the nature of the nucleotide that reacts with the dC^e unit of compound **25**. The following order of the efficiency of this reaction was established: $A \approx T \gg C \approx G$. The reaction occurs with each of the four bases to a certain degree. In some cases, only one by-product is formed in the interchain reaction. It is assumed⁹⁸ that under these conditions the reaction involves not only the opposite base in the other chain, but also one of the neighbouring bases of the duplex. The melting point of

duplexes with cross-linked chains is increased, on the average, by 15 °C (from 22 °C to 37 °C for a 21-membered AT-enriched duplex consisting of fifteen A·T pairs and six G·C pairs).

The main disadvantage of this method is the necessity of substitution of standard nucleoside phosphoramidites on Fmoc-containing ones. The Fmoc-group is extremely labile, therefore the yields of Fmoc-protected nucleosides are low and deoxyinosine must be used instead of deoxyguanosine. Moreover, the rate of the interchain reaction is too low (semiconversion period is 30 h) and therefore these oligonucleotides cannot be used as inhibitors of mRNA expression *in vitro*. On the other hand, the proposed method of interchain cross-linking⁹⁷ is devoid of such shortcomings as the necessity of activation of the alkylating function and low level of specificity. The latter can be due to the excessive reactivity of the alkylating group.

The majority of the known methods for the preparation of duplexes with covalently cross-linked chains are based on the interaction of a single-stranded DNA with oligodeoxyribonucleotide containing a reactive group. Recent reports suggest an alternative variant, which consists in the cross-linking of an oligonucleotide to double-stranded DNA within a triple helix (triplex).^{7, 88, 100–109} Thus, a method has been proposed for specific cross-linking of dC^e oligonucleotides with units of the type **25** described above to double-stranded DNA within the triplex.¹⁰⁰ In this case, the oligonucleotide is recognised by Hugstee's pairs and intercalates into the large groove of the target DNA duplex. In the $dC^e \cdot G \cdot C$ triplex, the electrophilic methylene group of N^4,N^4 -ethano-5-methyldeoxycytidine comes close to the N(7)- and O(6)-nucleophilic centres of deoxyguanosine.



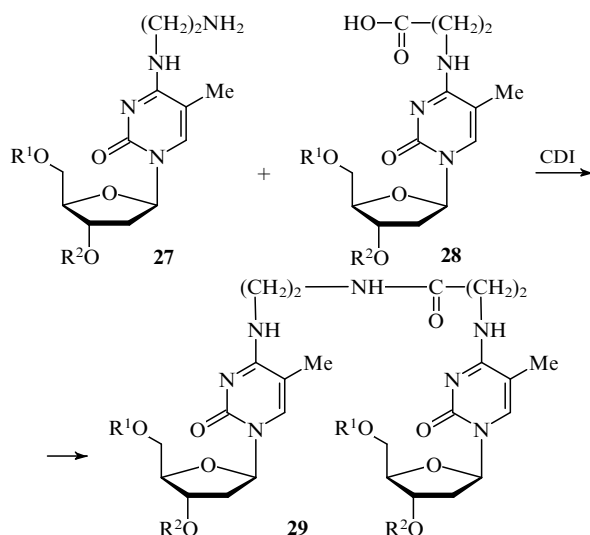
$R^1 - R^3$ are oligonucleotides.

The ethyleneimine ring interacts with one of the guanine bases of the double helix of the target DNA. The reaction between the chains occurs under physiological conditions in more than 95% yield and is completed within 16 h. This method can be promising for specific *in vivo* inhibition of DNA transcription and replication due to the formation of an untwistable triplex.^{100, 101}

As has been mentioned above, one of the main problems connected with the introduction of new functional groups into the oligonucleotide is that under conditions of automated synthesis the DNA chain that is elongated is exposed to the action of acids, bases, and electrophilic reagents. The functional group to be introduced must withstand these treatments either as such or after protection. Since N^4,N^4 -ethano-5-methyldeoxycytidine is sensitive to nucleophiles,¹⁰¹ it can be incorporated only into oligothymidylates but not into an oligonucleotide containing nucleosides of all the four types, because only the former do not require post-synthesis ammonia treatment to remove protective

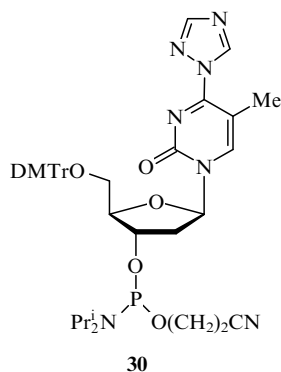
groups. This restricts the possible application of such oligonucleotides as substrates that can covalently bind to the DNA target. An attempt to apply this synthetic scheme to deoxyadenosine was even less successful.¹¹⁰ It was found that N^6,N^6 -ethanodeoxyadenosine was a weaker electrophile than N^4,N^4 -ethano-5-methyldeoxycytidine.

In a recent study, devoted to the synthesis of oligonucleotide duplexes with covalently cross-linked chains Shabarova *et al.*¹³ also described modification of the heterocyclic bases of deoxycytidine. Two approaches to the design of DNA duplexes with cross-links between oligonucleotides in the predetermined positions of the double helix were proposed. The first one consisted in the formation of an amide bond between the amino and carboxy groups of modified bases localised in the opposite chains, while the second one entails the formation of a covalent 'bridge' as the Schiff's base between the two amino groups using dialdehydes of the aliphatic series. To this end, deoxycytidine in the self-complementary oligonucleotide 5'-d(TAATGCATTA) was replaced by a 5-methyldeoxycytidine derivative containing an aliphatic amino group (oligonucleotide 10'', **27**) or a carboxy group (oligonucleotide 10', **28**). These functional groups occupied terminal positions at the spacer linked to the exocyclic amino group of 5-methyldeoxycytidine. In the formation of the DNA duplex **29**, the carboxy and amino groups turned to be close to each other, which enabled the reaction resulting in the formation of an amide bond between the chains to occur.



R^1 and R^2 are fragments of oligonucleotide chains.
CDI is $\text{EtN}=\text{C}=\text{N}(\text{CH}_2)_3\text{NMe}_2 \cdot \text{HCl}$.

Synthesis of a self-complementary oligonucleotide precursor, which is common for compounds **27** and **28**, viz., 5'-d(TAATGC*ATTA) **29**, where C* is the cytidine residue containing triazole at position 4, was carried out by the phosphoramidite method, and the triazolyl derivative of thymidine **30** was introduced in the reaction.

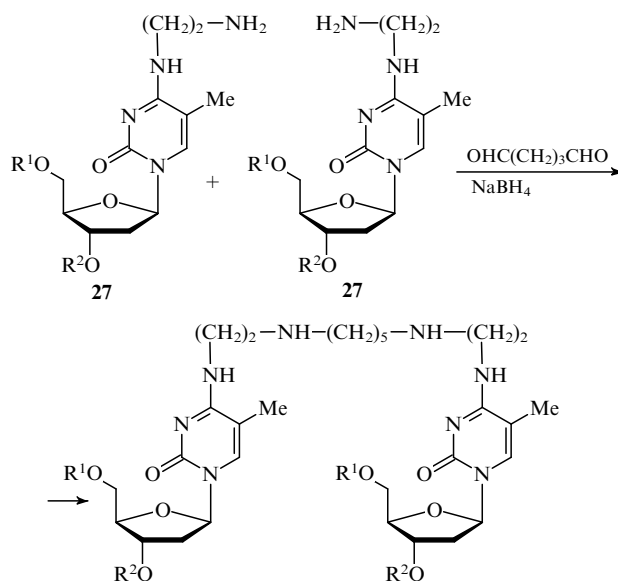


30

After completion of the synthesis, the polymer with the immobilised oligonucleotide was divided into two equal parts. One of them was treated with ethylenediamine to give compound **27**, while the other one was treated with β -aminopropionic acid to give compound **28**. The reaction between the chains was carried out with water-soluble CDI as the condensation reagent at 0 °C, which facilitated the formation of a double-stranded complex.

It must be noted that this system favours the formation of three types of oligonucleotide duplexes: $(10''):(10')$, $(10''):(10'')$, and $(10'):(10')$, since the original oligonucleotide is self-complementary. It was found that the $(10''):(10'')$ complex was the most stable, presumably owing to the electrostatic contacts between the amino and phosphate groups of the opposite chains. The predominance of the $(10''):(10'')$ complex in solution is responsible for the low yield of the target product, which can be formed from the $(10''):(10')$ complex. The optimum pH value for this reaction lies in the range of 5.5–6.0. Any deviation from this interval increases the amount of by-products as a result of modification of heterocyclic bases with carbodiimide. In addition, the formation of an adduct of the oligonucleotide $(10')$ with carbodiimide involving the carboxy group took place as a side process.

In the alternative version, the reaction between the chains of the 5'-d(TAATGC*ATTA)/3'-d(ATTAC*GTAAT), $(10''):(10'')$, duplex was carried out with glutaraldehyde. The Schiff's base formed initially was reduced with sodium borohydride to give a stable secondary amine. The yield of the target, cross-coupled duplex was brought to 20%.



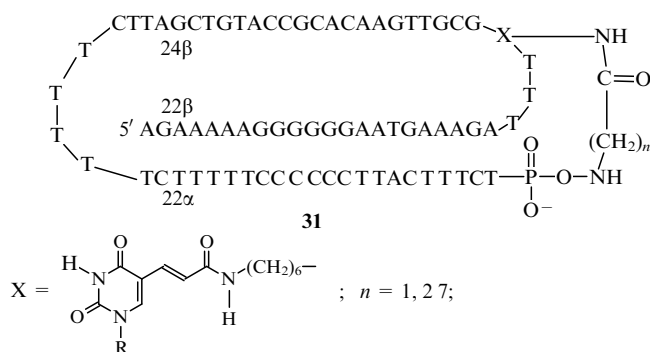
R^1 and R^2 are fragments of oligonucleotide chains.

The low yield can be explained by several reasons. First, besides the aliphatic amino groups that have been introduced, oligonucleotides contain other reaction centres capable of reacting with glutaraldehyde (e.g., exocyclic amino groups of heterocyclic bases). Second, it is difficult to select conditions where two aliphatic amino groups of the modified duplex will react with the same molecule of glutaraldehyde, since the reaction is carried out with an excess of the aldehyde. Third, most probably, the optimum mutual arrangement of reactive amino groups was not realised, since they were localised in adjacent base pairs. Preliminary molecular modelling of the optimum mutual arrangement of reactive groups in the reaction centre has now become a standard procedure.

At the same time, it was demonstrated that oligonucleotides containing an aliphatic amino and a carboxy group can be used for the synthesis of DNA duplexes with an amide bond between the chains.¹³ It must be noted that the system was designed in such a way as to enable polymerisation of the duplex with covalently

cross-linked chains under the action of DNA-ligase. This gives a DNA-like polymer containing a repeating consensus Pribnow sequence, which is the main binding site for RNA-polymerase in the initiation of transcription. This requires unwinding of the DNA double helix with the formation of an open complex. As the presence of cross-links between DNA chains prevents unwinding, these compounds can be used for the study of initiation of transcription and, apparently, for influencing this process.

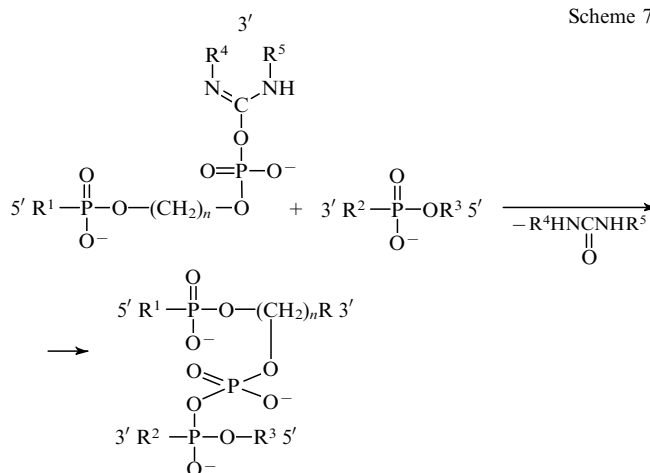
Gottikh *et al.*¹¹¹ have synthesised an unusual oligonucleotide derivative **31** with covalently cross-linked chains. This compound has a 'snail-like' structure and represents a chimeric oligonucleotide comprising an α -nucleotide cluster. Unlike ordinary DNA, the α - and β -oligonucleotides form a parallel duplex, which allows the chimeric oligonucleotide to occur as an intramolecular duplex. The cross-link is formed between the amino group attached through a spacer to a thymidine analogue in a single-stranded region and the 3'-terminal phosphate of the α -fragment. As expected, no reaction occurred directly between these groups because of steric hindrances. Therefore, an amino acid $\text{NH}_2-(\text{CH}_2)_n-\text{COOH}$ ($n = 1, 2, 7$) was coupled with the terminal phosphate of the α -fragment activated in the form of *N*-hydroxybenzotriazole ester. Then the reaction was carried out between the incorporated carboxy and amino groups using water-soluble CDI as the coupling reagent.



Owing to the presence of an interchain cross-link in compound **31**, this is highly resistant to nuclease degradation. It has been shown that RNAase H cleaves an oligoribonucleotide in the chimeric duplex involving compound **31**. The study¹¹¹ illustrates the possibility of conferring useful properties to a compound by cross-linking of oligonucleotide chains. Presumably, the oligonucleotide derivative **31** can be effectively used for the regulation of RNA expression.¹¹¹

A method for the synthesis of DNA duplexes in which the chains are cross-linked through a substituted pyrophosphate group was developed (Scheme 7).⁹⁶ This involves the reaction between the activated terminal phosphate group linked to an oligonucleotide through a spacer and the spatially close internucleotide phosphate group of the complementary oligonucleotide. The activation of the terminal phosphate group was carried out with water-soluble CDI.

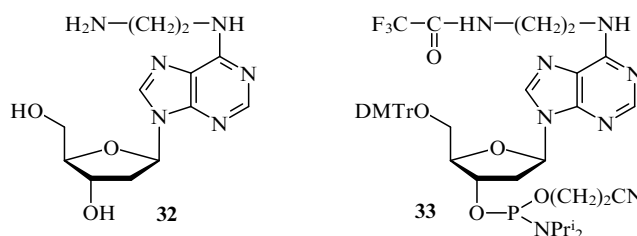
The DNA duplexes containing a trisubstituted pyrophosphate internucleotide group in one of the chains are stable in aqueous buffer solutions (pH 6.0–8.75) in the absence of strong nucleophiles. At the same time, they are readily and selectively cleaved at this group with nucleophilic reagents, such as *N*-methylimidazole, amines, and some amino acids. In this case, the nucleophilic substitution reaction involves both phosphate groups of the trisubstituted pyrophosphate group and is accompanied by a cleavage of the interchain bond and transfer of one of the duplex residues to the nucleophile.⁹⁶ In contrast with DNA duplexes containing a disubstituted pyrophosphate internucleotide group in one of the chains, the reaction of nucleophilic substitution at the phosphorus atom in the DNA duplexes containing a trisubstituted pyrophosphate interchain internucleotide group can occur with



R^1-R^3 are fragments of oligonucleotide chains; $n = 3, 4, 7, 12$.

the involvement of both di- and tri-substituted phosphate groups to yield a complex mixture of oligonucleotides. Obviously, such DNA duplexes will be unstable in cell cultures. The method considered allows the synthesis of DNA duplexes with a reactive group between the chains. The interest in the synthesis of such compounds is connected with the possibility of their application for binding with proteins.

A method of preparation of cross-linked duplexes involving deoxyadenosine residues was proposed.¹¹² *N*⁶-(2-Aminoethyl)-deoxyadenosine (**32**) is converted into the phosphoramidite derivative **33**, which can be incorporated at any predetermined position of an oligonucleotide. *N*⁶-(2-Aminoethyl)deoxyadenosine **32** was obtained by treatment of 6-iododeoxyadenosine with ethylenediamine, and the amino group was protected by subsequent treatment of the reaction product with *S*-ethyltrifluoroethioacetate. The trifluoroacetyl protection is ideally suited for the incorporated aliphatic amino group.



A dinucleoside monophosphate containing the *N*⁶-modified deoxyadenosine **32** with an aliphatic amino group was synthesised.¹¹² The synthesis was carried out by the phosphoramidite method in solution; the yield was 95%. Higher oligonucleotides were not synthesised; however, this method is a model study aimed at the incorporation into oligonucleotides of compound **33** as a potential tool for interchain cross-linking.

The oligonucleotide synthesis involving the phosphoramidite derivative **33** was free of side reactions.¹¹² However, the effectiveness of this modification for the synthesis of duplexes with covalently cross-linked chains is unclear. It was proposed¹¹² to perform the reaction between the chains in the following way:¹¹² after hybridisation with the template, the aliphatic amino group has to be localised in the vicinity of the pyrimidine base of the complementary chain. The reaction of this base with the bisulfite ion at positions 5 and 6 facilitates the subsequent nucleophilic attack at position 4. The aliphatic amino group of *N*⁶-(2-aminoethyl)deoxyadenosine **32** will act as the nucleophile. This method of interchain cross-linking must not bring significant disturbance to the structure of the double helix. A disadvantage of this method is its inapplicability to cross-linking of oligonucleotides to extended DNA, since in the presence of the bisulfite anion

deoxycytidine in single-stranded regions can undergo side conversions into 2'-deoxyuridine, which is undesirable.

VII. The use of sulphhydryl derivatives for the synthesis of cross-linked nucleic acid duplexes

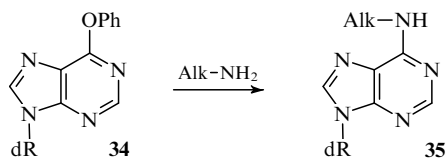
Oligonucleotides containing SH-groups have received wide acceptance in recent years. They not only allow the synthesis of various types of oligonucleotide derivatives, but also of cross-linked DNA duplexes in the predetermined positions of the double helix. The so-called 'convertible nucleoside approach' of oligonucleotide synthesis has become widespread.¹¹³ It consists in the incorporation of a precursor of the modified nucleoside carrying an SH group into the oligonucleotide that is synthesised. This precursor carries a different group, which is usually more resistant to synthetic and post-synthetic treatments. Later (sometimes even after hybridisation with the template), the precursor is converted into the target nucleoside with a thio group, which becomes involved in the reaction between the chains.

This strategy has considerable promise for it permits an access to various types of modified oligonucleotides from the same precursor because the incorporation of a functionalised linker is performed after completion of the oligonucleotide synthesis. This approach does not envisage the synthesis of a new starting monomer or a new modified oligonucleotide in order to change the length of the linker or the nature of the functional group. Another advantage of this method is that it allows a post-synthetic addition to oligonucleotide derivatives of ligands (oligopeptides, *etc.*) unable to withstand the treatments used in the oligonucleotide synthesis.

A characteristic feature of this method is that the monomer used in the synthesis contains a leaving group, which undergoes nucleophilic substitution. When a bifunctional nucleophile is used, reactive oligonucleotide derivatives are formed. At the same time, the bifunctional nucleophile fulfils the function of a linker.

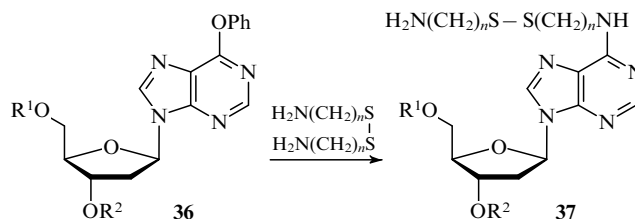
In order to attain the maximum efficiency, a number of conditions must be observed.¹¹³ The nucleoside in question must be stable under conditions of automated synthesis of DNA and be rapidly and completely converted into a reactive derivative by a nucleophile. Incorporation of a linker must cause minimum disturbance to the structure of the DNA double helix. As a rule, this process should not involve the terminal oligonucleotide units so as to retain the possibility of further enzymic reactions, such as radioactive labelling, elongation of the oligonucleotide, or its incorporation into a plasmid.

Ferentz and Verdine¹¹³ have 'converted' deoxyinosine into modified deoxyadenosine. Earlier, these authors had shown¹¹⁴ that *O*⁶-phenyldeoxyinosine **34** was quantitatively converted into *N*⁶-alkyldeoxyadenosine **35** on aminolysis with alkylamines.



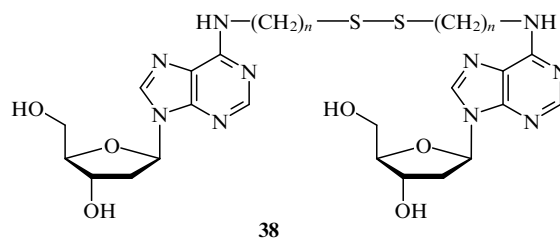
dR is the 2'-deoxyribose residue.

*O*⁶-Phenyldeoxyinosine 3'-phosphoramidite was synthesised and introduced into automated synthesis to give the oligonucleotide 5'-d(GCGAI*TTTCGC) **36**, where I* is the residue of the nucleoside **34**. After completion of the synthesis, the oligonucleotide **36** was treated with bis(2-aminoethyl) disulfide or bis(3-aminopropyl) disulfide, resulting in compound **37**.



R¹ and R² are fragments of the oligonucleotide chain; *n* = 2, 3.

The oligonucleotide **37** obtained was self-complementary and formed a duplex in which the modified bases are localised in neighbouring units. Treatment of the duplex with dithiothreitol led to the conversion of the disulfide into thiol and then the disulfide bond between the chains was closed by oxidation with the atmospheric oxygen. This binding is reversible. Repeated treatment of the duplex with dithiothreitol results in the cleavage of the interchain cross-link. It was shown¹¹³ that the products of enzymic hydrolysis of the DNA duplex with covalently cross-linked chains contain the dinucleoside **38**; the shape of the helix of the DNA duplex corresponds to the B-form of DNA, while the modified bases form ordinary Watson-Crick pairs.



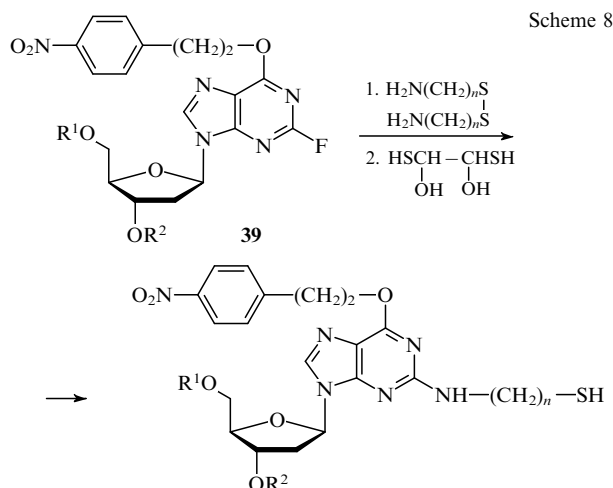
n = 2, 3.

Computer simulation has revealed that the linker is localised in the large groove of DNA and does not cause any significant distortions in the spatial structure of the duplex. The original duplex and the duplex with covalently cross-linked chains have similar melting curve profiles. This indicates that the cross-linking between the chains does not disturb the duplex structure itself. Under these conditions, the melting point of the duplex with covalently cross-linked chains (75 °C) was by 18 °C higher than that for the original duplex in 1 M NaCl, whereas in 0.1 M NaCl it was by 30 °C higher.

Thus, the formation of a disulfide bond between the chains has a number of advantages. First, it increases significantly the stability of the DNA duplex. Second, it does not result in noticeable distortions in the DNA structure. DNA duplexes with chains linked by disulfide bonds can be used for the study of processes involving the unwinding of DNA by enzymes, *e.g.*, transcription, replication, and recombination.

Yet another approach to the synthesis of a DNA duplex with covalently cross-linked chains by the 'convertible nucleoside approach' has been described.¹⁴ *O*⁶-[2-(*p*-Nitrophenyl)ethyl]-2-fluorodeoxyinosine^{115, 116} was introduced into a self-complementary 18-membered oligonucleotide in the process of oligonucleotide synthesis. Treatment of this oligonucleotide with bis(aminoalkyl) disulfides (Scheme 8) or *N*-(2-methylthioethyl)-amine **39** led to the substitution of the fluorine atom for *N*-(ω-aminodithioalkyl)amino group or the *N*-(2-methylthioethyl)amino group.¹⁴

Following treatment with dithiothreitol, the reaction between the chains was carried out in the presence of atmospheric oxygen. The presence of a cross-link was proved by an analysis of a correlation between the melting point of the duplex with covalently cross-linked chains and the ability of these cross-links to induce entropic stabilisation of DNA.¹¹⁷



R^1 and R^2 are fragments of the oligonucleotide chain; $n = 2, 3$.

The melting point of the duplex cross-linked by a bis(2-aminoethyl) disulfide linker ($n = 2$) was lower than that of the duplex cross-linked with a bis(3-aminopropyl) disulfide linker ($n = 3$). Presumably, a shorter linker causes greater torsional tension in the DNA structure. Comparison with an oligonucleotide duplex containing the (2-methylthioethyl)amino groups revealed that this modification as such has little effect on the melting point of the duplex.¹⁴

The DNA duplexes thus synthesised with covalently cross-linked chains were used for the study of DNA methylation. This process plays an important role in the development of mammals and in the resistance of bacteria to viral infections.¹⁴ DNA-5-cytosine-methyltransferase (CMTase) catalyses transfer of the methyl group from *S*-adenosyl-L-methionine to cytosine. The enzyme recognises the symmetrical site of DNA, *viz.* 5'-d(GGCC)/3'-d(CCGG), and transfers the methyl group to the internal deoxycytidine residue of each chain. It was assumed¹⁴ that if the methylation site contains an interchain cross-link, the unwinding of the DNA double helix as an element of the enzyme action mechanism will be hampered considerably during the transfer of the methyl group.

It turned out that the enzyme actually induces a distortion of the double helix. In order to establish a correlation between the effect of interchain cross-linking and the recognition of the methylation site by the enzyme, the equilibrium binding has been studied under non-catalytic conditions. It was found that the duplex with a dithiooctamethylene bridge between the chains binds to the enzyme with the same efficiency as does the non-modified duplex, whereas the duplex with a dithiahexamethylene bridge binds 43 times more weakly. Thus, the presence of a cross-link between the chains has no effect on the enzyme binding with DNA (at least, for a longer linker). Moreover, in the latter case cross-linking between the chains results in allosteric activation of the protein binding. Most probably, this is due to the fact that the presence of an interchain cross-link generates torsional tension, which decreases the thermodynamic barrier to DNA unwinding. However, in contrast to cross-linking, methylation occurs much more slowly in comparison with the natural duplex. Nevertheless, under conditions of substrate saturation both duplexes with covalently cross-linked chains serve as substrates for CMTase and the degree of methylation is 10% relative to that of the non-modified duplex. This study illustrates the applicability of DNA duplexes with covalently cross-linked chains for gaining insight into the mechanisms of action of DNA-recognising enzymes.

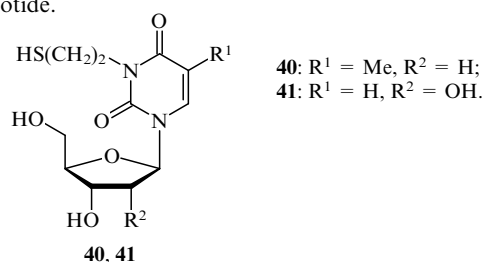
Erlanson *et al.*¹⁴ have carried out computer simulation of the spatial structure of DNA duplexes with covalently cross-linked chains. The data obtained were compared with the results of X-ray analysis.¹¹⁸ The molecular dynamics methods were used to study the effect of the interchain cross-linking on the secondary struc-

ture of DNA. This made it possible to estimate the extent of distortions induced by cross-linking in the duplex structure and to evaluate its effect on the dynamic behaviour of DNA. Spatial structures of the self-complementary decanucleotide 5'-d(GCGAATTCGC) in the form of a duplex and of two modified duplexes with the same primary structure and a cross-link between the amino groups of deoxyadenosine residues in the central A·T pair were studied. The lengths of the linkers were six (dithiahexamethylene) or eight dithiaoctamethylene atoms (the nitrogen atoms were not taken into account).

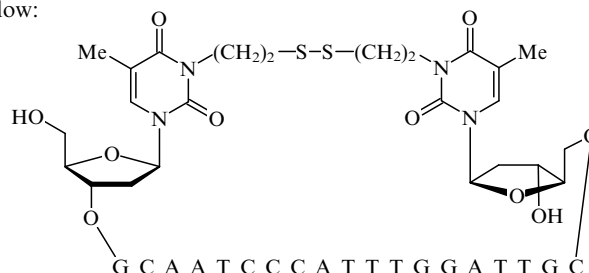
It was shown¹¹⁸ that the canonical B-form of DNA and the Watson-Crick type of base pairing are preserved by all DNA duplexes in question. The parameters of the duplex helices with covalently cross-linked chains, of the large and small grooves, and of the base pairs, as well as the torsional angles of the sugar-phosphate backbone are also mostly similar to the corresponding parameters for the crystalline structure of the non-modified duplex. Yet, the presence of cross-links between the chains endows certain disorder in the geometry of the double helix. The deviations observed are insignificant: no more than 1.2 Å from the canonical B-form of DNA and no more than 1.3 Å from the experimentally determined parameters for the crystal of a non-modified duplex. These changes are more substantial with the shorter interchain linker. The dynamic properties of the duplexes with covalently cross-linked chains are also similar to those of the non-modified duplex. Certain changes are observed in a region adjacent to the cross-linking site and are especially pronounced in the case of a shorter linker. Structural distortions of general character are manifested in decreased mobility at the cross-link site irrespective of the linker length.

Thus, the changes in structural parameters originate mostly from the modification of the amino groups of deoxyadenosines rather than from the presence of a cross-link between the chain. On the whole, the presence of a cross-link between the chains induces insignificant changes in the duplex structure;¹¹⁸ therefore, these duplexes may be used for the study of proteins that interact with nucleic acids.

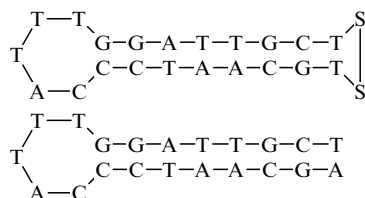
Yet another original procedure for obtaining DNA duplexes with covalently cross-linked chains on the basis of thiols has been proposed.¹¹⁹ Two residues of *N*³-(2-mercaptoethyl)thymidine **40** were incorporated into an oligodeoxyribonucleotide and two residues of *N*³-(2-mercaptoethyl)uridine **41**, into an oligoribonucleotide.



The phosphoramidite derivative of compound **40** was attached to the 5'- and 3'-ends of an oligodeoxyribonucleotide in the automated synthesis. The disulfide bond between the ends of a hairpin was closed by oxidation of the thio groups with atmospheric oxygen. The structure of the interchain cross-link at the end of the hairpin formed by two residues of compound **40** is shown below:



The structures of a covalently closed hairpin and its natural analogue are shown in Scheme 9. Their conformational structure was studied by NMR spectroscopy. It was found that the 8-membered double-stranded region in both hairpins has a canonical B-form; structurally both hairpins are completely isomorphic.



Scheme 9

In this case, the presence of an interchain cross-link neither influences the spatial structure of the hairpin nor interferes with the native B-conformation of the double helix. It should be noted that although in this study the cross-link was formed at the end of the DNA duplex, the modified nucleoside could be incorporated into any predetermined position of an oligonucleotide. This method can thus be applied for obtaining a set of various cross-linked oligonucleotide duplexes.

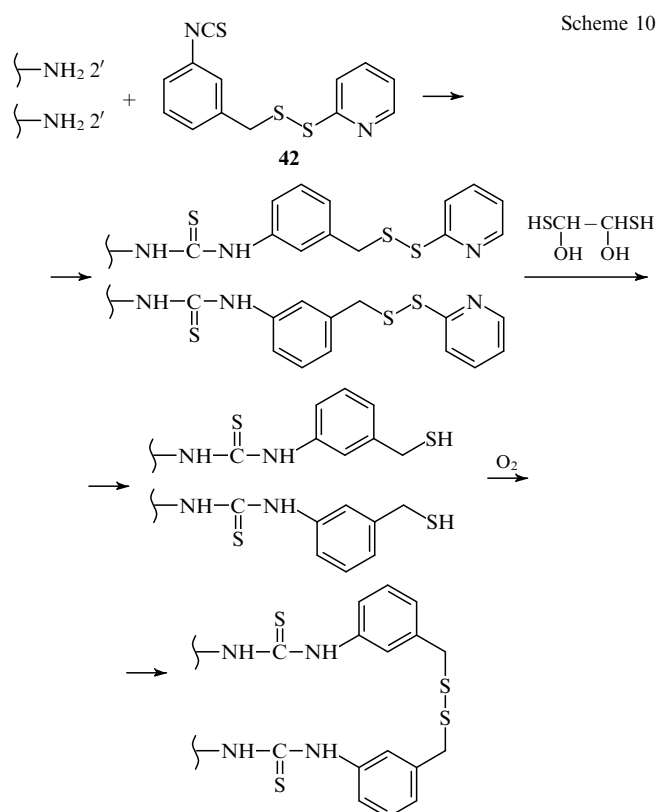
Thus, the synthesis of duplexes with covalently cross-linked chains based on sulfhydryl derivatives has a number of advantages over the use of alkylating agents, which do not ensure sequence-specific cross-linking of chains. The latter circumstance restricts their application in the engineering of interchain cross-links.

The disulfide method was used to cross-link fragments of the ribozyme RNA chain.¹⁷ The reaction was carried out between spatially close (but not complementary) regions of the RNA chain. Hence, here we do not deal with the formation of cross-links between the RNA chains within the duplex; however, this method is so elegant that it deserves special mention. Eckstein *et al.*¹⁷ took advantage of modification of the 2'-positions of certain sugar residues. Oligoribonucleotides with incorporated 2'-amino-2'-deoxyribonucleotides were synthesised for this purpose. Synthesis of 2'-amino-2'-deoxyribonucleosides has been described earlier.^{120–126}

The sulfhydryl groups were introduced as follows. First, the oligoribonucleotides were treated with the bifunctional reagent **42** (Scheme 10) containing the isothiocyanate and a protected sulfhydryl group. It was shown that compound **42** selectively reacts with the 2'-amino groups of the modified ribonucleotides.¹⁷

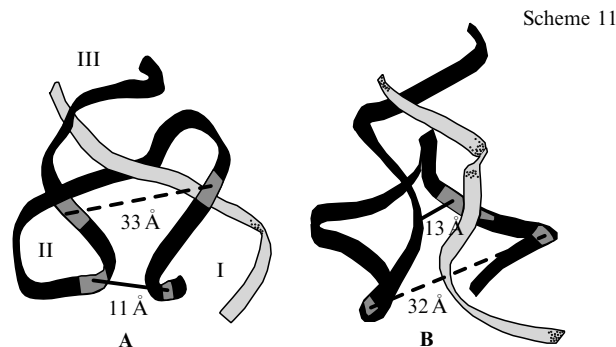
The reaction between the fragments of the ribozyme chain was initiated by dithiothreitol, which deprotected the sulfhydryl groups. This enabled the reaction between the ribozyme chains under the action of atmospheric oxygen (Scheme 10). The presence of a cross-link between the chains was confirmed by limited alkaline hydrolysis. One cleavage of the ribozyme chain at the site between the modified residues gave a single product with the same molecular weight as that of the original ribozyme.

Ribozymes with covalently cross-linked chains obtained by the above-described procedure were used to study the tertiary structure of the ribozyme in relation to the catalytic mechanism of RNA cleavage. The parameters of the ribozyme tertiary structure obtained earlier by X-ray analysis (Scheme 11, **A**) and fluorescence resonance energy transfer (FRET) solution measurements (Scheme 11, **B**) were different. [Ribbon representation of the tertiary structures of the hammerhead ribozyme based on (**A**) X-ray crystallography and (**B**) FRET solution measurements. Ribozymes and substrates are coloured black and light gray, respectively. Residues that are close in space according to the X-ray structure and the FRET model (dark gray) are connected by solid lines and the broken lines represent the corresponding long distances in the other model.] At the same time, both putative structures had identical general geometry. The difference between them lay in the orientation of the two helical regions of RNA relative to each other (helices I and II, Scheme 11). In order to compare these two spatial models of the ribozyme and to choose



Scheme 10

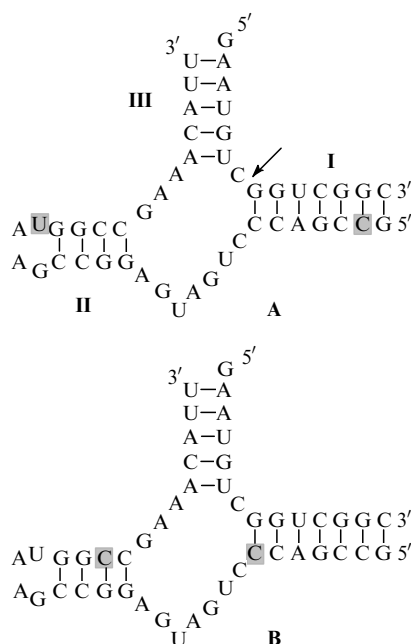
the model corresponding to the genuine biologically active structure, synthetic ribozymes with covalently cross-linked chains were used.



Scheme 11

The authors¹⁷ have succeeded in stabilising the spatial structure of the ribozyme according to each of the putative models. After hybridisation of the modified ribozymes with a non-hydrolysable substrate analogue containing a deoxynucleoside in the reaction centre, the reaction mixtures were treated with oxygen for 30 h. This permitted a highly efficient reaction between the chains irrespective of the localisation of the modified units in the ribozymes (Scheme 12). Roman numerals indicate the number of the helices. An arrow indicates the site of cleavage. Residues contained a 2'-amino function and utilised for cross-linking are filled by dark gray colour. The yield of the ribozymes with covalently cross-linked chains after all purification procedures was 15%.

The cross-links between the chains stabilised the spatial structure of the ribozyme in accordance with the predetermined one, which made it possible to measure the catalytic activity of two synthetic ribozymes with different spatial structures. As expected, the catalytic activity of the ribozyme depends on the localisation of the cross-link between the chains. The cross-link between the adjacent regions of the helices corresponding to the X-ray model (Schemes 11, 12, **A**) had practically no effect on the catalytic



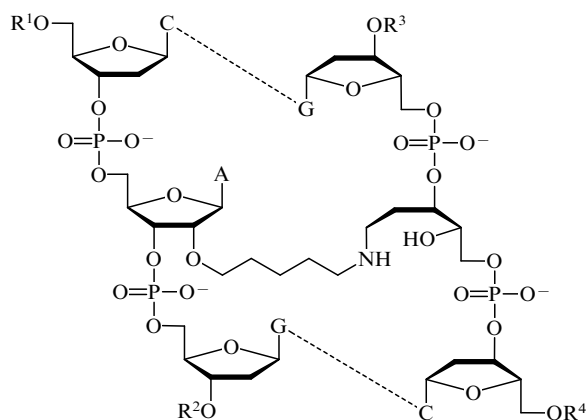
Scheme 12

activity of the ribozyme. On the other hand, the cross-link between the adjacent nucleotides according to the other model (Schemes 11, 12, **B**) decreased the rate of the ribozyme-induced cleavage of the corresponding substrate by three orders of magnitude. It was thus concluded that the X-ray model corresponds to the real structure and that the previous methods that have previously been used in the study of the tertiary structure of RNA are inadequate. The results obtained by Eckstein *et al.*¹⁷ have provided the basis for further studies on ribozymes.¹²⁷

VIII. Synthesis of cross-linked nucleic acid duplexes using sugar moieties of nucleosides

In contrast to studies devoted to the modification of heterocyclic bases and phosphate groups of oligonucleotides, reports on the reactions between chains involving sugar residues are scarce.

A method for the synthesis of a duplex was proposed,¹⁵ which entails the formation of a cross-link between the amino group attached through a spacer to position 2 of the sugar residue of adenosine, on the one hand, and the aldehyde group in a non-nucleoside insert of the complementary chain, on the other hand.



$R^1 - R^4$ are the fragments of oligonucleotide chains.

Synthesis of this type of compound has been patented.¹⁶ In this case, the aldehyde group results from enzymic elimination of uracyl by uracyl-DNA-glycosylase from 2'-deoxyuridine incorporated into the oligonucleotide. The elimination of the heterocyclic

base is accompanied by the sugar ring opening and the formation of the aldehyde group. Treatment of the latter with the primary amine gives a Schiff's base, which is reduced to give a stable secondary amine. However, enzymic treatment does not yet allow the preparative synthesis of these compounds, which restricts their application as therapeutic agents.

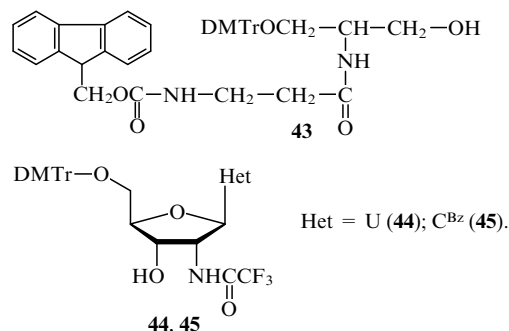
As mentioned above, the main drawback of many procedures employed in the synthesis of cross-linked DNA duplexes is their low specificity. It is the specific cross-linking of DNA chains that allows the development of the most convenient tools for the study of protein-nucleic acid interactions. Therefore, in recent years most studies have been aimed at the elaboration of methods of site-specific cross-linking of chains in synthetic DNA duplexes.

A series of publications¹²⁸⁻¹³¹ are devoted to elaboration of a new effective method for the synthesis of cross-linked DNA duplexes that involves sugar residues of nucleosides. This method required the use of oligonucleotides modified at the carbohydrate fragment and containing a primary aliphatic amino group or a carboxy group. The existing procedures for incorporation of modified units into oligonucleotides permit introducing them into any predetermined position of the oligonucleotide chain or incorporate several modified units into the same oligonucleotide by a standard protocol of solid-phase phosphoramidite oligonucleotide synthesis.

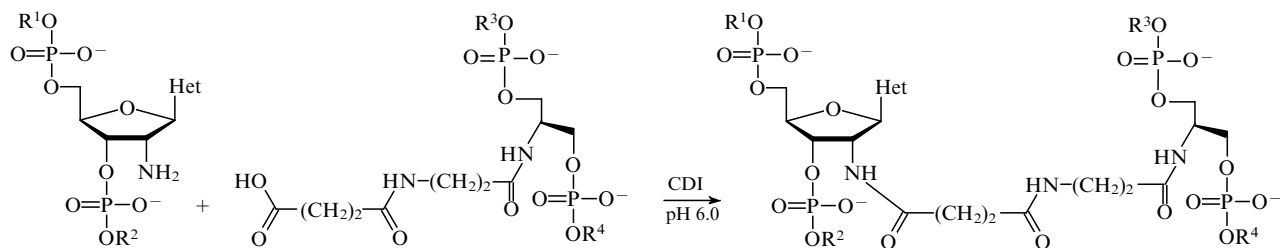
The reaction between the primary amino group and the carboxy groups selected for the cross-linking of the duplex chains is activated by water-soluble CDI and results in the formation of an amide bond between the chains.

In the early 90's, several methods for the synthesis of 2'-amino-2'-deoxynucleotides were developed.¹²⁰⁻¹²⁶ High reactivity of the 2'-amino groups of 2'-amino-2'-deoxynucleosides in acylation reactions¹²⁰⁻¹²² has led to an idea of formation of a cross-link between the 2'-amino group in one chain and the carboxy group derived upon acylation of the 2'-amino-2'-deoxynucleoside of the complementary chain by a dicarboxylic acid anhydride. However, preparation of purine 2'-amino-2'-deoxynucleosides by transglycosylation (substitution of a heterocyclic base) of preformed 2'-amino-2'-deoxyuridine^{123, 124} inevitably resulted in the formation of a complex mixture of products and extremely low yield of the target product.

Thus, a non-nucleoside insert was used instead of purine 2'-amino-2'-deoxynucleosides. On the one hand, this disturbs the hydrogen bonds in the pair in which one heterocyclic base is missing. On the other hand, the use of this nucleoside substitution has a number of benefits. Compound **43** can be synthesised by a combination of simple high-yielding chemical reactions.^{128, 129} The distance of three carbon atoms between the phosphate groups, which is characteristic of natural oligonucleotides, is preserved in the structure of the non-nucleoside insert. This compound is resistant to synthetic and post-synthetic treatments of the oligonucleotide.



Synthesis of specifically protected pyrimidine 2'-amino-2'-deoxynucleosides **44** and **45** has been described.^{120, 121} The reaction between the chains of a modified duplex is performed in the following steps. First, a carboxy group is introduced into one chain. This is achieved by acylating the amino group incorporated



Scheme 13

Het = U, C^{Bz}; R¹–R⁴ are fragments of oligonucleotide chains.

into the oligonucleotide with a dicarboxylic anhydride. Molecular simulation allowed one to select succinic anhydride as the acylating reagent. Then the reaction between the chains was conducted in a morpholinoethyl sulfonate buffer (pH 5.0–6.7) for 1–3 days at 0–20 °C using water-soluble CDI as a condensation reagent (Scheme 13).

Previously, it had been demonstrated^{128, 129} that the reaction between the strands of modified DNA duplexes with a primary aliphatic amino group in one of them and a carboxy group in the other proceeds much more efficiently with the free amino group of 2'-amino-2'-deoxycytidine. This is explained by the fact that the pK_a value for this amino group (6.2)¹²¹ is much lower than that for the amino group of aliphatic amines, so this group exists mainly in a deprotonated form under the reaction conditions.

The effects of some other factors, such as the mutual arrangement of modified units, their number, nucleotide environment, thermodynamic stability of the precursor duplex, *etc.*, on the efficiency of the reaction between the chains, were studied.^{130, 131} Under optimum conditions, the yield of the corresponding DNA duplexes with covalently cross-linked chains reached 85% for certain systems.

The yields of the target products differ considerably for a 20- and a 25-membered systems (26% and 85%, respectively). This is accounted for by the fact that the efficiency of the reaction increased with an increase in the melting point of the original modified duplex.

Depending on the nucleotide environment of the modified units, the yield of the target product varied from 50% to 85%.^{130, 131} Substitution of 2'-amino-2'-deoxyuridine for 2'-amino-2'-deoxy-*arabino*-adenosine does not affect significantly the yield of the DNA duplex with covalently cross-linked chains.

The thermodynamic stability of DNA duplexes with incorporated modified units was in all cases lower than that of non-modified duplexes of the same primary structure. The decrease in the melting point depends on the length and the composition of the DNA duplex. In contrast, for duplexes with covalently cross-linked chains the melting point was higher than that for the corresponding modified and non-modified duplexes. The increase in the melting point was 4–8 °C relative to natural analogues, while that for the corresponding modified duplexes was 15–33 °C.^{128, 129}

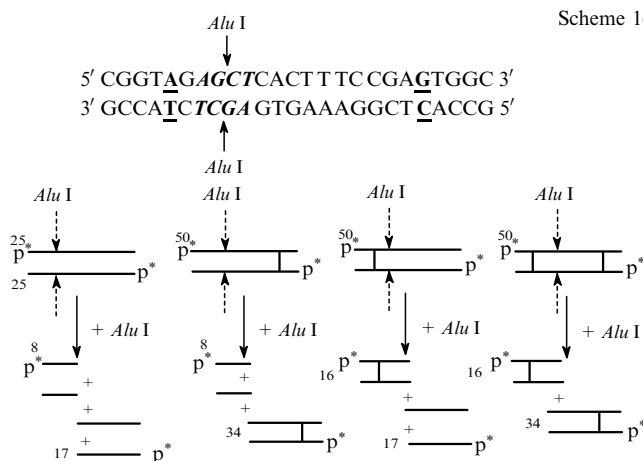
Duplexes with covalently cross-linked chains are much more resistant to the action of a mixture of snake venom phosphodiesterase and alkaline phosphatase than those devoid of interchain cross-links. Under conditions where natural and modified duplexes are completely hydrolysed to give nucleosides, duplexes with covalently cross-linked chains maintain their structure by no less than 70%. Such a low level of hydrolysis under these conditions is due to the presence of a cross-link between the chains.

Comparative kinetics of enzymic hydrolysis of a 25-membered duplex with covalently cross-linked chains and of a non-modified duplex of the same primary structure by snake venom phosphodiesterase was carried out.¹³² Under selected conditions, enzymic hydrolysis of single-stranded oligonucleotides and a non-modified duplex occurred at a high rate. Single-stranded oligonucleotides

were completely hydrolysed to give nucleotides in 5 min, whereas the duplex with covalently cross-linked chains was not completely hydrolysed under identical conditions even in 3 h. Relatively easy splitting of two or three units was observed together with accumulation of products of partial hydrolysis with chains shortened by no more than 3–8 units. After scission of eight units, the reaction is appreciably retarded. Thus, the presence of a cross-link between the chains causes strong inhibition of the effect of snake venom phosphodiesterase.

In order to prove the ability of compounds obtained to serve as substrates of enzymes binding with unique nucleotide sequences of DNA and to confirm their structure, DNA duplexes with covalently cross-linked chains were site-specifically cleaved with restriction endonuclease *Alu* I.^{130, 131} The primary structure of covalently cross-linked DNA duplexes corresponded to the 25-membered non-modified DNA duplex; its nucleotide sequence is shown in Scheme 14. The recognition site of restriction endonuclease *Alu* I is given in *italics*; the sites of incorporation of the corresponding modified units **43** and **44** are underlined.

The position of cross-links between the chains relative to the recognition site of restriction endonuclease *Alu* I in DNA duplexes determines the composition of the hydrolysate. The formation of oligonucleotides of different lengths resulting from hydrolysis of DNA duplexes with covalently cross-linked chains and the non-modified duplex is illustrated by Scheme 14.



Scheme 14

p* is ³²P-phosphate.

The composition of reaction mixtures for all DNA duplexes is in agreement with the theoretical Scheme 14. Thus, it has been shown that the presence of cross-links between the chains in synthetic DNA duplexes does not prevent their cleavage with restriction endonuclease *Alu* I. The formation of a series of products of a definite length confirms the presence and position of cross-links between the chains in the synthetic DNA duplexes.

The experimental results^{128–131} suggest that DNA duplexes with covalently cross-linked chains can be used as efficient 'traps' for proteins binding with nucleic acids.

IX. Conclusion

The data presented in this review testify to the existence of efficient methods for preparing DNA duplexes with covalently cross-linked chains. Cross-linking of DNA chains can be achieved either nonspecifically (statistically) or at predetermined positions of the double helix.

Owing to existing methods, the synthesis of these compounds is no longer a very complicated task. DNA duplexes with covalently cross-linked chains have become a convenient tool for the study of protein–nucleic acid interactions. Convincing evidence for the significant potential of this approach can be derived from the investigations cited in the review.

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^d — *Biochemistry (Engl. Transl.)*

Epoxidation of substituted norbornenes. Stereochemical aspects and accompanying intramolecular transformations

L I Kasyan

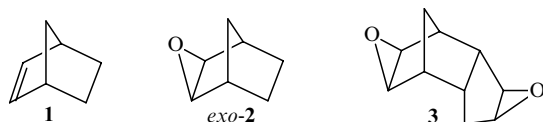
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Abstract. Traditional and new procedures for epoxidation of substituted norbornenes are described. The stereochemistry of this reaction and the influence of substituents on the reactivity of the substrate are analysed. The molecular rearrangements and heterocyclisation reactions that can accompany epoxidation are considered; examples of selective attack of oxidants at one of the double bonds in norbornenes containing an unsaturated substituent and also at a multiple bond in some polycyclic di- and triene systems are given. The bibliography includes 252 references.

I. Introduction

A great number of studies have been devoted to norbornene **1**, epoxynorbornane **2**, and their derivatives. This is mostly due to the fact that processing of norbornene-based epoxides gives practically valuable products and also to the fact that these compounds are readily produced from cyclopentadiene, which is a large-scale side product of the coke and petroleum processing industries. Thus dicyclopentadiene diepoxide **3** found application for the industrial manufacture of various polymeric compositions as early as the 1970s.



The special position occupied by norbornene and its derivatives in the synthesis of epoxides is due to the high reactivity of the strained double bond, stereoselectivity of the attack by oxidants, high stability of the resulting epoxides in neutral and alkaline media, and their clear-cut susceptibility to skeletal rearrangements in the presence of acids. No reviews specially devoted to epoxidation of substituted norbornenes have been published;

some information on this point can be found in reviews dealing with more general topics.^{1–10} The interest in the use of various epoxidising agents for preparing compounds of this type becomes even greater because the known attempts to use the halohydrin method in the synthesis of some epoxynorbornanes have failed. In the case of stereoisomeric *exo*- and *endo*-bicyclo[2.2.1]hept-2-ene-5-carbonitriles, bromohydrination is accompanied by Wagner–Meerwein rearrangement and yields adducts with a non-vicinal arrangement of the bromine and the hydroxyl precluding their transformation into epoxides in the presence of bases.¹¹

II. Methods for synthesis of epoxynorbornanes

Epoxynorbornane (2,3-epoxybicyclo[2.1.1]heptane or 3-oxatricyclo[3.2.1.0^{2,4}]octane) was first synthesised in 1954 by two research groups working independently by treatment of norbornene with peroxy acids.^{12,13} Later, norbornene has become a convenient model for the investigation of the mechanism of epoxidation of alkenes.^{1,4,5,14–17} This is due to the fact that among cycloalkenes, norbornene is the most reactive towards oxidation, irrespective of the particular oxidant used. This high reactivity of norbornene is explained by its strained character, caused by the fact that, according to a number of theoretical and experimental studies,¹⁸ the double bond in this molecule is non-planar (the strained state of the norbornene molecule is also manifested in spectroscopic and chemical characteristics^{18–22}). Norbornene has been epoxidised by, for example, organic peroxy acids^{23–29} (including those supported on polymeric substrates³⁰), alkyl hydroperoxides,^{2,6,31–33} peroxyimide acids in two-phase systems,³⁴ α -hydroperoxydiazenes,³⁵ and α -azo-hydroperoxides.³⁶ Quite promising for this purpose are Caro's acid,³⁷ peroxysulfur intermediates based on the superoxide anion (O_2^-),³⁸ as well as the new large class of dioxiranes generated from salts of Caro's acid and acetone.³⁹ Murray and coworkers³⁹ demonstrated the possibility of obtaining the labile monoepoxide and (previously unknown) diepoxide of norbornadiene using dimethyldioxirane. This permits the above experimental procedure to be highly appreciated (some modifications of this method have been reported, in particular, epoxidation of norbornene and other alkenes *via* oxaziridinium salts⁴⁰). The use of sodium perborate as the oxidant also seems quite promising.⁴¹

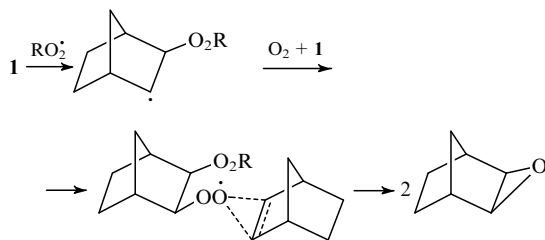
Molecular oxygen is used both for spontaneous oxygenation of norbornene (which is due to the highly strained character of

L I Kasyan Dnepropetrovsk State University, per. Nauchnyi 13, 320625 Dnepropetrovsk, Ukraine. Fax (7-056) 268 36 13. Tel. (7-056) 246 31 43

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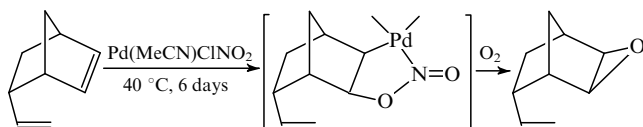
alkenes of this series)⁴² and for sensitised oxidation.^{43–45} Study of the latter reaction demonstrated that it occurs as stereospecific *exo*-addition of the peroxy radical to the strained π -bond of the substrate:



The oxidation of norbornene by oxygen has been carried out in the presence of silver catalysts^{46,47} and also specially prepared titanium silicate.⁴⁸ Photooxidation of norbornene catalysed by various compounds,⁴⁹ in particular, sulfur dioxide⁵⁰ has also been studied. Epoxidation of norbornene and other cycloalkenes using the oxygen of water as the oxidant in the presence of platinum complexes has been reported.⁵¹

In a number of studies, oxidation of norbornene derivatives by singlet oxygen has been described.^{52,53} The reaction with singlet oxygen in the presence of phosphites was assumed to involve the *in situ* formation of phosphadioxirane intermediates.⁵⁴

A convenient method for epoxidation of norbornene and its derivatives by oxygen in the presence of nitropalladium complexes has been proposed.^{55–58} The strained double bond in norbornene, vinylnorbornene, and methylnorbornene ensures the formation of a stable five-membered transition state, the yield of epoxide reaching 50%.



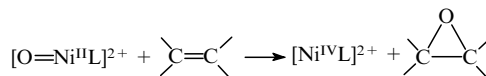
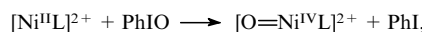
This method has also been used to oxidise a number of terminal alkenes and substituted cyclohexenes: the former are converted into ketones, while the latter form mixtures of epoxides, ketones, enols, and other products or do not react at all.⁵⁵

The reactivity of the intermediate complex can be changed by adding copper(II) chloride; in the presence of this salt, the thermal destruction leading to the epoxide is completely suppressed, and rearrangement of the substrate occurs instead.⁵⁶

Takai *et al.*^{59,60} found that norbornene and its derivatives are easily transformed into epoxides upon treatment with oxygen (as oxidant) and secondary or primary alcohols (as reducing agents) in the presence of catalytic amounts of 1,3-diketonoxyvanadium(IV) complexes. Later, a similar transformation was accomplished using nickel⁶¹ or iron⁶² complexes as catalysts in the presence of aldehydes. The reactions were carried out under atmospheric pressure at a moderate temperature, and the epoxides were obtained in high (up to quantitative) yields.⁶³ Heteropoly compounds of the type $(\text{NH}_4)_5\text{H}_4\text{PV}_6\text{W}_6\text{O}_{40}$ were also proposed as catalysts for this process.⁶⁴

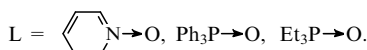
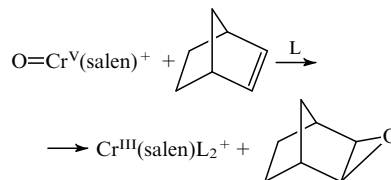
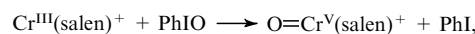
An important aspect of the chemistry of norbornene derivatives is investigation of the regularities of liquid-phase catalytic oxidation reactions in which peroxides of transition metals (copper, nickel, cobalt, chromium, molybdenum, vanadium, rhenium, and manganese) are formed as active intermediates.^{31,65–77} Nickel(II) complexes with tetraaza-macrocycles, Schiff bases, and bidentate phosphines have also been studied.^{31,68} Thus in the oxidation of norbornene with iodosylbenzene in the presence of a nickel complex, the complex is activated by reducing iodosylbenzene to iodobenzene. During the transfer of oxygen, the resulting oxo-nickel(IV) intermediate experiences the influence of various factors: the nature of the solvent, concentrations of the reactants, and the temperature. In

particular, when H_2O^{18} is used, the labelled oxygen atom proves to be incorporated in the epoxide (80%).



This method cannot be used to epoxidise cycloalkenes. For example, cyclohexene is converted under these conditions into a mixture of the epoxide, cyclohex-2-enol, and the corresponding ketone (the yields are 36%, 49%, and 15%, respectively).⁶⁸

The use of chromium(III) salicylaldehyde complexes (*salen*) Cr^{III} has several advantages over the method described above (the yield of epoxynorbornane increases to 85%, and the method becomes applicable to some cycloalkenes). The catalytically active species in this reaction are chromium(V) oxo complexes resulting from interaction of the initial complexes (*salen*) Cr^{III} with iodosylbenzene. When pyridine, triphenylphosphine, or trimethylphosphine oxides are used as the ligands L, the activity of the complex increases by several orders of magnitude.⁷¹

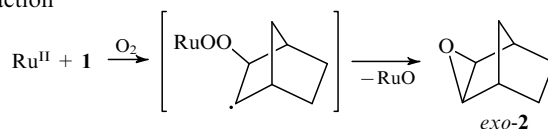


The use of cyanopyridinium chlorochromate as the oxidant for norbornene and other cycloalkenes leads to products of another type, namely, chloro ketones.⁷⁸

Agarwal *et al.* have studied oxidation of cycloalkanes catalysed by $\text{Fe}(\text{III})$,⁷⁹ $\text{Cr}(\text{III})$,⁸⁰ $\text{Mn}(\text{III})$,^{81,82} and $\text{Ru}(\text{III})$ ⁸³ complexes with Schiff bases. Later, manganese complexes with Mannich bases have also been tested as catalysts for this reaction.⁸⁴ Among the cycloalkenes studied, norbornene was found to be the most reactive, and, what is especially important, to undergo the most selective epoxidation.⁷⁹

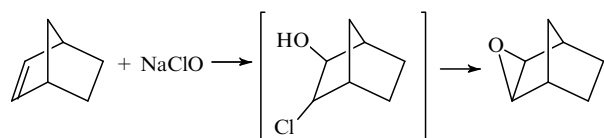
The epoxidation of alkenes with aqueous solutions of hydrogen peroxide, is accomplished using heteropolytungsten complexes of transition metals (chromium, iron), because they are stable with respect to solvolysis,^{85,86} and also complexes based on $\text{Ru}(\text{III})$ and $\text{Ru}(\text{II})$.^{87–90}

Drago *et al.*⁹⁰ successfully epoxidised norbornene using oxygen and sterically hindered ruthenium complexes (the selectivity of epoxide formation was 94%). The homolytic mechanism of this reaction



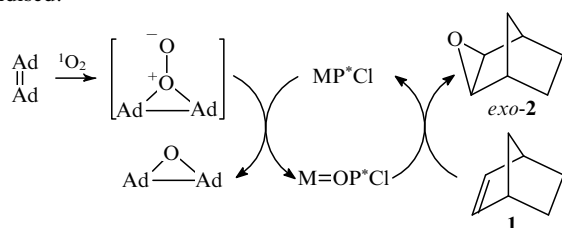
was confirmed experimentally.

At present, considerable attention is paid to the use of metal porphyrins as catalysts for this reaction, because oxidation involving these compounds is quite similar to the enzymic epoxidation and hydroxylation catalysed by cytochrome P-450⁹¹ or P-420.⁹² Considerable progress has already been achieved along this line: methods for asymmetric epoxidation have been developed;⁹¹ biomimetic electrochemical systems for the oxidation of hydrocarbons, in particular norbornene, by molecular oxygen have been constructed;⁹³ (usually, iodosylbenzene, peroxy acids, or alkyl hydroperoxides are used for oxidation).⁹⁴ The hypothesis of formation of the chlorohydrin intermediate during the oxidation of norbornene by sodium hypochlorite have been rejected based on stereochemical considerations.⁹⁵



Photocatalytic oxygenation of norbornene by molecular oxygen in the presence of iron tetraarylporphyrinates has been studied.⁹² Whereas cyclohexene and cycloheptene are oxidised to give mixtures of products containing only 20%–35% of the epoxide, norbornene **1** is entirely converted into epoxynorbornane **2** under the same conditions.

Ando *et al.*⁹⁶ proposed a peculiar scheme for the preparation of the compound **2** by joint oxidation of norbornene **1** and adamantylideneadamantane in the presence of iron(III) porphyrins. The results of kinetic studies suggest that the first stage consists in oxidation of adamantylideneadamantane; after that, the oxygen atom from the perepoxy intermediate thus formed is transferred to the metal porphyrin, and then norbornene is oxidised:

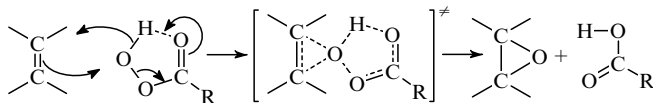


Ad is adamantylidene, P* is the porphyrin ligand.

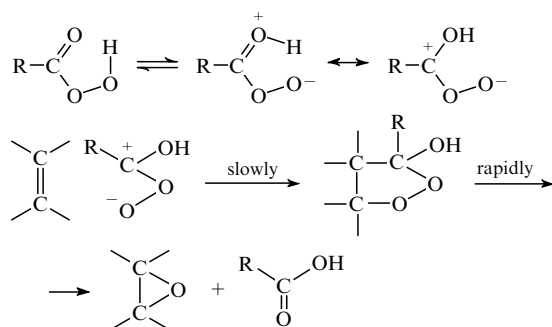
Interesting results have been obtained with ruthenium porphyrin complexes as the catalysts.^{97,98} Oxidation of ruthenium tetramesitylporphyrinate by *m*-chloroperbenzoic acid (MCPBA) yielded stable crystalline dihydroxoruthenium(IV) tetramesitylporphyrinate, which was used to carry out aerobic oxidation of norbornene.⁹⁸

III. Reaction mechanism

Norbornene is a convenient model to study the mechanism of epoxidation. This process is described most often in terms of the scheme proposed by Lynch and Pausacker,¹⁷ who rationalised epoxidation of alkenes with peroxy acids as a synchronous process including formation of a three-membered cyclic transition state.



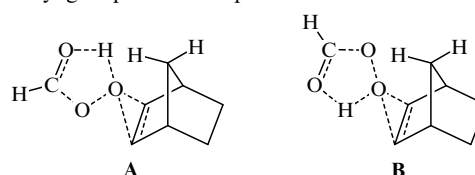
Since the above simple scheme is suitable only for describing processes carried out in weakly polar solvents, Kwart *et al.*^{99,100} proposed a different mechanism according to which this reaction is rationalised as dipolar 1,3-cycloaddition; this was confirmed by calculations.¹⁷



The structure of the cyclic transition state (three- or five-membered) has been discussed on the basis of a study of epoxidation kinetics, norbornene being used as the model com-

pound. It was found that the ratio of the rate constants for epoxidation of norbornene and cyclohexene by peroxyauric acid, equal to 1.2, differs sharply from the corresponding ratios found for the reactions of the same substrates with phenyl azide (6.5×10^3) or picryl azide (8.0×10^3).¹⁰¹ This is evidence against the 5-membered transition state in epoxidation. In fact, the strain in the three-membered transition state should smooth out the differences between the epoxidation patterns observed for various types of alkenes. Later, similar kinetic calculations served as the key for elucidation of the mechanism of oxidation of alkenes with ozone,¹⁰² xenon trioxide,¹⁰³ osmium tetroxide,¹⁰² and chromic acid.¹⁰⁴

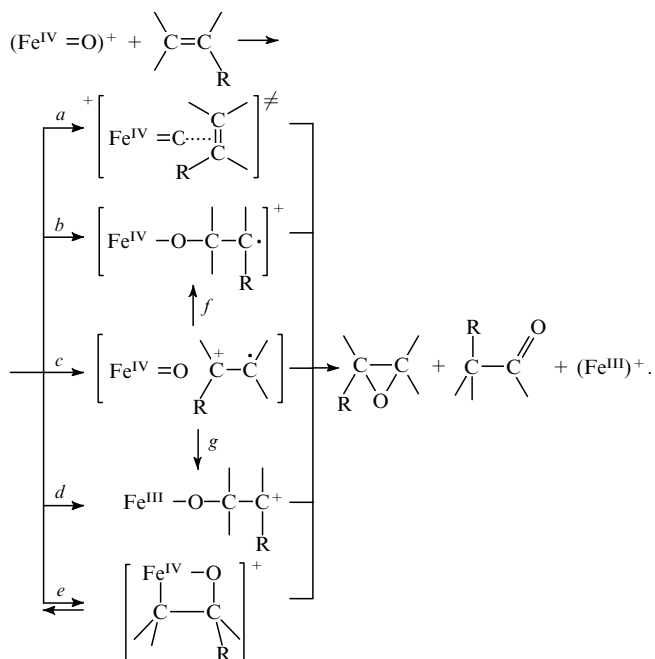
Epoxidation of norbornene and its derivatives by performic acid has been studied.¹⁰⁵ Two variants (A and B) for the primary orientation of norbornene in relation to the plane of the peroxy-carbonyl group atoms are possible.



According to calculations, both transition states are first-order saddle points; however, in the former case the activation enthalpy ($\Delta H^\ddagger$) is lower by 4.7 kJ mol⁻¹.

In the case of iron porphyrinates,¹⁰⁶ the mechanism of epoxidation includes the formation of a high-valence metal porphyrin radical cation, for example, (Fe^{IV}=O)⁺, which acts as the direct oxidising agent, different key steps of the reaction being possible.

This might be the direct transfer of the oxygen atom [path (a)], homolytic addition followed by fast closure of the epoxide ring [path (b)], electrophilic addition and subsequent cyclisation [path (d)], reversible formation of metal oxetane followed by recyclisation and epoxide formation [path (e)] and electron transfer [path (c)] followed by transformation into a radical cation [path (f)] or a carbocation [path (g)].¹⁰⁴

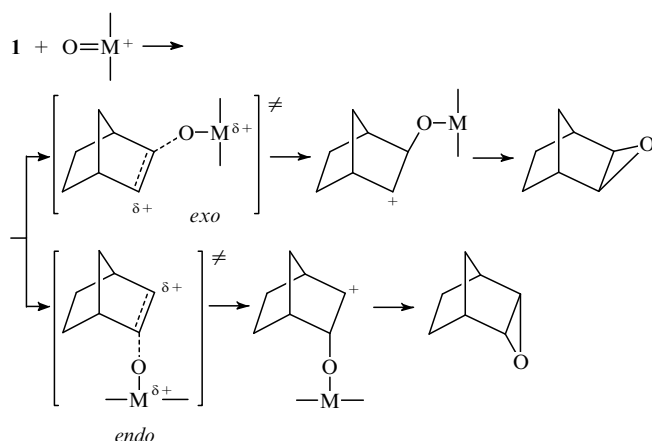


In this case, unlike the traditional scheme for epoxidation by peroxy acids, a mechanism involving the intermediate formation of a radical cation [path (f)] has also been proposed.¹⁰⁷ This is confirmed by the composition of the reaction products and by kinetic data obtained for epoxidation of various alkenes. The logarithms of the rate constants for the epoxidation were found to

obey a linear correlation with the ionisation potentials of the alkenes.

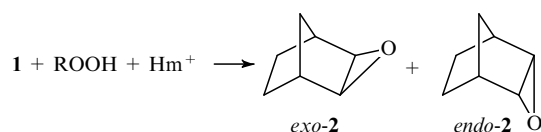
The reaction mechanism was developed with allowance for the stereochemical data obtained for epoxidation of norbornene.^{107, 108} Traylor *et al.*¹⁰⁹ showed that the *exo*-stereoselectivity of epoxidation, typical of norbornene, does not hold in the presence of metal porphyrins, and the ratio of the yields of *exo*- and *endo*-epoxynorbornanes depends appreciably on the type of metal incorporated in the porphyrin nucleus and the type of substituents in the benzene rings of a substituted tetraphenylporphyrin.¹⁰⁹ Thus the ratio of *exo*- to *endo*-epoxynorbornanes amounts to ~1000 for electropositive Cr complexes and ~6 for electronegative Fe(III) complexes, the amount of the rearranged products decreasing in parallel. When norbornene is oxidised by pentafluoriodobenzene in the presence of iron tetra(4-methylphenyl)- or tetra(2,6-dichlorophenyl)porphyrinates, the yield of the epoxide is 45% or 82%, and the ratio of *exo*- to *endo*-stereoisomers is 71 or 9, respectively (in the case of oxidation by peroxy acids, this ratio is 600–700). Moreover, it was found that the logarithm of the (*exo/endo*) ratio correlates with the σ -Hammett constants of the substituents in the porphyrin benzene rings.¹⁰⁹

This finding can be explained by assuming a change of the reaction mechanism: in place of the electron transfer [path (*f*)], electrophilic attack [path (*d*)] occurs, resulting in the formation of a transition state consisting of the alkene weakly bound to the attacking reagent.



The electron density on the central metal atom in metal porphyrins increases in the following sequence of metals: iron(III) < manganese(III) < chromium(III). In the same series, the bond between the alkene and the attacking reagent in the transition state becomes stronger and the C...O distance decreases; simultaneously, steric hindrance becomes more significant, and the *exo*-stereoselectivity is enhanced.¹⁰⁹

Traylor *et al.*¹⁰⁹ who studied oxidation of norbornene with hydrogen peroxide and *tert*-butyl hydroperoxide catalysed by iron porphyrinate with fluorinated benzene rings, obtained the same *exo* : *endo* ratio (22 : 1) as was found using pentafluoriodobenzene as the oxidant.¹⁰⁹ As has been shown previously, this oxidising agent reacts with the porphyrinates giving iron(IV) radical cation (oxene). Traylor *et al.*¹¹⁰ were able to demonstrate that in the presence of iron porphyrinates, including hemin (Hm^+), as the catalysts, hydrogen peroxide and *tert*-butyl hydroperoxide undergo heterolytic cleavage to give oxene:

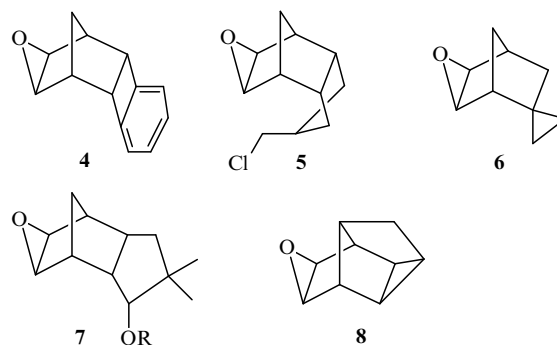


The approach to the mechanism of norbornene oxidation outlined above has been confirmed by investigating this reaction in the presence of new porphyrin catalysts¹¹¹ and new oxidants.¹¹²

In a study of joint oxidation of α -methylstyrene and norbornene with MCPBA or *o*-chloroperbenzoic acid in the presence of iron(III) porphyrinates, it was found that the selectivity of epoxidation changes crucially depending on the solvent.¹¹³ It was found that the formation of oxoferryl porphyrin radical cation is not the preferential route.

In some cases, fine structural features of the ligand have a substantial influence on the stereochemistry of epoxidation of norbornene.¹¹⁴ In particular, the use of isomeric ligands incorporating 3- and 4-pyridyl fragments leads to different results: in the former case, a mixture of stereoisomeric epoxides is formed, while in the latter case, only the *exo*-isomer is produced. Agarwal *et al.*¹¹⁴ explained these differences by specific features of coordination of the nitrogen atoms of the pyridine ligands to the manganese atom.

When MCPBA was used as the oxidant, the reaction gave various polycyclic structures (for example, 4–8) incorporating epoxynorbornane or related fragments.^{115–120}



IV. Stereochemistry of epoxidation of substituted norbornenes with peroxy acids

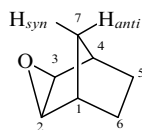
The stereochemical outcome of the epoxidation of substituted norbornenes with peroxy acids, namely, the formation of an *exo*-epoxide ring, is a particular case of the known Alder rule.¹²¹ It has been discussed in detail in a number of studies.^{122–125} Earlier, the configuration of the epoxides has been studied by converting them into known norbornanols; thus, it was found that the epoxynorbornane formed contains only a slight amount of the *endo*-epoxide (6%,¹²⁶ 0.5%¹²⁷). Brown *et al.*¹²⁷ attributed the *exo*-attack to the predominant steric hindrance of the *endo*-area by the norbornene fragment. As model compounds, they chose norbornene (1), *cis*-bicyclo[3.3.0]octene, and *endo*-5,6-trimethylenenorbornene 10. The increase in the steric hindrance of the *endo*-area of the ring was judged by the increase in the *exo*-stereoselectivity.¹²⁷

Compound			
<i>exo</i> : <i>endo</i> ratio of epoxides	87 : 13	99.5 : 0.5	99.9 : 0.1

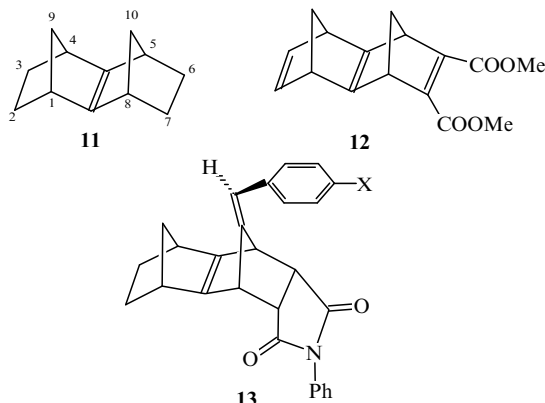
Later, the selectivity of the attack and the high reactivity of norbornene have been explained by the influence of hyperconjugation and out-of-plane deformation. Theoretical studies showed that the =C–H bonds in norbornene, unlike those in cyclohexene or bicyclo[2.2.2]octene, are bent by 2–5° to the *endo*-area. In the transition state, the *endo*-bending ensures both *exo*-stereoselectivity and a high rate of the attack by an electrophilic reagent. The presence of the *endo*-bending was attributed to the repulsion between the π -orbital and the occupied orbitals of the methylene bridge.

In fact, the vast majority of known epoxynorbornanes have *exo*-configuration in which the protons of the C(7)H₂ bridge are appreciably non-equivalent, one of them being arranged directly

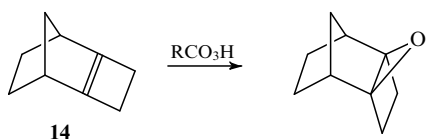
above the plane of the epoxide fragment and experiencing substantial paramagnetic shielding.



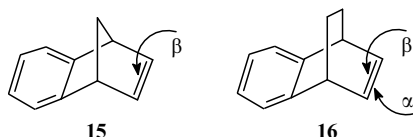
The non-equivalence of the bridging protons in the ^1H NMR spectrum as well as the unusual shielding of the C(7) atom in the ^{13}C NMR spectrum are the two criteria, which can be used to determine the stereochemistry of an epoxynorbornane fragment.^{125, 128} The *exo*-configuration has been confirmed by X-ray diffraction analysis.^{129, 130} *exo*-Stereoselective epoxidation has also been observed for the 7-oxa analogue of norbornene¹³¹ and for polycyclic compounds, related to norbornene but much more complicated, such as *syn*-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanonaphthalene **11** and its derivatives **12** and **13**.



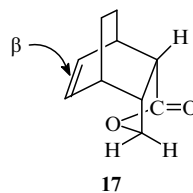
In this case, the *endo*-shielding is even more significant: the distances between the internal hydrogen atoms H(9), H(10) and H(3), H(6) are 3.416 and 2.728 Å,¹³² respectively; since, the $sp^2 \rightarrow sp^3$ transition relieves strain, these alkenes and polyenes are readily epoxidised.^{133, 134} The presence of a fulvene group in the compound **13** does not change the stereoselectivity of the attack by oxidants (peroxy acids, oxygen) directed at the strained double bond.¹³⁵ The *exo*-attack is also characteristic of the strained system **14** with a cyclobutene fragment.¹³⁶



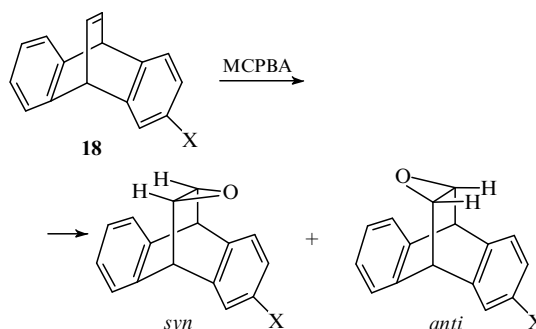
As the ring becomes less strained and/or shielding of the two directions of the attack becomes equal, this stereochemical course no longer predominates; thus bicyclo[2.2.2]octene **16**, unlike benzonorbornene **15**, undergoes non-stereospecific epoxidation giving rise to *exo*(β)- and *endo*(α)-epoxides.^{13, 137}



The stereochemistry of epoxidation of the anhydride or esters of *endo*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid with trifluoroperoxyacetic acid is also non-stereospecific; the reaction mixture contains both epoxides together with products of lactonisation, whereas in the case of unsaturated lactone **17**, only the β -attack is observed, due to steric interactions involving the internal hydrogen atom of the methylene group.¹³⁸



The through-space interaction between the double bond and the aromatic fragment in benzobicyclo[2.2.2]octadienes¹³⁹ and dibenzobicyclo[2.2.2]octatrienes¹⁴⁰ has been studied by quantum chemistry and photoelectron spectroscopy. The results of the influence of substituents in the benzene ring of dibenzobicyclo[2.2.2]octatrienes **18** on the stereoselectivity of epoxidation are shown in Table 1.¹⁴⁰



It was found that electron-withdrawing substituents (NO_2 , F) facilitate the *syn*-attack, whereas electron-donating substituents do not exert this type of influence.

Table 1. Ratio of the *syn*- and *anti*-isomers in the products of electrophilic oxidation of 2-substituted dibenzobicyclo[2.2.2]octatrienes **18**.

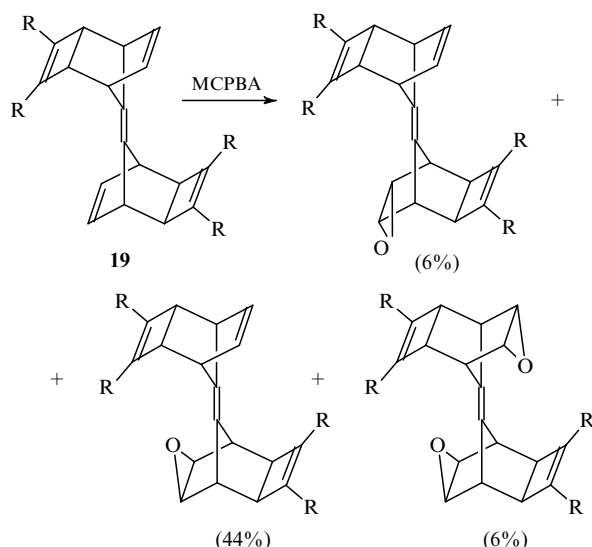
Oxidant	Substituent X	Yield (%)	Ratio <i>syn</i> : <i>anti</i>
MCPBA	H	88	50 : 50
	NO_2	46	77 : 23
	OMe	63	48 : 52
	F	86	58 : 42
OsO_4	H	90	50 : 50
	NO_2	67	85 : 15
	OMe	96	48 : 52
	F	96	68 : 32
KMnO_4	H	58	50 : 50
	NO_2	48	88 : 12

Gandolfi *et al.*¹⁴¹ have found that the 80%–96% *syn*-stereoselectivity of the attack by MCPBA on the double bond of *endo,exo*-5,6-disubstituted bicyclo[2.2.0]oct-2-enes (containing OAc, CN, *etc.* as substituents) is controlled by hyperconjugation of the σ^* -orbitals of the bonds being formed with antiperiplanar σ -bonds of the allylic fragments.

In studies of epoxidation of anhydrides, nitriles, and esters of the norbornene series,^{142–145} it has been found that these compounds undergo only the *exo*-attack by peroxy acids. The reported formation of *endo*-epoxides on treatment of 5-substituted norbornenes with *O*-benzylmonoperoxyacetic acid⁶ seems doubtful; apparently, in this case, too, *exo*-epoxidation occurs.¹⁴⁶

exo-Stereoselective epoxidation has also been observed for the 7-oxa analogues of substituted norbornenes,^{147–150} for bicyclic nitrogen-containing systems with a similar structure,¹⁵¹ and for a broad range of bis-adducts of cyclopentadiene with various dienophiles.¹⁵² The *exo*-stereoselectivity of the Prileschajew reaction is strictly observed for unsaturated propellanes related to norbornene. For complex polyenes (for example, for the com-

pound **19**), stereoselectivity is retained, together with the chemoselectivity of the attack at the double bond.¹⁵³

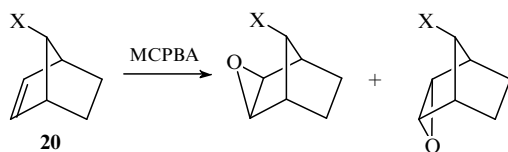


According to the known Bartlett, Lynch, and Pausacker scheme,¹⁷ it can be assumed that formation of the transition state in the epoxidation of substituted norbornenes faces difficulties if the *exo*-area of the norbornene fragment contains bulky groups belonging to any of the two reacting molecules. The influence of methyl groups in various positions of the norbornene fragment on the stereochemistry of epoxidation by MCPBA has been estimated quantitatively (Table 2).^{30, 154, 155} It can be seen from Table 2 that only the *syn*-Me group at the 7-position prevents the attack. These data are consistent with the results obtained earlier for epoxidation of bornylene. For example, the formation of a mixture of isoborneol, borneol, epiisoborneol, and epiborneol^{156, 157} upon the reduction of bornylene epoxide proves unambiguously the presence of a mixture of stereoisomers of the epoxide, the quantitative composition of the resulting mixture of alcohols being indicative of predominant *endo*-attack in epoxidation.

Table 2. Influence of the position of methyl groups on the stereochemistry of epoxidation of substituted norbornenes.

Compound	Epoxide yield (%)	Content of <i>exo</i> -isomer (%)
Norbornene	87	99.0
7,7-Dimethylnorbornene	87	6.0
1-Methylnorbornene	88	99.0
2-Methylnorbornene	100	99.5
1,7,7-Trimethylnorbornene	80	5.0

To estimate the influence of the size of various groups on the stereochemistry of epoxidation, epoxidation of *syn*-7-substituted norbornenes by MCPBA was carried out^{158, 159} (Table 3).



X = H, Cl, SnMe₃, Br, Me, Bu^t.

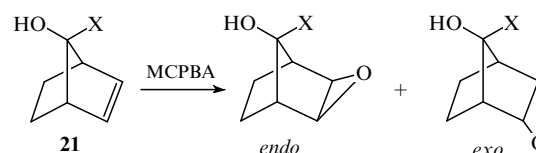
It can be seen from Table 3 that neither the van der Waals radius nor the length of the C–X bond are crucial for the efficiency of the *endo*-attack. The found *exo* : *endo* ratios vary in parallel with the size of the ‘open space’ between the double bond and the substituent, calculated by Davis *et al.*¹⁵⁹ by the procedure

Table 3. Influence of the character of substituents on the stereochemistry of epoxidation of substituted norbornenes **20**.

Substituent X	Content of <i>exo</i> -isomer (%)	<i>exo</i> : <i>endo</i>	C–X bond length /Å	Van der Waals radius of the substituent /Å
H	99.0–99.5	100	1.10	1.20
Cl	62.0	1.6	1.77	1.80
SnMe ₃	55.0	1.2	(2.18)	—
Br	45.0	0.8	1.94	1.95
Me	6.0–14.0	0.1	1.54	2.00
Bu ^t	0.0	0.0	(1.54)	—

proposed by Wilcox.¹⁶⁰ Any influence of the polar factor can be ruled out because the outcomes of the epoxidation and hydroboration reactions are identical.

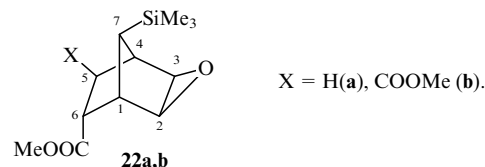
Gassman *et al.*¹⁶¹ showed that methyl and nitrile groups have different effects on epoxidation of the double bond in substituted *anti*-bicyclo[2.2.1]hept-2-en-7-ols **21**.



X = Me (*exo* : *endo* = 22 : 78), CN (*exo* : *endo* = 45 : 55).

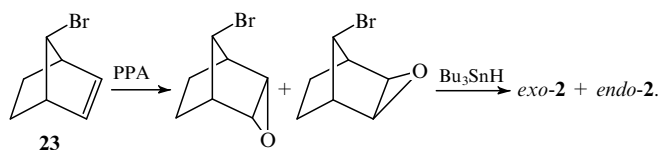
Epoxidation of 7,7-dibromomethylnorbornene yielded the isomers in approximately equal amounts.¹⁶²

The data presented above^{161, 162} disprove the results obtained in another study¹⁶³ in which the products **22a,b** obtained by epoxidation of substituted norbornenes with a *syn*-7-trimethylsilyl group were identified as containing an *exo*-epoxide ring.



In the light of the data available from the literature, the *exo*-attack by a peroxy acid seems relatively unlikely. Moreover, the ¹H NMR spectral parameters reported by Fleming and Michael¹⁶³ unambiguously point to the *endo*-configuration of the epoxide ring. In fact, the H(2) and H(3) protons are responsible for chemical shifts of 3.63 and 3.53 ppm (**22a**) and 3.62 ppm (**22b**). The chemical shifts of the corresponding protons in *syn*-7-bromo(chloro or trimethylstannyl)-*exo*-2,3-epoxybicyclo[2.2.1]heptanes are 3.24, 3.26, and 2.97 ppm, whereas those in the corresponding *endo*-epoxides are 3.67, 3.70, and 3.45 ppm.^{158, 159}

The influence of steric hindrance on the epoxidation of *syn*-7-bromobicyclo[2.2.1]hept-2-ene **23** by peroxyphthalic acid (PPA) has been studied.²⁵ The stereoisomeric bromoepoxides formed in this reaction [mostly, the *endo*-isomer, 1.8 : 1] were subsequently reduced by tributyltinhydride at 140 °C.

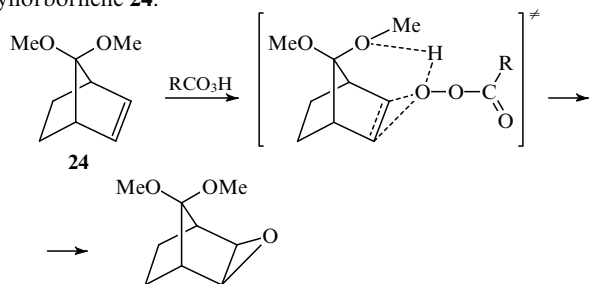


The resulting *endo*-2,3-epoxynorbornane **2** was studied by spectroscopy and by kinetic methods.

The *syn*-substituents at the 7-position, which are arranged in space close to the double bond, should certainly influence not only the direction but also the rate of epoxidation. The rates of the reactions of *anti*-7-*tert*-butylbicyclo[2.2.1]hept-2-ene, containing

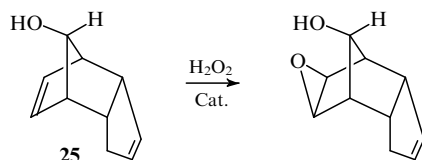
the bulkiest *tert*-butyl group, with diimide, hydrogen, mercury acetate, and MCPBA are lower than the rates of the same reactions of norbornene by factors of 1.55, 3.77, 5.49, and 5.16, respectively.¹⁶⁴ Unfortunately, no data concerning epoxidation of the *tert*-butyl-substituted *syn*-isomer are presented in the study cited;¹⁶⁴ however, it does not enter into the complex-formation reaction with Ag^+ or reactions with diimide, mercury acetate, or benzenethiol even in the *endo*-direction. This might be due to the repulsion of the ethylene fragment from the *tert*-butyl group resulting in a distorted molecular geometry and hampered *endo*-attack.

However, in some cases, substituents in the bridge facilitate the *exo*-attack. This is possible when the polar factor proves to be more significant than steric strain, for example, for 7,7-dimethoxynorbornene **24**.¹⁶⁵



In the opinion of the researchers cited,¹⁶⁵ the *exo*-addition is a consequence of formation of a hydrogen bond between the attacking peroxy acid and the oxygen of the 7-methoxy group.

The involvement of a hydroxy group in epoxidation is apparently a general reaction route. For instance, it accounts for the chemo- and stereo-selectivity of the oxidation of the alcohol **25** in the presence of a molybdenum catalyst¹⁶⁶ and also of other reactions.¹⁶⁷



V. The influence of substituents in the bicyclic system of norbornene on the reactivity of the double bond towards peroxy acids

Only a few studies specially devoted to the kinetics of epoxidation of substituted norbornenes have been published. Thus Brown *et al.*¹⁶⁸ demonstrated that the steric effect of the 7,7-dimethyl substitution is manifested as the change in the orientation of the attack by the oxidant (MCPBA) and as a 100-fold decrease in the reaction rate compared with that observed for norbornene, *exo*-epoxidation being retarded by more than three orders of magnitude.

A kinetic study dealing with epoxidation of 5,6-disubstituted (Cl, Br, COOMe) norbornene derivatives by perbenzoic acid (PBA) has been published.¹⁶⁹ The rate constants for this reaction, which correlate with the Hammett constants increase slightly in the following series of isomers: 5,6-*exo-cis* < 5,6-*trans* < 5,6-*endo-cis*. The researchers believe that these substituents exert mainly a polar influence, the effect of *exo*-substituents being stronger.

The crucial role of the inductive effect has been found for epoxidation of stereoisomeric norborn-2-ene-5-carboxylic acids and their esters.^{1, 142, 144, 145} According to the kinetic studies of Berti *et al.*,¹⁴⁴ the possibility of an influence of the carboxyl group on the rate-determining step of this reaction can be ruled out, because the ratio of the reaction rates for the *endo*-acid and its ester proved to be similar to that found for *ortho*-stilbenecarboxylic acids and their esters. The situation changes dramatically in

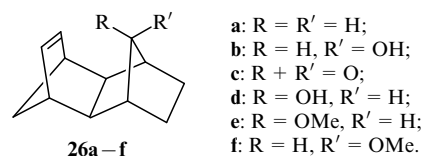
those cases where the substituent assists the reaction, as has been observed for epoxidation of norbornene derivatives containing *endo*-5-hydroxymethyl and *endo*-carboxamide groups.^{1, 144, 145, 170, 171} In both cases, intramolecular rear attack by the nucleophilic group on the electrophilic centre in the intermediate 'alkene-peroxy acid' complex results in cyclisation. Epoxidation of the corresponding *exo*-stereoisomers follows the normal pathway.^{172–174} (see also Section VII).

The influence of solvation and specific interactions has been clearly demonstrated in relation to epoxidation by peracetic acid of a number of stereoisomeric nitriles, acids, esters, amides, and alcohols, and also *endo*-stereoisomeric nitro- and bromomethyl-derivatives of norbornene.¹⁵⁴ In the presence of functional groups possessing clear-cut proton-donor or proton-acceptor properties, the inductive influence of substituents is masked by solvation effects; this has an influence on the correlation of the rate constants with the Taft constants of substituents. The effects of carboxyl and carboxamide groups on the epoxidation depend substantially on their orientation; in *exo*-isomers these groups are 'open' to the formation of intermolecular hydrogen bonds, whereas in *endo*-isomers they are shielded by the carbon cage of the molecule.

Quantum-chemical PM3 calculations for a number of transition states formed during epoxidation of substituted norbornenes by performic acid and comparison of the calculated parameters with the results of kinetic studies made it possible to find a correlation between the logarithms of the rate constants ($\lg k$) and the calculated activation enthalpies ($\Delta H^\ddagger$).¹⁰⁵

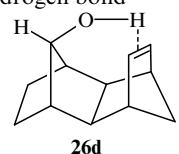
Comparison of the results of correlation analyses of substituted norbornenes and propenes (the ρ constants for these reaction series at 40 °C are -0.446 and -1.31 , respectively) implies that epoxidation of bicyclic alkenes is less sensitive to the inductive effect of substituents, because the bicyclic system smoothes out its influence.¹⁷⁵

Kinetic data concerning the interaction of the π -bond with closely arranged groups in polycyclic systems related to norbornene can be found in several studies. The through-space interaction has been studied in relation to epoxidation of substituted propellanes **26a–f**.

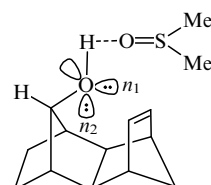


These reactions are *exo*-stereoselective in all cases; the reactivity of the double bond decreases in the following sequence (the relative epoxidation rates are given in parentheses): **26e** (13.20) > **26a** (1.00) > **26f** (0.36) > **26c** (0.04).^{176, 177}

Analysis of the IR spectra recorded in weakly polar solutions proves that the compound **26d** contains a strong intramolecular hydrogen bond

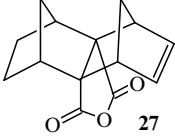
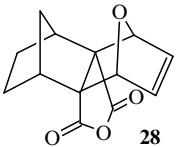
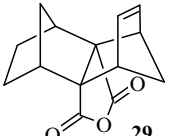
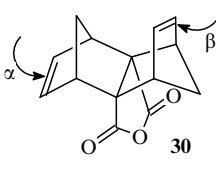
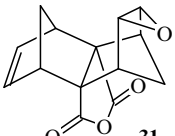
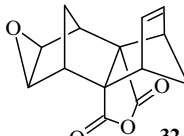


which deactivates the double bond. In aprotic bipolar solvents, the OH group participates in the formation of an intermolecular H bond with a solvent molecule.



The through-space $n_1-\pi$ orbital interaction arising in the latter case increases the nucleophilic properties of the double bond. The same is true for the *syn*-methoxy group in **26e**. The reactivity of the ester **26e** is 340 times higher than the reactivity of the ketone **26c** in which this type of interaction does not occur.

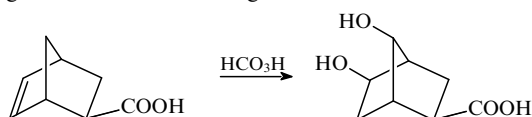
Comparison of the relative rates of epoxidation by MCPBA of the double bonds in 1,4,5,8-dimethano-1,4,4a,5,6,7,8,8a-octahydronaphthalenes (**27–32**), incorporating an anhydride group, indicates that the *syn*-arrangement of this group largely passivates the double bond. Comparison of the rates of epoxidation of the compound **27** and its oxa-analogue **28** shows that in the presence of the oxygen bridge, the nucleophilicity of the double bond further decreases.¹³⁰

Compound		
Relative epoxidation rate	1.00	0.58
Compound		
Relative epoxidation rate	19.00	1.20(α), 9.00(β)
Compound		
Relative epoxidation rate	0.40	8.30

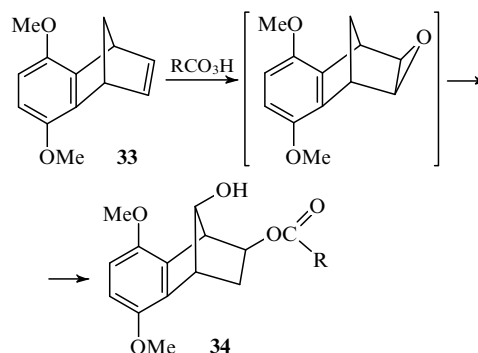
VI. Molecular rearrangements during epoxidation of norbornene

A peculiar feature of the epoxidation of norbornene derivatives is the formation of various isomeric products including those resulting from the Wagner–Meerwein rearrangement and hydride shifts.¹⁷⁸

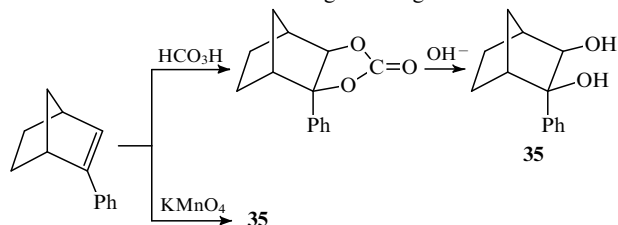
Electron-withdrawing groups at the 5- and 6-positions of the norborn-2-ene molecule prevent the C(1)–C(6) and C(4)–C(5) σ -bonds from participation in the delocalisation of charge at the C(2) and C(3) atoms; this decreases the role of nucleophilic assistance and, hence, the amount of rearranged products formed falls. For example, treatment of *exo*-bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylic acid¹⁷⁹ and its 7-oxa analogue¹⁸⁰ with performic acid gives rise to the corresponding *exo*-epoxy acids. Trifluoroperoxyacetic acid can also be used as the oxidant in this reaction. When the molecule contains only one *exo*-carboxyl group, the reaction with performic acid is accompanied *in situ* by the Wagner–Meerwein rearrangement.¹⁴⁴



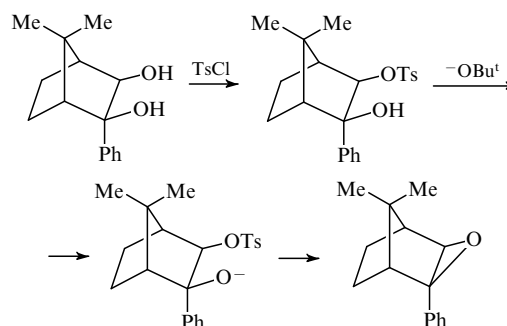
Electron-donating groups at the 5- and 6-positions increase the probability of the rearrangement during epoxidation; the rearrangement occurs even in those cases where one might expect the 'normal' reaction pattern. Thus, unlike benzonorbornene, epoxidation of which by various peroxy acids follows the normal route, the corresponding dimethoxy-derivative **33** reacts with trifluoroperoxyacetic or peracetic acid giving rise to the rearranged product **34**.



The addition of sodium acetate to peracetic acid makes it possible to retain some of the epoxide, whereas epoxidation by PBA gives the epoxide as the only reaction product.^{181, 182} Problems arise in those cases where the substituents at the double bond are capable of stabilising the carbocationic centre. These groups facilitate molecular rearrangements. For example, the Wagner–Meerwein rearrangement accompanies epoxidation of 2-phenylnorbornene with MCPBA^{183, 184} and 2-(*p*-anisyl)norbornene with peracetic acid even when a buffer solution has been added. Treatment of 2-phenylnorbornene with performic acid affords carbonate, due to the formation of a phenonium ion; hydrolysis of the carbonate results in the formation of *cis*-1,2-diol **35**. The latter can also be obtained from the same alkene using the Wagner method.¹⁸⁵



Nevertheless, aryl-containing epoxides were successfully obtained by using peroxybenzimidic acid as the oxidant in a weakly alkaline medium.¹⁸⁶ It was also found that *exo*- and *endo*-2,3-epoxy-2-phenylbornanes can be synthesised from the corresponding *cis*-*exo*- and *cis*-*endo*-diols.¹⁸⁵

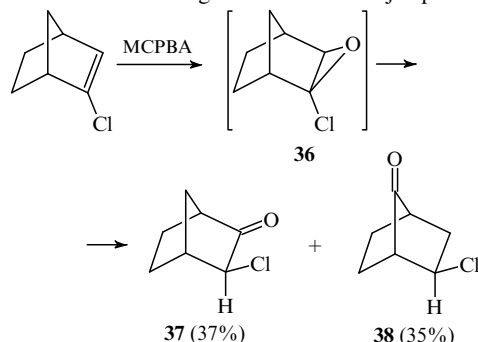


Stereoisomeric 2-methoxy-2,3-epoxynorbornanes have been prepared in a similar way.¹⁵⁸

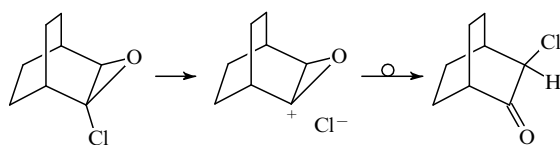
Later, diaryl-substituted oxiranes of the norbornene series have been synthesised from the corresponding diols on treatment with triphenylphosphine or other reagents.¹⁸⁷

Chlorine atoms at the double bond of norbornene exert a similar influence. Epoxidation of 2-chloro- and 2,3-dichloronorborn-2-ene by MCPBA yields extremely unstable epoxides.^{188–190}

Thus epoxide **36** decomposes at room temperature with heat evolution giving rise to a mixture of nine bicyclic compounds, ketones **37** and **38** being formed as the major products.



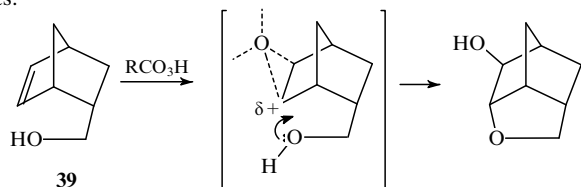
Oxidation of optically active (–)-(R)-2-chloronorbornene provided evidence indicating that the rearrangement involves a chloride shift rather than a hydride shift and that isomerisation is intramolecular. Unlike the epoxide **36**, 2,3-epoxy-2-chlorobicyclo[2.2.2]octane isomerises only at 100 °C in a sealed tube giving 3-chlorobicyclo[2.2.2]octan-2-one and no Wagner–Meerwein rearrangement products.⁷³



Aliphatic and alicyclic α -chloroepoxides behave in a similar way.

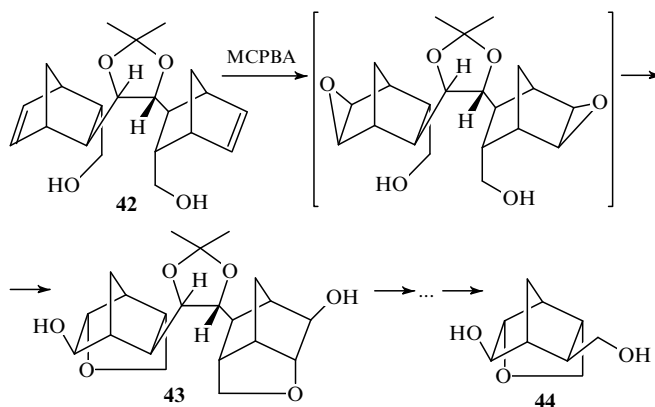
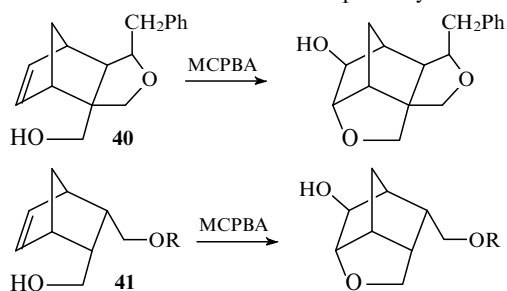
VII. Intramolecular cyclisation in reactions of substituted norbornenes with peroxy acids

Electrophilic intramolecular cyclisation of alkenes is a well-known reaction.¹⁹¹ Whereas epoxidation of acyclic alkenes is rarely accompanied by cyclisation, for substituted norbornenes reactions of this type are quite common.⁴ Nucleophilic groups, for example, a hydroxy group, present in the rear *endo*-area are often involved in epoxidation giving rise to cyclisation products.^{145, 192, 193}



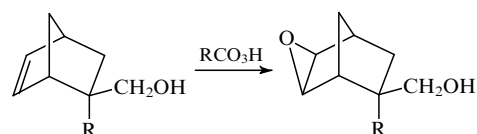
This is due to the favourable arrangement of the nucleophile in the area of antibonding π^* -molecular orbital of the epoxide ring being formed. In accordance with the Kerten–Hammett principle, the possibility of realisation of molecular conformations, convenient for the formation of activated complexes, is especially significant in this case.

It is noteworthy that alcohol **39** reacts with perbenzoic acid forty times faster than the corresponding acetate.¹⁴⁴ Oxidation of norbornenes **40–42** follows a similar pathway.^{194–197}

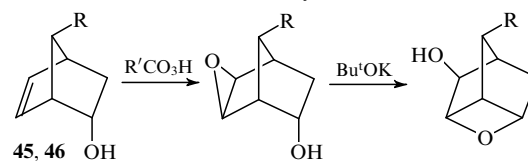


Bis-ether **43** is an intermediate in the synthesis of natural loganin **44**.¹⁹⁸

Epoxidation of *exo*-hydroxymethyl substituted stereoisomers proceeds in a traditional way.¹⁴⁵

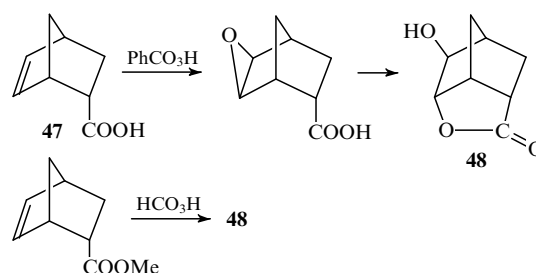


The hydroxy group in *endo*-5-hydroxynorborn-2-enes **45a,b** does not participate in cyclisation.¹⁴⁵ Shibasaki *et al.*¹⁹⁹ and, later, Holton and Kennedy²⁰⁰ have converted the alcohols **45a,b** into stable epoxy alcohols, which have been subsequently converted into various cyclised and rearranged products by treatment with potassium *tert*-butoxide in tetrahydrofuran.

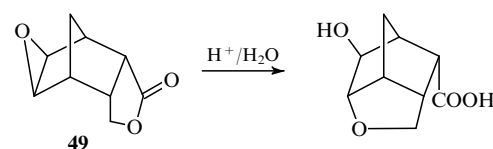


$\text{R} = \text{H}$ (**45**), OCH_2Ph (**46**).

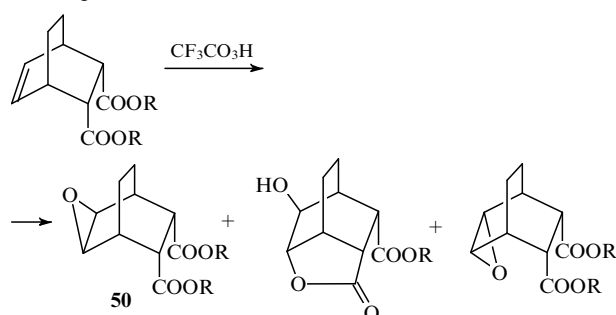
Epoxidation of acids of the norbornene series differs from that of alcohols in that in this case, the resulting epoxide intermediates are relatively stable. Thus, according to the data of IR spectroscopy, oxidation of acid **47** by perbenzoic acid yields initially an epoxy acid, which rapidly isomerises into hydroxy lactone **48**.¹⁴⁴



The lactone **48** can also be obtained from methyl 5-norbornenecarboxylate by treating it with performic acid. Treatment with other peroxy acids results in the conventional transformation of this ester into the epoxide.^{1,6} The different reactivity of hydroxymethyl and carboxyl groups towards cleavage of the oxirane fragment is reflected in the pattern of hydrolysis of epoxy lactone **49**.²⁰¹

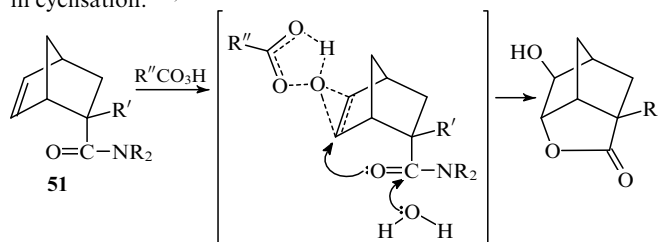


It has been shown^{142,202} that epoxidation of dicarboxylic acids of the norbornene series is accompanied by lactonisation, if at least one of the carboxyl groups occupies an *endo*-position. Unlike substituted norbornenes, *endo*-acids and esters of the bicyclo[2.2.2]octene series are converted under similar conditions into mixtures of *exo*- and *endo*-epoxides and lactones; judging from the results of a special study,¹³⁸ the latter are produced only from *exo*-epoxides **50**.



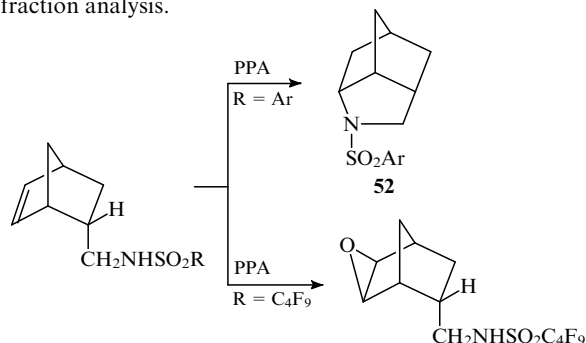
Comparison of the behaviour of the two related bicyclic systems reveals two substantial points distinguishing bicyclo[2.2.2]octenes from substituted norbornenes, namely, the absence of *exo*-stereospecificity in the attack by a peroxy acid and a decrease in the ability to form lactones. Apparently, this is due to different degrees of strain and to specific conformational features of these systems.

It has been reported that the amide group can also participate in cyclisation.^{170,171}



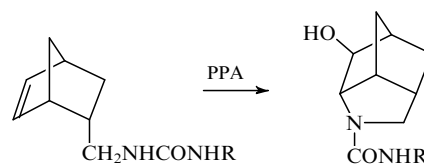
Lactonisation of *endo*-carboxamides **51** ($R = \text{Alk, Ar, H; } R' = \text{Me}_3\text{N}$) occurs apparently *via* intramolecular rear attack by the carbonyl oxygen on the electrophilic centre in the intermediate 'alkene-peroxy acid' complex or in the intermediate compound. The corresponding *exo*-stereoisomers are readily converted into epoxides.^{173,174}

The formation of similar heterocyclic derivatives containing other heteroatoms has been little studied. Formation of epoxide from unsaturated sulfone has been reported.²⁰³ The attempt to obtain nitrogen-containing products of cyclisation from norbornenedicarboxamides failed.²⁰⁴ In 1994, substituted 4-azatri-cyclo[4.2.1.0^{3,7}]nonanes **53** (azabrendanes) were prepared by treatment of *endo*-(*N*-arylsulfonyl)bicyclo[2.2.1]hept-2-en-5-ylmethylamines with peroxyphthalic acid.^{205,206} The structure of the polycyclic cage of azabrendanes was confirmed by X-ray diffraction analysis.



Later, it was shown that the decrease in the basicity of the nitrogen atom following the replacement of the arylsulfonamide

group by perfluoroalkylsulfonamide group prevents intramolecular cyclisation.²⁰⁷ However, in the case of similar reactions of *endo*-ureas, substituted azabrendanes were isolated.²⁰⁸

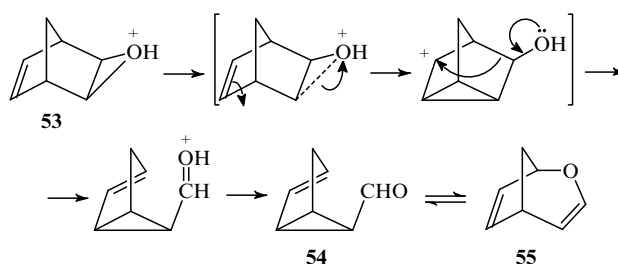


exo-Stereoisomeric derivatives readily form epoxides under similar conditions.²⁰⁵⁻²¹⁰

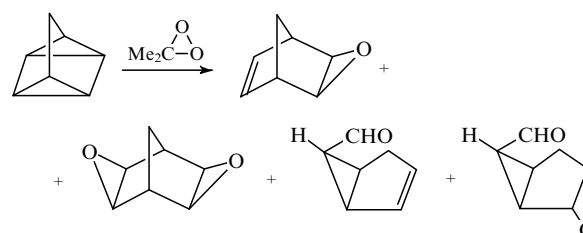
VIII. Epoxidation of diene systems incorporating norbornene or related fragments

In the case of a favourable arrangement of the double bonds in a molecule of bicyclic diene, π -bonds may be involved in epoxidation, instead of σ -bonds which normally participate in transformations of norbornene; this should increase the probability of the *endo*-attack by a peroxy acid. In fact, the products of epoxidation of norbornadiene by perbenzoic, monoperoxyphthalic, or peroxyacetimidic acid were found to contain 13% of *endo*-epoxynorbornene.²¹¹ The stereoisomeric *endo*-epoxides synthesised from 7-methylnorbornadiene are stable upon refluxing in benzene containing traces of toluene-*p*-sulfonic acid.²¹² The oxidation of 7-phenylnorbornadiene gives no *endo*-epoxide, which might be due to coordination of the peroxy acid to the electron-donating benzene ring.²¹²

However, the major product of the oxidation of norbornadiene is *exo*-2,3-epoxynorborn-5-ene; the participation of a π -bond in the transformations precludes the traditional rearrangements (Wagner-Meerwein rearrangement, hydride shifts) and results in the formation of *endo*-bicyclo[3.1.0]hex-3-ene-6-carbaldehyde **54** in equilibrium with cyclic ether **55**.^{213,214} The transformation thus discovered is referred to as the Meinwald rearrangement. The different behaviour of the stereoisomeric *exo*- and *endo*-epoxides demonstrates the importance of a favourable arrangement of the frontier orbitals for donor-acceptor interactions to occur. These $\pi-\pi^*$ interactions reflect the general type of behaviour of norbornadiene in electrophilic reactions.

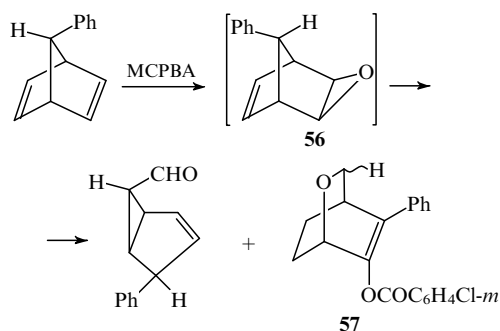


It should be noted that oxidation of norbornadiene with dimethyldioxirane yields both mono- and diepoxide;²¹⁵ the starting norbornadiene was prepared *in situ* by isomerisation of quadricyclene.

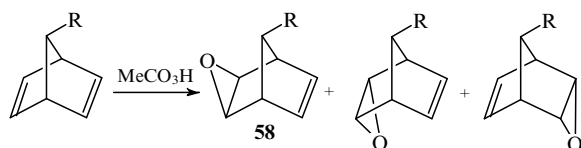


The rearrangement to bicyclic aldehydes induced by peroxy acids is also typical of *exo*-epoxides formed from 7-methyl- and 7-phenyl-norbornadiene;²¹² in the latter case, the main reaction product **56** undergoes epoxidation followed by cleavage of the

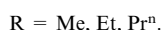
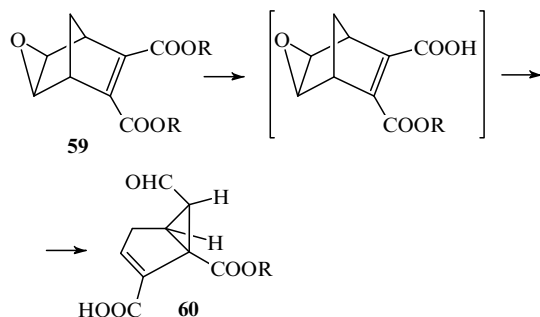
epoxide ring with rearrangement and by cyclisation being thus converted into side product **57**.



This rearrangement was used to prepare an intermediate compound in the synthesis of prostaglandins. Thus *exo*-epoxide **58** resulting from oxidation of 7-alkenylnorbornadiene (80%) was used in subsequent transformations.²¹⁶

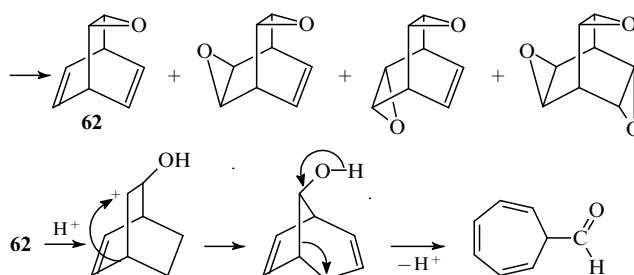
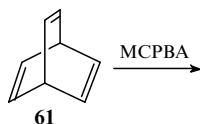


Apart from the labile epoxides with alkyl substituents described above, their quite stable analogues **59** with electron-withdrawing alkoxy-carbonyl groups at the double bond are also known.²¹⁷ However, acid esters prepared *in situ* by enzymic hydrolysis of symmetrical diesters immediately undergo the Meinwald rearrangement giving bicyclo[3.1.0]hex-2-ene derivatives **60** in nearly quantitative yields.²¹⁷

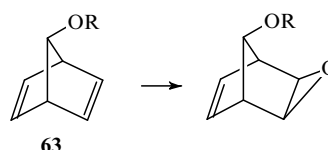


The stability of the epoxides can be increased by introducing additional electron-withdrawing fragments. In fact, the 7-oxa-analogue of the epoxide **59** was prepared in a quantitative yield and used successfully in the synthesis of the nucleoside antibiotic cordycepin.²¹⁸

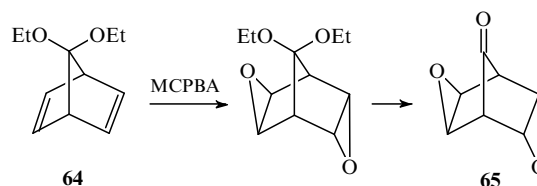
As opposed to norbornadienes, the less strained bicyclo[2.2.2]octadiene, on treatment with perbenzoic acid, adds only one equivalent of the acid, the addition occurring from the less shielded *endo*-side, which is richer in electrons.²¹⁹ When an excess of the peroxy acid was used, stable diepoxide was obtained. Based on barrelene **61**, mono-, di-, and tri-epoxides have been obtained.²²⁰ They can be isolated but are easily transformed in acidic media. Thus monoepoxide **62** is easily converted into cycloheptatriene-7-carbaldehyde.²²⁰



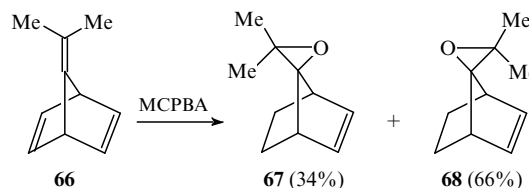
Oxidation of 7-alkoxynorbornadienes **63** occurs through *exo*-attack by a peroxy acid. Even in the case of 7-*tert*-butoxy-substituted derivative, despite the obvious steric hindrance, the reaction involves the *syn*-double bond.¹²²



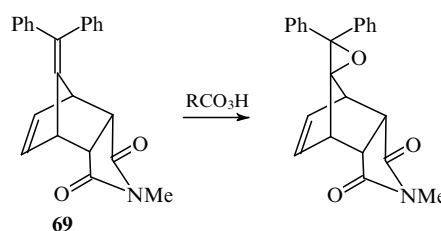
However, a study has been published, which casts doubt upon the amazing electronic influence of the *tert*-butoxy group.²²¹ In fact, it was found that in the case of 7,7-diethoxynorbornadiene **64**, both multiple bonds undergo epoxidation. The structure of diepoxide **65** was reliably confirmed by NMR spectroscopy; however, the order of introduction of the epoxide fragments has not been studied in this work.²²²

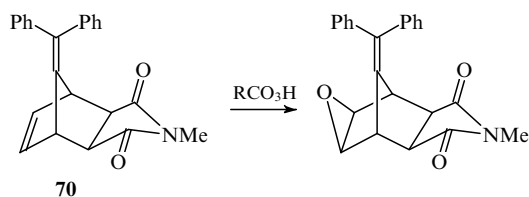


In recent years, considerable attention has been devoted to epoxidation of dienes of the norbornene series containing exocyclic double bonds. It was shown that treatment of 7-isopropylidenenorbornene **66** with an equimolar amount of MCPBA results in selective epoxidation of the exocyclic double bond, the ratio of products **67** and **68** being equal to 34:66, due to the preferential *anti*-attack.^{139, 223}

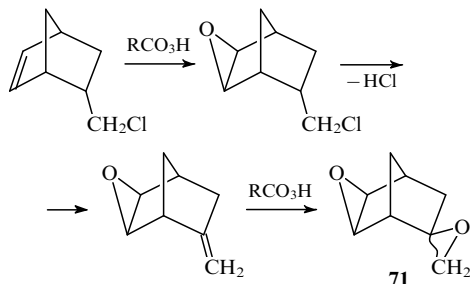


A similar picture has also been observed for 9-isopropylidenebenzonorbornenes; the introduction of chlorine or fluorine atoms into the aromatic ring facilitates formation of the *syn*-product. Epoxidation of stereoisomeric 7,7-diphenylmethylene-*N*-methylnorbornene-2,3-dicarboximides **69** and **70** demonstrated that the stereochemistry of the dicarboximide group has crucial influence on the direction of the process.²²⁴

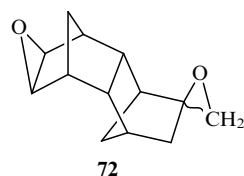




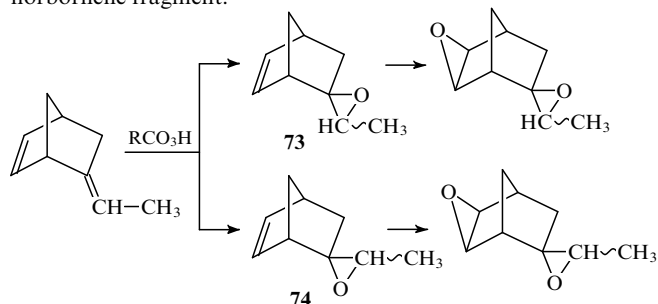
Epoxidation of 5-chloromethylnorborn-2-ene to give diepoxide **71** is described in a patent.²²⁵



Later, the product **71** and its tetracyclic analogue **72** were obtained from the adducts of cyclopentadiene with allyl chloride (or bromide).²²⁶



In recent years, particular attention has been devoted to epoxidation of available vinyl- and ethylenenorbornenes and the dimer of cyclopentadiene. Vinyl- and ethylenenorbornenes have been oxidised by peracetic, peroxyphthalic, *m*-chloro- and *p*-nitro-peroxybenzoic, and peroxyimide acids. Earlier, it has been noted that vinylnorbornene can be oxidised to give the monoepoxide by oxygen in the presence of nitropalladium complexes.^{126, 227, 228} When ethylenenorbornene is epoxidised by peracetic acid, the ratio of the products of oxidation at the endo- and exo-cyclic double bonds, found by ¹H NMR spectroscopy, is equal to 1 : 6.²²⁸ When equimolar amounts of the reactants are used, the reaction yields monoepoxides **73** and **74** incorporating a norbornene fragment.²²⁷

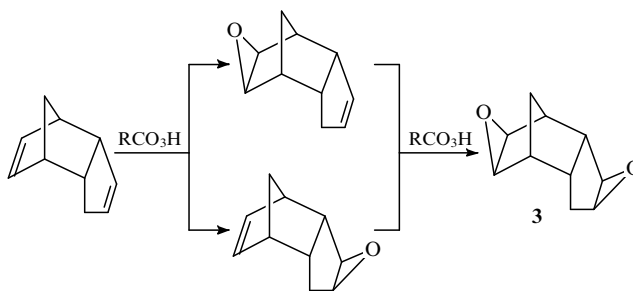


The monoepoxide **73** obtained using peroxyphthalic acid isomerises to give *endo*-5-acetylbicyclo[2.2.1]hept-2-ene. The different behaviour of the isomers is indicated by the fact that reactions of the diene with the above peroxy acids result in different ratios of the monoepoxides. Further epoxidation of the monoepoxides **73** and **74** affords stereoisomeric diepoxides.²²⁷

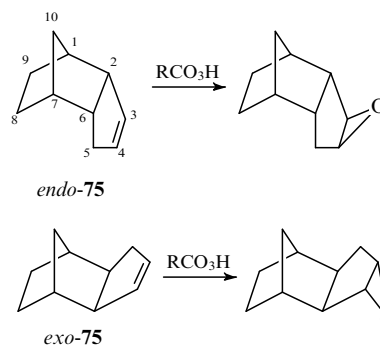
As the double bond moves away from the norbornene fragment, their mutual influence becomes less significant and the double bond in the ring becomes more reactive. Voronenkov *et al.*²²⁹ found that the logarithms of the rate constants for epoxidation are correlated with the first vertical ionisation potentials for a broad range of dienes of this type.

Numerous studies have been devoted to epoxidation of the cyclopentadiene dimer (CPDD) containing double bonds in the norbornene fragment and in the five-membered ring. The interest aroused by this object is due both to its accessibility and to the valuable properties of various polymeric materials based on epoxide derivatives of CPDD.²³⁰ Oxidation is usually carried out by peracetic,^{231, 232} peroxyphthalic,^{230, 233–235} and monoperoxy-maleic^{236, 237} acids (both free peroxy acids and those obtained *in situ* from the corresponding anhydrides and hydrogen peroxide have been used).^{233, 236}

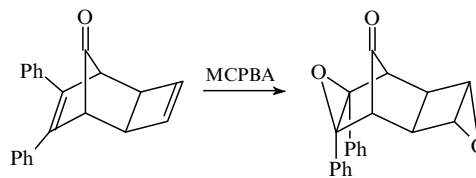
The high sensitivity of the norbornene system in the transition state to steric effects results in that, of the four possible stereoisomers, only one product **3**, characterised by the *exo*-arrangement of both epoxide fragments, is produced. When the oxidant is in deficit, a mixture of monoepoxides is formed, the substituted epoxynorbornane being the major product.^{238, 239} The ratio of the monoepoxides depends substantially on the oxidant used.⁶⁴



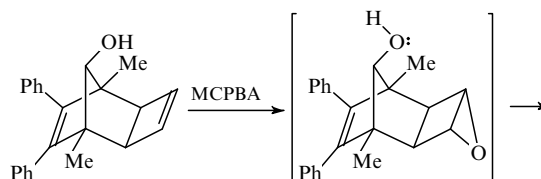
It is of interest that during epoxidation of *endo*-tricyclo[5.2.1.0^{2,6}]dec-3-ene **75**, the attack occurs from the side of the methylene bridge, whereas the *exo*-isomer is attacked from the opposite side.

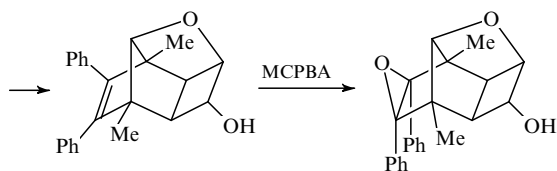


An attack by a peroxy acid from the *endo*-area has also been observed for polycyclic systems with a cyclobutene fragment.²⁴⁰

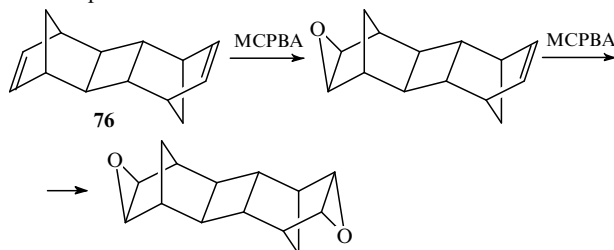


The oxidation of the corresponding alcohol occurs chemoselectively only at the cyclobutene fragment and is accompanied by intramolecular cyclisation.

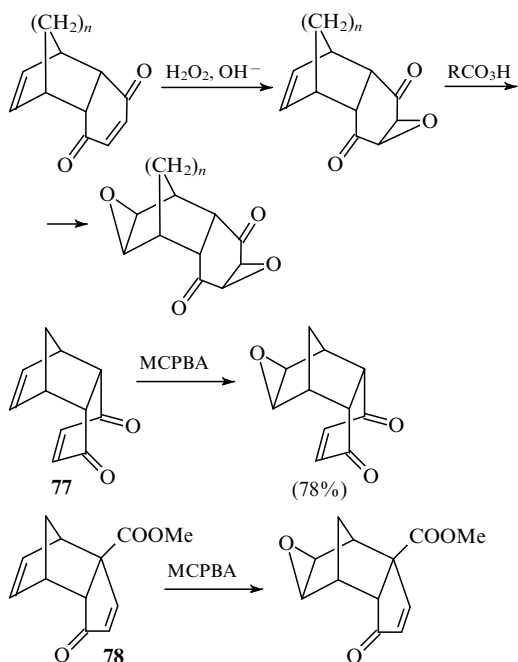




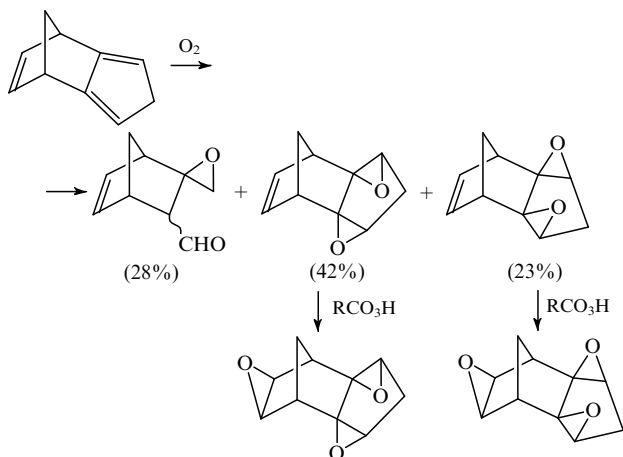
Mono- and di-epoxidation of the norbornadiene dimer **76** has been accomplished.¹²⁹



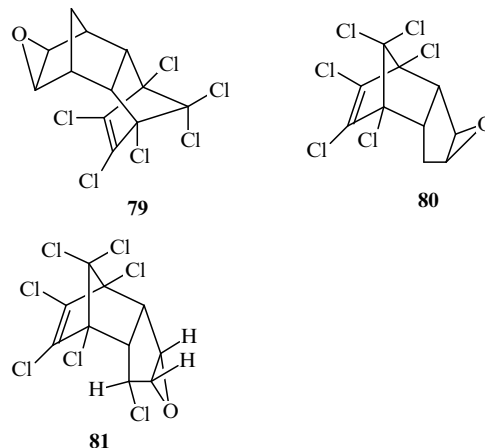
The double bonds can be epoxidised successively or selectively; in particular, this occurs for the adducts of cyclic dienes with benzoquinone and their analogues ($n = 1, 2$).²⁴¹



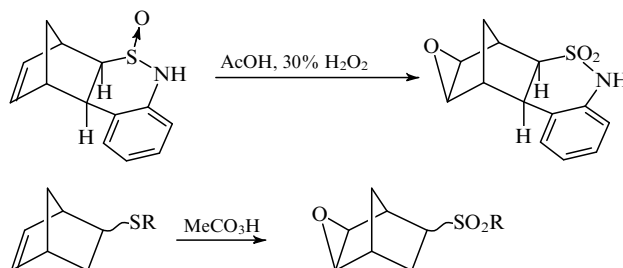
The first stage of interaction of the diene **77** with peroxy acids is complicated by side processes,²⁴² whereas electrophilic epoxidation of the diene **78** occurs smoothly.²⁴³ Consecutive oxidation of a triene system has been described.²⁴⁴



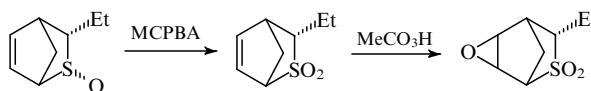
Electron-withdrawing substituents decrease the nucleophilicity of the double bond in the bicycloheptane fragment of the norbornene and cyclopentadiene dimers; this results in selective epoxidation of the double bonds in the diene fragment. The syntheses of dieldrin (**79**), endrin (**80**), and other epoxides can serve as typical examples.^{194, 245, 246} In the case of heptachloro-derivative **81**, the oxirane fragment is *endo*-oriented.²⁴⁷



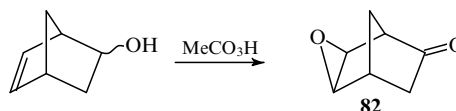
Of special interest are non-chemoselective reactions in which other fragments of the molecule are oxidised in parallel with the double bond.^{248–250}



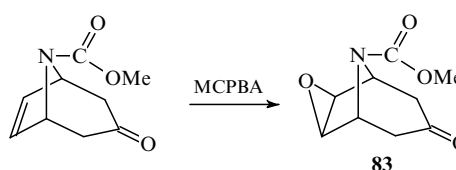
However, by choosing appropriate peroxy acids and reaction conditions, one can attain a high degree of selectivity of the oxidation.²⁵¹



It should be noted that the epoxide **82** prepared from hydroxynorbornene cannot be obtained by epoxidation of the corresponding unsaturated ketone, because the double bond is deactivated by the electron-withdrawing carbonyl group, and the latter is selectively attacked by the peroxy acid.²⁵²



When the carbonyl group is located far from the double bond, stable epoxy ketones can be prepared, in particular, ketone **83**, which is a precursor of alkaloids of the tropane series.¹⁵¹



In most cases, epoxidation of ketones and alcohols is carried out with protected carbonyl or hydroxy groups, because the

epoxide derivatives of substituted norbornenes are especially unstable in the presence of acids.^{218, 251}

IX. Conclusion

In this review, the known methods for epoxidation of substituted norbornenes and dienes incorporating a norbornene fragment are described and diverse transformations accompanying epoxidation, in particular, molecular rearrangements, which often end with the formation of new heterocyclic systems, are considered. The information presented here demonstrates that norbornene and its derivatives occupy a special place in the chemistry of epoxidation of cycloalkenes. This is due to special structural features and to the strained character of the carbon cage, which predetermines the possibility of chemo- and stereoselective transformations during the oxidation of these compounds.

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Haloalkenes activated by geminal groups in reactions with N-nucleophiles

A Yu Rulev

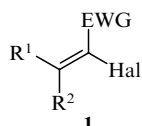
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Abstract. Reactions of nitrogen nucleophiles with haloalkenes in which the halogen atom occupies α -position with respect to an electron-withdrawing group are considered. Primary attention is devoted to the elucidation of the dependence of the reaction path on the nature of the nucleophile and substrate and on the reaction conditions. Possible mechanisms of nucleophilic substitution of vinylic halogen atoms in alkenes with activating and leaving groups attached to the same carbon atom are discussed. The bibliography includes 169 references.

I. Introduction

Modern strategy of organic synthesis is based on the use of polyfunctional but relatively simple building blocks in chemo-, regio-, and stereo-selective syntheses of complex molecules. In recent years, the methodologies of tandem and domino transformations have been actively developed. This makes it possible to minimise the number of synthetic steps, the expense, and the amount of wastes and to accelerate as much as possible the advance to the target objects.^{1,2} In the design of diverse complicated molecules, it is useful to proceed from compounds with so-called 'compositional functional groups'.³ Thus 'symbiosis' of a carbonyl (or cryptocarbonyl) group and a halogen atom at the α -carbon atom in a substrate not only activates each functional group but also opens up new prospects for the use of such substrates in synthesis.^{4,5} This type of compound is represented, for example, by haloalkenes **1** containing a geminal electron-withdrawing group (EWG). These derivatives are often used as the initial compounds in the syntheses of amino acid derivatives, various biologically important nitrogen-containing heterocycles, and analogues of natural compounds.



EWG = CN, COOR, C(O)R.

A Yu Rulev Irkutsk Institute of Chemistry, Siberian Branch of the Russian Academy of Sciences, ul. Favorskogo 1, 664033 Irkutsk, Russian Federation. Fax (7-395) 235 60 46. Tel. (7-395) 246 06 85

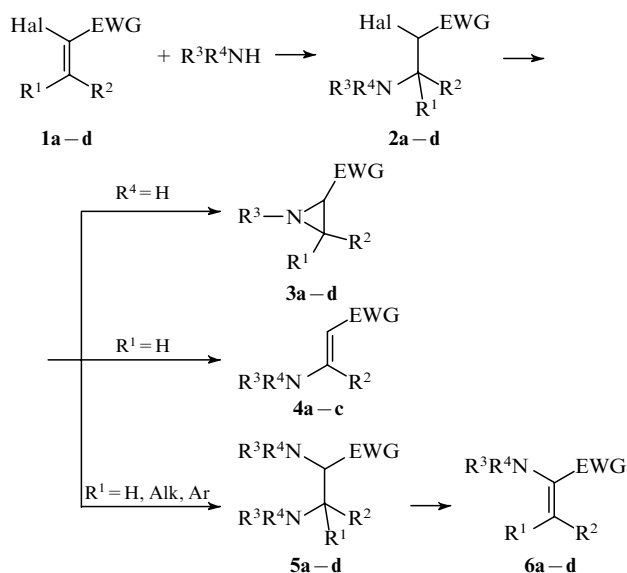
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The studies on reactions of haloalkenes activated by a geminal group with nitrogen-containing nucleophiles (referred to below as N-nucleophiles) began apparently in 1904, when Watson⁶ discovered the ability of piperidine to react with bromo(benzyl-idene)acetophenone yielding mono- and di-amino-derivatives. Further progress in this field appears to be a series of trials and errors, findings and delusions as follows from subsequent critical analyses of the early publications.^{7–9}

In this review, we attempt to trace the general regularities of the reactions of the haloalkenes **1** activated by geminal substitution with N-nucleophiles, which were mainly reported during the last 15 years.

In most cases, interaction of the haloalkenes **1** with N-nucleophiles can be represented by the following simplified scheme:



Hal = Cl, Br; EWG = CN (a), COOR (b), C(O)R (c), CHO (d).

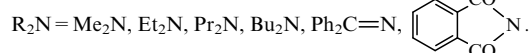
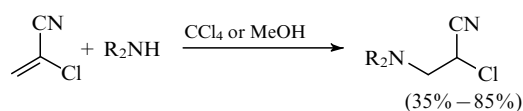
The reaction products include Michael adducts **2**, substituted aziridines **3**, aminoalkenes with a vicinal (**4**) or geminal (**6**) activating group, and α,β -diamino-derivatives **5**. Other routes of transformations involving the activating group or the functional groups in the substituent are also possible. Even slight changes in the structure of the initial substrate or in the nature of the nitrogen-containing nucleophile, variation of the temperature, the solvent, the molar ratio and the order of mixing of the

reactants, *etc.* often result in the formation of absolutely different reaction products. Despite certain difficulties of prediction, some general rules governing the reactivity of the haloalkenes **1** in reactions with N-nucleophiles have been discovered. Thus the nature of the activating EWG is a crucial factor in all the cases considered. Analysis of the published data makes it possible to claim that the reactivity of the haloalkenes **1** with geminal substitution increases with increase in the electron-withdrawing properties of the EWG. In terms of their activating capacity, these groups can be arranged in the sequence $\text{CN} \leq \text{COOR} < < \text{C(O)R} < \text{CHO}$,¹⁰ which shows a good correlation with the activity series of unsaturated compounds of the $\text{CH}_2 = \text{CH} - \text{EWG}$ type in the Michael reaction with amines.¹¹

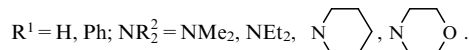
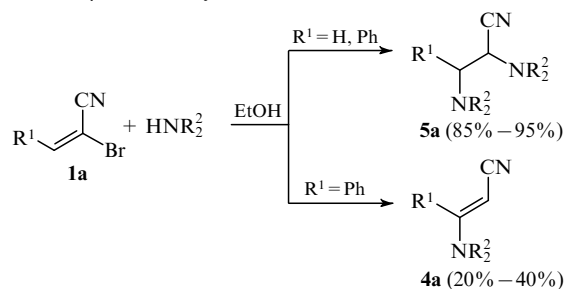
II. Reactions of haloalkenes activated by geminal groups with N-nucleophiles

1. Haloalkenes activated by a cyano group

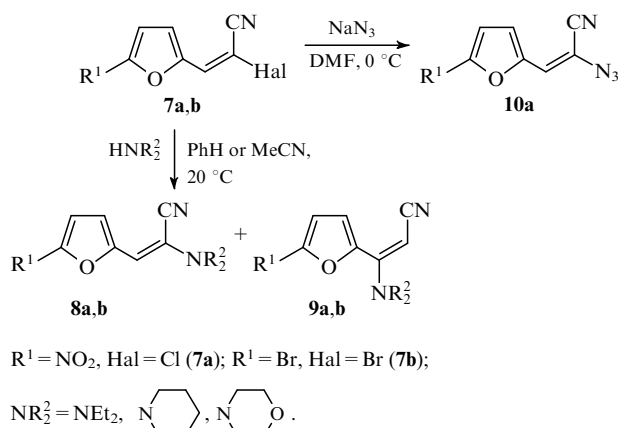
As should be expected, haloalkenes **1a** with a *gem*-cyano group enter into the Michael reaction with secondary amines yielding initially β -amino- α -halo-derivatives **2a**. The chloro-derivatives have been isolated in a pure state.¹² Secondary amines and phthalimide add to α -chloroacrylonitrile on refluxing in methanol.¹³ The addition of diphenylmethyldeneamine to the same substrate occurs under mild conditions and gives no side products.¹⁴



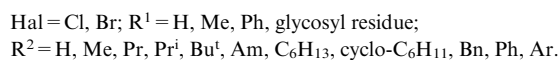
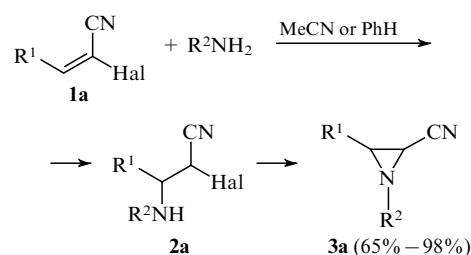
The replacement of chlorine in the initial nitrile by bromine decreases the stability of the Michael adducts to such an extent that the corresponding β -amino- α -bromo-derivative **2a** cannot be even detected. In this case, the addition of amine is accompanied either by substitution of the halogen atom giving α,β -diamino-derivative **5a** or by elimination of hydrogen bromide giving rise to substituted β -aminoacrylonitriles **4a**.¹⁵



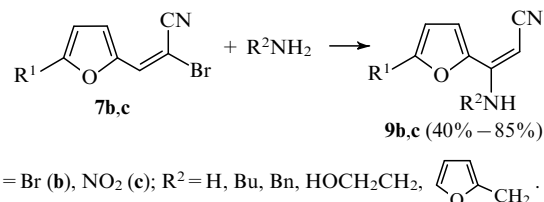
The use of sterically hindered amines (benzimidazole, 1,2,4-triazole) or substrates containing bulky substituents at the β -position usually results in the formation of β -aminoacrylonitriles **4a** as the only^{16–18} or predominant^{19,20} products. However, there are some exceptions. For example, treatment of furylhaloacrylonitriles **7a,b** with secondary amines (piperidine, morpholine, diethylamine) yields mixtures of α -amino- (**8a,b**) and β -amino- (**9a,b**) derivatives,^{19,20} whereas treatment with azides affords α -substituted acrylonitriles **10a** as the only products.²¹



Reactions of the cyanoalkenes **1a** with primary amines generally occur according to the scheme given above. However, in this case, there is a possibility of intramolecular cyclisation of the products **2a** to the corresponding aziridines. In fact, primary aliphatic and aromatic amines and even ammonia readily react with α -haloacrylonitriles **1a** to give aziridines **3a** in high yields.^{22–26} The stereochemistry and the mechanism of the addition have been studied.^{22,26}



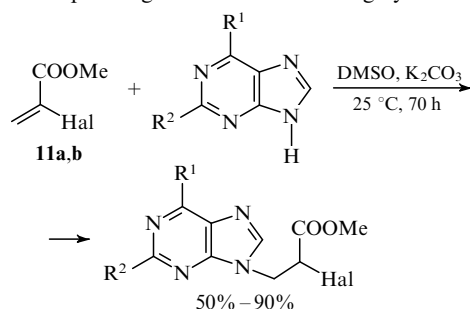
The fact that the aziridine derivatives **3a** are actually formed *via* the Michael adduct **2a** was proved by detecting the latter by spectroscopy²² and by isolating it as a salt.²⁷ However, some examples have been reported in which the expected aziridines were not formed, and the adduct **2a** either remained unchanged^{13,28} or was converted upon dehydrohalogenation into 3-aminoacrylonitrile of type **4a** with a secondary amino group. This rare situation is realised, for example, for the nitriles **7b,c**, which react with primary amines giving only β -aminoacrylonitriles **9b,c** in good yields.²⁹



2. Haloalkenes activated by an ester group

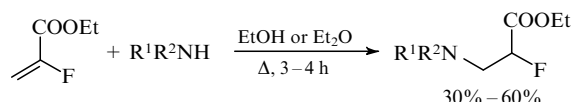
Similar transformations have been observed in the series of haloalkenes **1b** activated by a geminal ester group. A distinctive feature of this type of reaction is that in some cases, the activating group also reacts with amines. As in the series of α -haloacrylonitriles **1a**, the outcome of the reaction depends on the nature of the amine, the structure of the substrate (the presence of substituents, the nature of the halogen), and the experimental conditions.

The use of bulky or weakly basic nucleophiles as well as very active Michael acceptors leads to termination of the reaction at the initial stage, when the products of the addition at the double bond have been formed. For example, the reaction of purine bases with methyl α -chloroacrylate (**11a**) or α -bromoacrylate (**11b**) affords the corresponding Michael adduct in high yield.³⁰



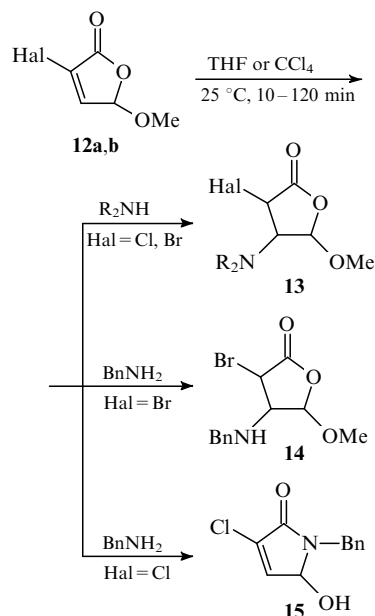
Hal = Cl (**a**), Br (**b**); R¹ = NH₂, R² = H; R¹ = Cl, R² = H; R¹ = R² = Cl.

A similar situation is observed when haloacrylates containing weakly nucleofugal fluorine are used. The suggestion³¹ that the ester group in α -fluoroacrylates might undergo ammonolysis by secondary and primary amines and by ammonia proved to be faulty. The attack by the N-nucleophile is directed at the β -carbon atom of the double bond and results in the formation of esters of *N*-mono- or *N,N*-di-substituted α -fluoro- β -alanine.³² No amides have been found among the reaction products.



R¹, R² = (CH₂)₅, (CH₂)₂; R¹ = R² = Et; R¹ = cyclo-C₆H₁₁, R² = H.

A mixture of diastereomeric products of conjugated addition **13** was obtained upon the interaction between equimolar amounts of a secondary amine and 3-chloro(or bromo)-5-methoxy-5*H*-furan-2-one (**12a,b**). In this case, the attack by the nucleophile occurs mostly from the side opposite to the methoxy group.³³



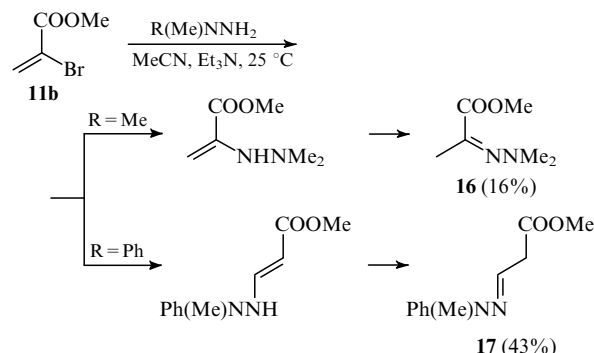
R₂N = N, N, Et₂N.

Primary amines and ammonia readily react with α -haloacrylates **1b** normally yielding the corresponding aziridines of type **3b**.^{34–38} The formation of the addition products was detected by

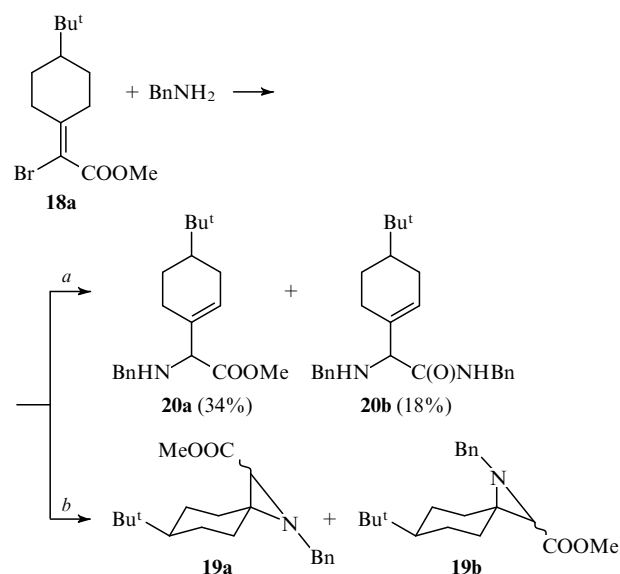
NMR spectroscopy,³³ and in the case of α -haloacrylic acids, the adducts were isolated as salts.³⁹

It should be emphasised that the structures of the substrate and the nucleophile as well as experimental conditions influence the reaction pathway so strongly that even slight variations often have fundamentally significant consequences. Thus replacement of bromine by chlorine in bromofuranone **12b** changes the direction of the nucleophilic attack: the reaction of 3-chloro-5-methoxy-5*H*-furan-2-one **12a** with benzylamine yields unexpectedly pyrrolinone **15** rather than the Michael type adduct **14** as the major product.³³

Methyl α -bromoacrylate prepared from methyl α,β -dibromopropionate reacts with 1,1-disubstituted hydrazines to give hydrazones **16** or **17** depending on the basicity of the N-nucleophile.⁴⁰



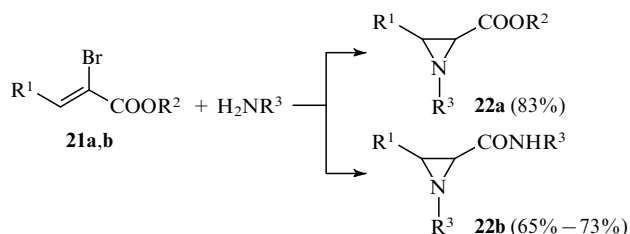
The influence of the experimental conditions on the reaction of α -haloacrylates with N-nucleophiles is clearly illustrated by the reaction of methyl bromo(4-*tert*-butylcyclohexylidene)acetate **18a** with benzylamine. At room temperature and atmospheric pressure, isomeric spiroheterocyclic compounds **19a,b** are formed as the only reaction products (yield 83%–85%). High pressure markedly increases both the rate and stereoselectivity of the reaction: the ratio of diastereomers with equatorial (**19a**) and axial (**19b**) orientation of the nitrogen atom ranges from 1.7:1 under ordinary pressure to 10:1 at 11 kbar. Refluxing a methanolic solution of the ester **18a** with two equivalents of benzylamine gives rise to a mixture of α -amino ester **20a** and the corresponding amide **20b**.^{36–38}



(a) MeOH, Δ , 18 days; (b) MeOH, 11 kbar, 25 °C, 4 days.

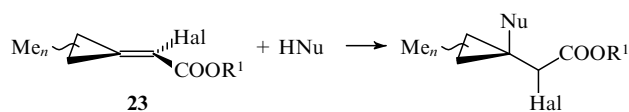
Aziridine derivatives can be easily obtained by reaction of primary amines with α -halo α,β -unsaturated esters.^{41–43} The ratio of *cis*- and *trans*-aziridines depends substantially on the solvent used. For example, the reaction of methyl α -bromocinna-

mate **21a** with primary amines in methanol yields *cis*-**22a** as the main product, whereas in benzene, the proportion of the corresponding *trans*-isomer increases to 45%.^{41,42} In the case of substrates **21b** containing a fluoroalkyl group at the β -position, closure of the aziridine ring is accompanied by amidation giving rise to compounds **22b**. This result has been attributed⁴³ to the influence of the electron-withdrawing polyfluoroalkyl substituent, which considerably enhances the reactivity of the ester group.



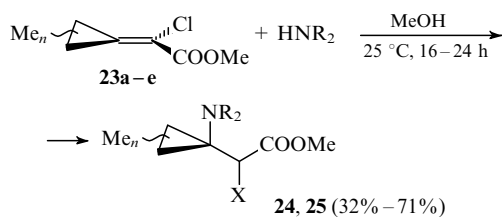
$R^1 = \text{Ph}$, $R^2 = \text{Me}$ (**a**); $R^1 = \text{CF}_3$, CHF_2CF_2 ; $R^2 = \text{Et}$ (**b**);
 $R^3 = \text{Me}$, C_6H_{13} , Bn .

Interesting results along this line have been obtained by de Meijere *et al.*^{44–46} As models, these researchers chose 2-halo-cyclopropylideneacetates **23**, which are highly reactive Michael acceptors. The higher reactivity of these compounds compared to other 3,3-disubstituted acrylates has been rationalised^{3,45,47} by the fact that the formation of the Michael adduct relieves the overall strain of the system, because during this reaction the *sp* hybridised carbon atom in the ring goes into the *sp*² hybridisation state. In fact, esters **23** easily add one equivalent of an N-nucleophile giving rise to 1'-substituted 2-chloro(or bromo)-2-cyclopropylacetates usually in good yields and with no side products.^{14,47–50}



$n = 0–4$; $\text{Hal} = \text{Cl}$; $R^1 = \text{Me}$, Bn , Bu^t ; $\text{Hal} = \text{Br}$; $R^1 = \text{Me}$;
 $\text{HNu} = \text{NH}_2\text{R}^2$, HNR_2^2 , HNAC_2 , $\text{HN}=\text{CPh}_2$, $\text{HN}=\text{CAR}_2$,
 $\text{HN}=\text{C(R)Ar}$, phthalimide.

However, in the case of primary amines, smooth addition to the substrates **23** is often accompanied by secondary reactions involving the chloromethine or alkoxy-carbonyl group. Acetamide and phthalimide, which are less nucleophilic, either do not react at all or give Michael adducts in low yields.⁴⁷ The best results were obtained in the reactions of chloro-substituted esters **23** with highly basic secondary amines and with diphenylmethyldeneamine in methanol. Aprotic and less polar solvents (DMF, Et_2O , CH_2Cl_2) markedly decreased the rate of addition.¹⁴ The halogen atoms in the Michael adducts tend to be substituted by other nucleophiles including amines. Thus the reaction of methyl chloro(cyclopropylidene)acetates **23a–e** with a five- or seven-fold excess of secondary amines leads to addition–substitution products **25** in good isolated yields.⁵¹

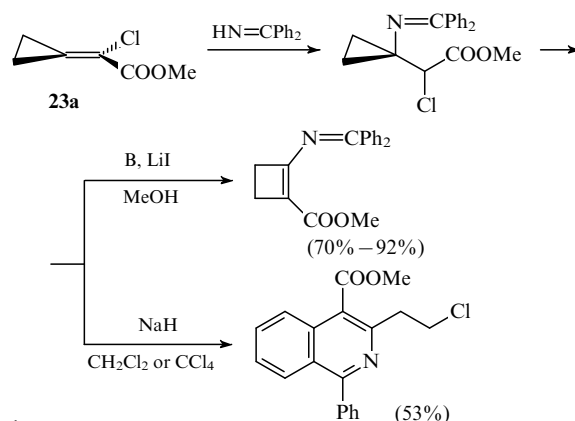


$n = 0$ (**23a**), 1 (**23b**), 2 (**23c**), 3 (**23d**), 4 (**23e**);
 $\text{X} = \text{OMe}$ (**24**), NR_2 (**25**); $\text{NR}_2 = \text{NMe}_2$, NEt_2 , N (cyclohexyl).

The outcome of the reactions of the esters **23a–e** with diethylamine, which is the bulkiest among the nucleophiles used, depends on the number of substituents in the cyclopropane ring of the

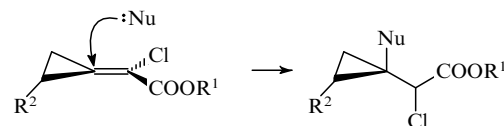
substrate. Tetramethyl-substituted chloro(cyclopropylidene)-acetate **23e** does not react with diethylamine even on prolonged refluxing (24 h, 70 °C). The substrate **23d** with three methyl groups in the ring is converted into **24** ($R = \text{Et}$). The formation of this product was rationalised by assuming the initial addition of diethylamine followed by substitution of the chlorine atom by methanol. The reaction of the dimethyl derivative **23c** with diethylamine under the same conditions affords two products, **24** and **25**. Finally, methyl chloro(cyclopropylidene)acetate **23a** with a non-substituted ring reacts with diethylamine giving rise to the Michael adduct and diamino ester **25** ($n = 0$, $R = \text{Et}$).

Methyl chloro(cyclopropylidene)acetate **23a** readily adds diphenylmethyldeneamine to give the corresponding adduct in 98% yield. Under certain conditions, the latter undergoes intramolecular substitution of chlorine and subsequent rearrangement being thus converted into β -aminocyclobutenecarboxylate or an isoquinoline derivative.^{52–54}



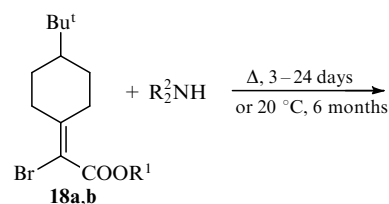
B is base.

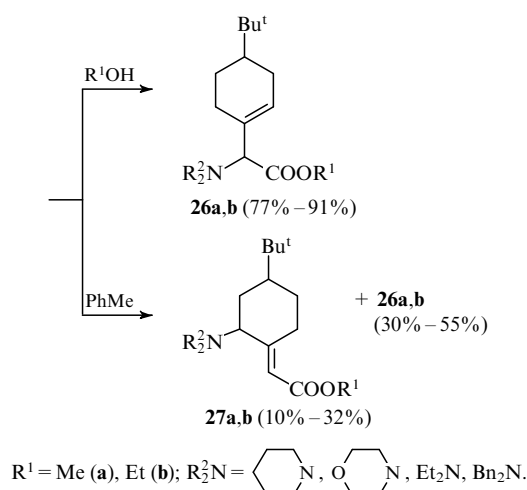
The addition of N-nucleophiles to the double bonds of the compounds **23** or their analogues containing substituents other than methyl is usually highly diastereoselective. The nucleophilic attack occurs at the *trans*-position in relation to the bulkiest substituent in the cyclopropane ring.^{51,55,56}



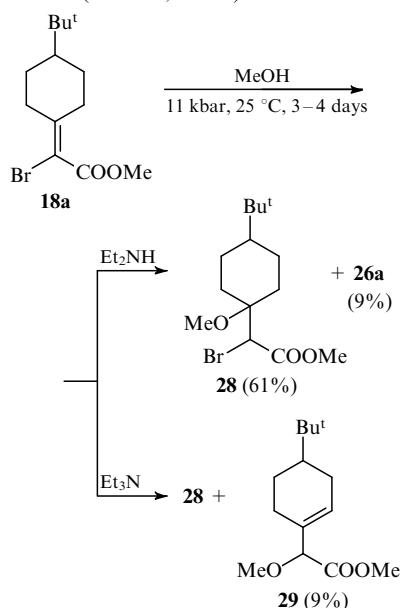
$R^1 = \text{Me}$, Bn ; $R^2 = \text{Me}$, Et , CH_2OMe , CH_2OBn , SMe .

On passing from the chloro(or bromo)(cyclopropylidene)acetates **23** to alkyl bromo(cyclohexylidene)acetates **18a,b**, the reaction route changes sharply. Thus prolonged (3–24 days) refluxing of methyl (**18a**) or ethyl (**18b**) bromo(4-*tert*-butylcyclohexylidene)acetate with acyclic or heterocyclic secondary amines affords either one product of bromine substitution or a mixture of two products, depending on the solvent used. When the reaction is carried out in the corresponding alcohol (methanol or ethanol), methyl or ethyl amino(4-*tert*-butylcyclohex-1-enyl)acetate **26a,b** is formed as the only product in a good yield. Conversely, the reaction in toluene always yields a mixture of the amino ester **26a,b** and its isomer **27a,b**.³⁸ No Michael adduct of type **2b** or product of halogen *ipso*-substitution like **6b** was detected. Sterically hindered secondary amines (for example, 2,2,6,6-tetramethylpiperidine) do not react with the esters **18a,b**.

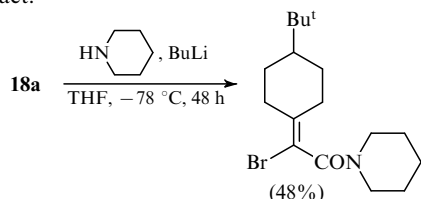




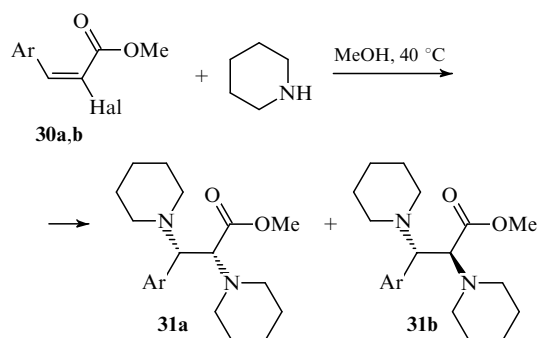
The reaction of amines with the same substrate **18a** at elevated pressures leads to absolutely different results.^{37, 38} In this case, the solvent (methanol) acts as a reactant, and adduct **28** is formed in 60%–70% yield together with a small (up to 9%) amount of the amino ester **26a** ($\text{R}^2 = \text{Et}$) or compound **29** (for reactions in the presence of di- and triethylamine, respectively). It is noteworthy that, as in the case of benzylamine, the nucleophilic attack of methanol results in predominant (up to 90%) formation of the isomer of **28** in which the methoxy group is equatorial. In the absence of amines or when dichloromethane is used as the solvent, the initial substrate **18a** remains unchanged under the same conditions (11 kbar, 25 °C).



Finally, the reaction of lithium piperidide with **18a** involves unexpectedly only the ester group, which is converted into an amide group. The double bond and the halogen atom remain intact.



The reaction of piperidine with methyl 3-aryl-2-haloacrylates **30a,b** occurs according to the classical addition–substitution pattern and yields a mixture of isomeric 2,3-dipiperidino-derivatives **31a** and **31b**, the *threo*-isomers **31b** being the predominant products.⁵⁷



$\text{Hal} = \text{Cl (a), Br (b)}; \text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, \text{4-BrC}_6\text{H}_4, \text{4-ClC}_6\text{H}_4, \text{4-O}_2\text{NC}_6\text{H}_4.$

Kinetic studies showed⁵⁷ that the rate of this reaction depends on the nature of substituent in the benzene ring, configuration of the alkene, and the nature of the halogen. For example, methyl (*E*)-2-bromo-3-phenylacrylate **30b** ($\text{Ar} = \text{Ph}$) reacts at 40 °C with piperidine 1200 times faster than the corresponding *Z*-isomer. Replacement of bromine in the substrate **30b** ($\text{Ar} = \text{4-O}_2\text{NC}_6\text{H}_4$) by chlorine decreases the reaction rate constant by a factor of ~6. Based on the kinetic measurements, it was concluded⁵⁷ that the nucleophilic attack at the β -carbon atom of the alkenes **30a,b** is the rate-determining step of the process.

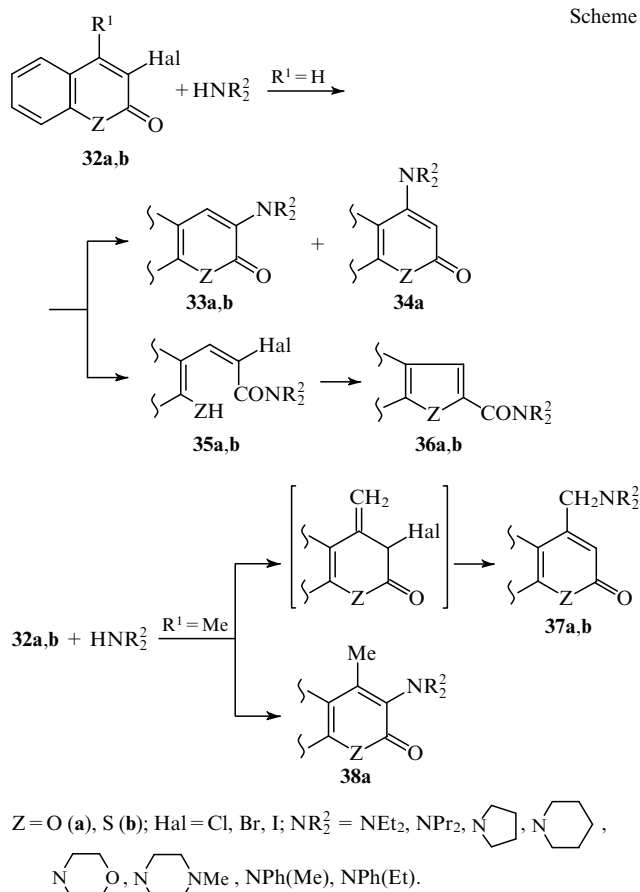
A large series of studies^{58–68} have been devoted to 3-halocoumarins **32a** and 3-halothiocoumarins **32b**, which can be regarded as cyclic esters. The discussion about the routes for their transformation induced by N-nucleophiles is still being continued. In principle, nucleophilic attack can be directed at any of the three electrophilic centres — at positions 2, 3, or 4.

In fact, the interaction of highly basic amines with 3-halocoumarins **32a** containing a hydrogen atom at the 4-position ($\text{R}^1 = \text{H}$) gives rise to complex mixtures of products (Scheme 1) in which the *ipso*- and *syn*-substitution products **33a** and **34a** are the major components.^{58, 59, 67} However, in some cases, the reaction is accompanied by pyrone ring contraction and yields benzofuran derivatives **36a**.^{60, 63} In the series of thio-derivatives **32b**, benzo-thiophene **36b** is, as a rule, the only reaction product.^{62, 63}

It is quite probable that the ring contraction reaction follows a domino transformation pattern. First, the ring is cleaved giving amides **35a,b**, which can be isolated in some cases.^{60, 64} The resulting hydroxy (or thiol) group participates in the substitution of bromine, and this gives furan (**36a**) or thiophene (**36b**) derivatives. The driving force of these transformations is the creation of an aromatic system. This pathway is realised more easily in the case of thio-derivatives **32b** owing to the higher nucleophilicity of the thiol group in the intermediate amide **35b**.^{62, 63}

The transformation of halo-coumarins **32a** and -thiocoumarins **32b** containing a methyl group at the 4-position includes initial 1,3-shift of the methyl proton. The subsequent substitution of the allylic halogen yields either the corresponding aminomethyl derivatives **37a,b**⁶⁵ or their mixtures with the products of nucleophilic vinylic substitution **38a**,^{66–68} depending on the nature of the amine.

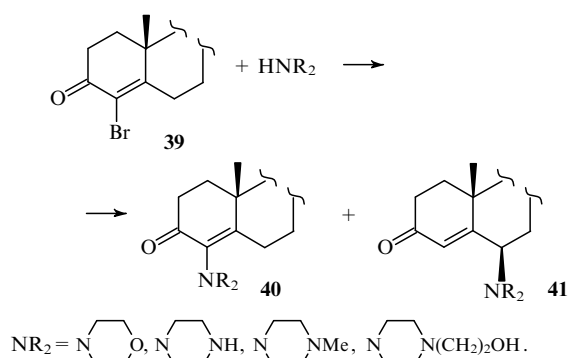
Scheme 1



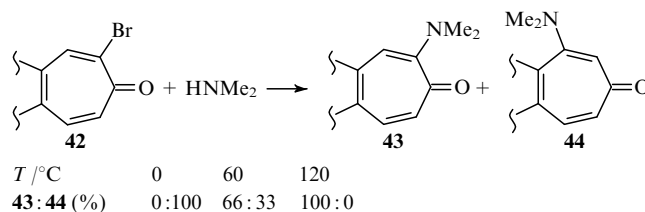
3. Haloalkenes activated by a carbonyl group

The haloalkenes **1c** and **1d** with a geminal acyl or formyl group are the most reactive towards N-nucleophiles. The possibility of condensation at the keto and especially formyl group extends the spectrum of the transformations observed.

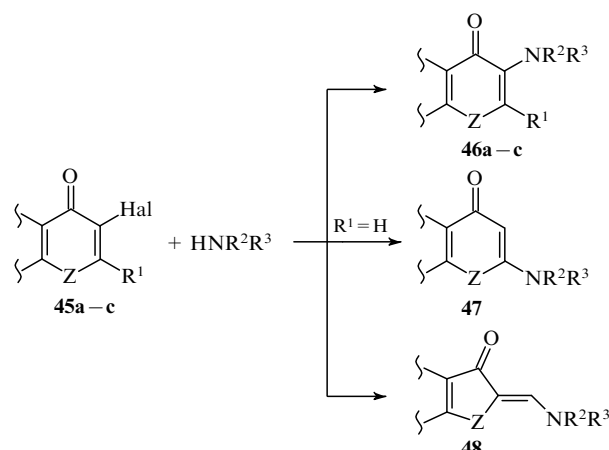
Similarly to esters and nitriles, α -halo α,β -unsaturated aldehydes and ketones react with secondary amines giving rise to α -, β -, or γ -amino-derivatives of α,β -unsaturated carbonyl compounds.^{16, 69–83} Thus reaction of 4-bromocholest-4-en-3-one **39** with heterocyclic amines affords a mixture of 4- and 6-amino-substituted cholestenones, **40** and **41**, respectively, the isomer **41** being the major product in all cases.^{77, 78}



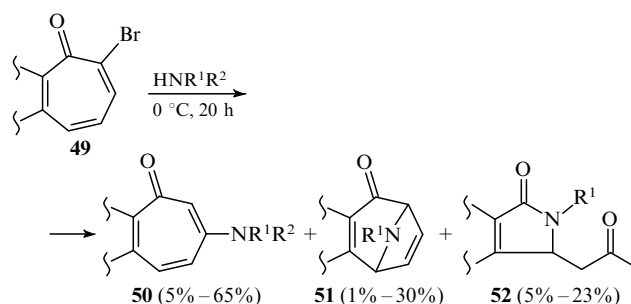
Impressive results have been obtained in a study of the temperature dependence of the regioselectivity of the amination of bromobenzotropone **42** with dimethylamine.⁸¹ An increase in the temperature is favourable for the formation of the *ipso*-substitution product **43**. At 0 °C, β -amino-derivative **44** is formed specifically, whereas the reaction at 120 °C yields amino ketone **43** as the only product.



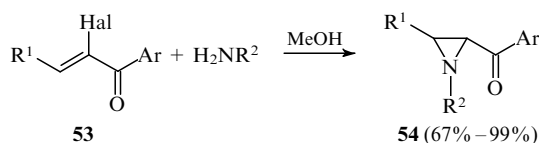
The reactions of 3-haloalkenones **45b,c** with amines yield in all cases only 3-aminoalkenones **46b,c**. However, when **45a** is introduced in this reaction, both the *ipso*-substitution products **46a** and compounds **47** are formed. In some cases, the reaction is accompanied by the γ -pyrone ring contraction and gives derivatives **48**.^{70–74, 82, 83} This difference between the behaviours of these compounds has not yet received any plausible explanation.



Complex mixtures containing *syn*-substitution products **50**, bridged compounds **51**, and lactams **52** are formed under mild conditions when α -bromo ketone **49** is made to react with primary amines. Secondary amines react with the same substrate giving rise to the corresponding β -enamino ketones **50**.⁸⁰



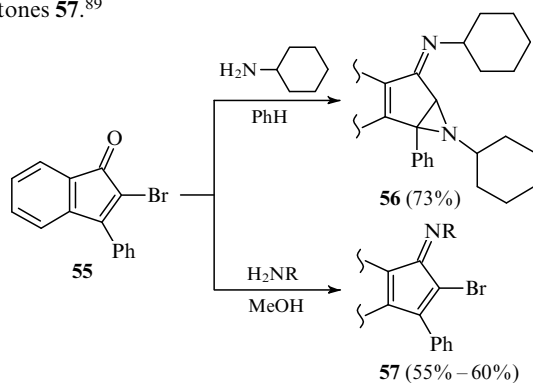
Nevertheless, in most cases, the reaction of 2-haloalk-2-enones **53** with ammonia and primary amines, like the reactions in the series of nitriles and esters, proved to be a versatile and efficient method for the synthesis of aziridinyl ketones **54**.^{84, 85} including those containing polyfluoroalkyl substituents.^{86, 87}



Hal = Cl, Br; R¹ = Me, Ph, CF₃; R² = Me, Bn, cyclo-C₆H₁₁, C₆H₁₃;
Ar = Ph, 4-PhC₆H₄.

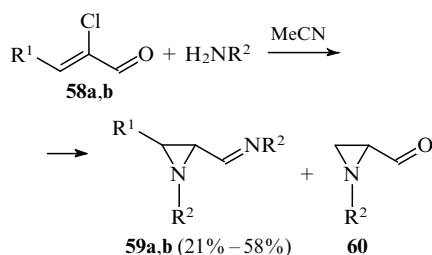
The main limitation in the synthesis of the aziridines **54** is the steric accessibility of the nitrogen atom. The carbon atom attached to the amino group should not be tertiary.⁸⁵ Thus *tert*-butylamine does not form the corresponding aziridines **54** with α -bromoaldehydes,⁸⁵ although some nitriles of type **1a** and some aldehydes of type **1d** can be converted into aziridine derivatives with a *tert*-butyl group.^{24, 88}

At the same time, the reaction often involves a carbonyl group. For instance, 2-bromo-3-phenylinden-1-one **55** reacts with N-nucleophiles containing a primary amino group to give ketimine derivatives of aziridines **56**⁷⁵ or of the initial bromo ketones **57**.⁸⁹



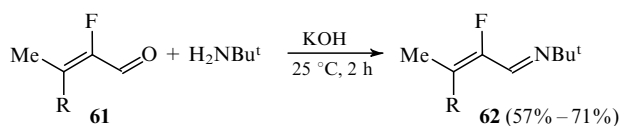
R = OH, NHPH.

A similar situation has been observed for 2-haloalk-2-enals **1d**.^{88, 90, 91} Thus 2-chloropropenal **58a** and 2-chlorobut-2-enal **58b** react with three equivalents of a primary amine giving rise to azomethine derivatives of aziridines **59a,b**.⁸⁸ Interestingly, the reaction of the aldehyde **58a** with a twofold excess of amine affords a small amount of aziridine derivative **60** together with the azomethine **59a**.⁸⁸



R¹ = H (a), Me (b); R² = Et, Pr^t, Bu^t.

The condensation of 3-alkyl-2-fluorobut-2-enals **61** with *tert*-butylamine involves only the aldehyde group and results in the formation of aldimines **62**.⁹¹ Neither the double bond nor the fluorine atom participate in the process.

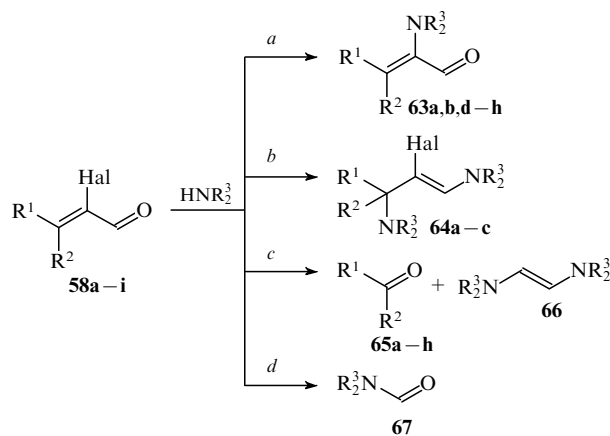


R = Me, Et, Bu^t.

The reactions of secondary amines with 2-haloalk-2-enals **58a–i** follow an unusual pathway and give an array of polyfunctional unsaturated compounds.^{9, 92–95}

The predominant route of transformations is mostly determined by the structure of the initial substrate. Thus the interaction of 2-chloropropenal **58a** with secondary amines gives mostly 1,3-diamino-2-chloropropenes **64a** [Scheme 2, pathway (b)]. The same reaction route is observed for 2-fluorobut-2-enal **58c**. Conversely, the reactions of 3-alkyl(or aryl)-2-chloro(or bromo)alk-2-enals **58b,d–g** with highly basic secondary amines normally yield *ipso*-substitution products **63b,d–g** as the major products [pathway (a)]. This route competes with fragmentation [pathway (c)], which results in the formation of carbonyl compounds **65b–h** and unsaturated diamines **66**. When the initial substrate contains a second alkyl substituent at the β -position (aldehyde **58h**), the *N*-formyl derivative of the initial amine **67** [pathway (d)] is produced, in addition to the substitution product **63h**, in a comparable amount. The presence of two phenyl groups in the substrate (**58i**) makes it completely inert towards secondary amines.

Scheme 2

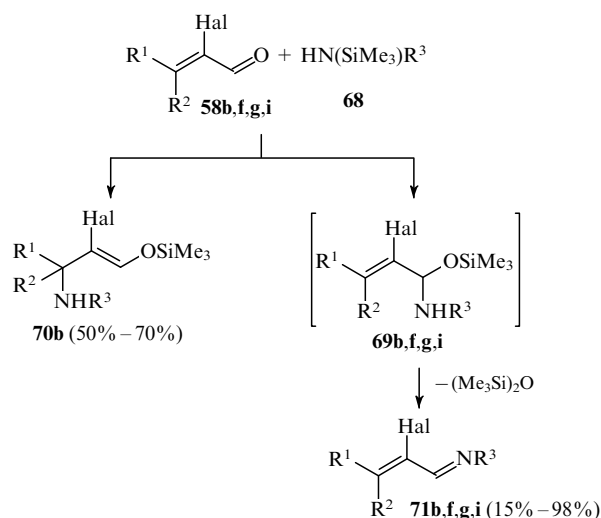


R¹ = R² = H, Hal = Cl (a); R¹ = Me, R² = H, Hal = Cl (b), F (c), Br (d); R¹ = Pr, R² = H, Hal = Cl (e); R¹ = Ph, R² = H, Hal = Cl (f), Br (g); R¹ = R² = Me, Hal = Cl (h); R¹ = R² = Ph, Hal = Cl (i);

NR³ = NEt₂, NBu₂, N-pyrrolidine, N-piperidine, N-morpholine.

The selectivity of the reaction does not correlate with the basicity of the nucleophile. Indeed, piperidine, pyrrolidine, and diethylamine in which the nitrogen atoms are close in basicity and steric accessibility react with the same substrate **58b** according to pathways (a), (b), and (c), respectively.⁹⁴ Aprotic solvents (benzene, THF, pyridine) facilitate the *ipso*-substitution reaction [pathway (a)], whereas in protic solvents, pathway (c) prevails.^{94, 95}

Considerable interest was aroused by the reaction of 2-haloalk-2-enals with alkylaminotrimethylsilanes **68** containing an N–H bond. These nucleophiles could behave like secondary amines being involved in, for example, *ipso*-substitution of halogen or like aminosilanes with a tertiary amino group, which would result in the formation of 1,2- or 1,4-addition products.⁹⁶ It turned out that the aldehydes **58b,f,g,i** readily react with one equivalent of the alkylaminotrimethylsilane **68** giving rise to the products of 1,2-addition (**69b,f,g,i**) and/or 1,4-addition (**70b**). The adducts **69b,f,g,i** are unstable; they eliminate siloxane to give aldimines **71b,f,g,i**. This is a facile and efficient method for preparing valuable azomethine derivatives of 2-haloalk-2-enals.⁹⁷



$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$, $\text{Hal} = \text{Cl}$ (**b**); $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{Hal} = \text{Cl}$ (**f**); $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, $\text{Hal} = \text{Br}$ (**g**); $\text{R}^1 = \text{R}^2 = \text{Ph}$, $\text{Hal} = \text{Cl}$ (**i**); $\text{R}^3 = \text{cyclo-C}_6\text{H}_{11}$, Bn , Ph .

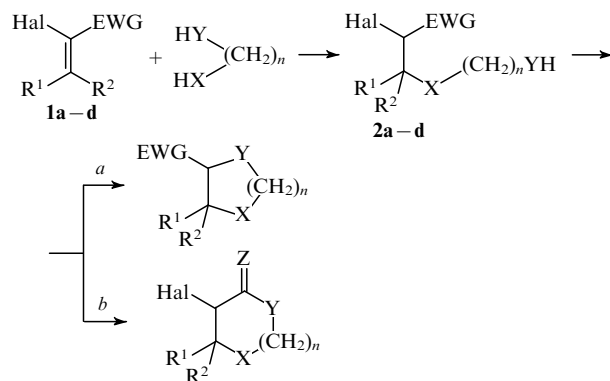
To summarise the foregoing, it should be emphasised that although most of these transformations are described by a common scheme, it is often difficult to predict the outcome of reactions of haloalkenes, activated by geminal substitution, with N-nucleophiles. Nevertheless, the regularities discovered promote the intense use of haloalkenes **1a–d** in the synthesis of various heterocyclic compounds.

III. Reactions of haloalkenes activated by geminal groups with binucleophiles

Reactions of haloalkenes **1** with bidentate nucleophiles of various types (from α,α to α,ω) have resulted in the synthesis of a wide range of N-, S-, or O-containing heterocyclic derivatives. It is significant that these reactions are usually highly chemo- and regio-selective.

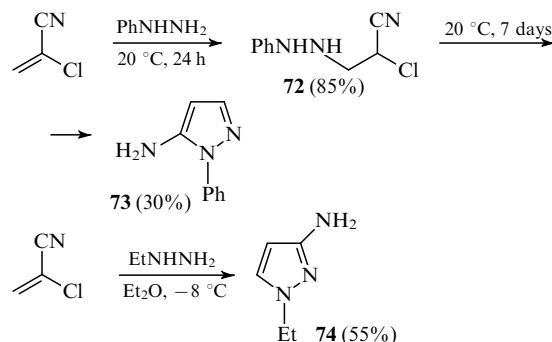
A possible route for interaction of the alkenes **1a–d** with binucleophiles is conjugated addition at the double bond. Depending on the activity of the electron-withdrawing substituent, the process is either terminated at the stage of formation of the Michael adduct **2a–d** or proceeds further as subsequent transformations of the adduct; these include nucleophilic substitution of the halogen atom [Scheme 3, pathway (a)] or nucleophilic attack at the activating group giving rise to a halo-containing heterocyclic derivative, which often undergoes subsequent transformations [pathway (b)]. The process can be directed at one or another route by varying the type of the activating group, the nature of the nucleophile, or experimental conditions.

Scheme 3

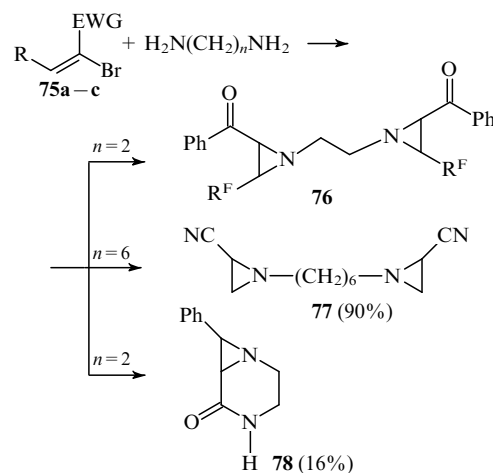


$n = 0-6$; $\text{X} = \text{Y} = \text{NR}^3$; $\text{X} = \text{NR}^3$, $\text{Y} = \text{O}$; $\text{X} = \text{S}$, $\text{Y} = \text{NR}^3$; $\text{R}^3 = \text{H}$, Alk , Ar ; $\text{Z} = \text{O}$, NH .

Thus phenylhydrazine readily adds to the double bond of 2-chloroacrylonitrile to give 2-chloro-3-phenylhydrazinopropionitrile **72** in a high yield; this product cyclises to give 1,5-disubstituted pyrazole **73**. In the case of more basic ethylhydrazine, the addition at the double bond involves the secondary amino group of the hydrazine, and this results in the formation of 1,3-disubstituted pyrazole **74**.²⁸

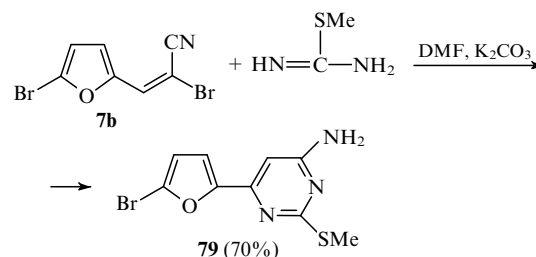


Despite the fact that unimolecular reactions are favourable from the entropy viewpoint, reactions of haloalkenes **1a–d** with N,N-binucleophiles can give rise to both intra- and inter-molecular cyclisation products. For instance, reaction of α -bromo α,β -unsaturated ketone **75a** with ethylenediamine affords derivative **76**.⁹⁸ 2-Bromoacrylonitrile **75b** reacts with hexamethylenediamine in a similar way and gives bis-aziridine **77** in a high yield.²⁴ Conversely, the reaction of ethyl α -bromoacrylate **75c** with ethylenediamine initially proceeds by a usual pathway but then an amide ring is closed, and 5-oxo-7-phenyl-1,4-diazanorcan **78** is formed as the final product.⁹⁹



$\text{EWG} = \text{COPh}$, $\text{R} = \text{R}^F$ (**75a**); $\text{EWG} = \text{CN}$, $\text{R} = \text{H}$ (**75b**); $\text{EWG} = \text{COOEt}$, $\text{R} = \text{Ph}$ (**75c**).

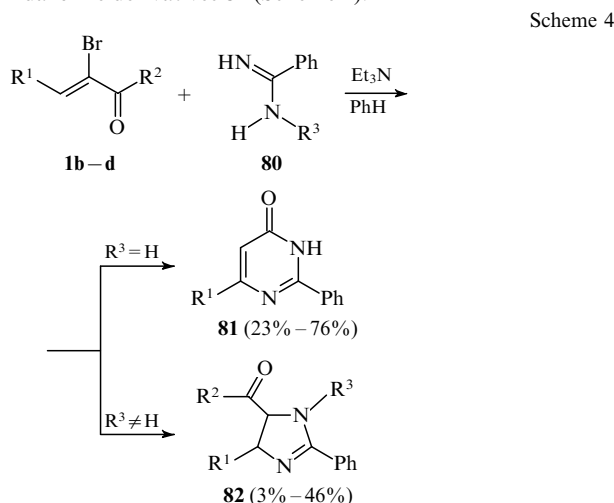
The reaction of substituted 2-bromoacrylonitrile **7b** with S-methylisothiourea leads to pyrimidine **79**.¹⁰⁰



Pyrimidine derivatives have also been obtained in reactions of urea and thiourea with β -substituted α -haloacrylates.^{101–104}

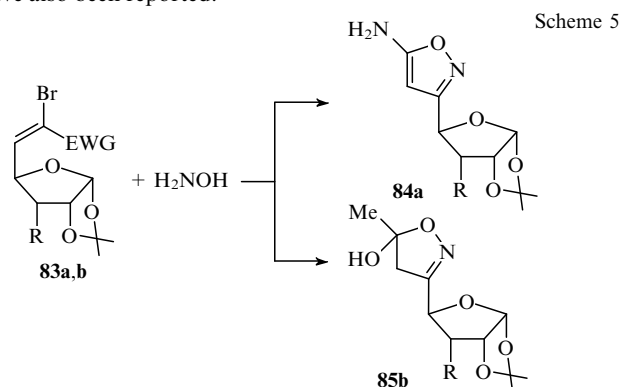
The influence of the steric accessibility of the nitrogen atom in the nucleophile on the direction of the attack has been demon-

strated in a number of studies.^{103–105} Thus benzamidine **80** ($R^3 = H$) with a primary amino group converts haloalkenes **1b–d** into pyrimidinones **81**. Mono-*N*-substituted amidines react with the same substrates under the same conditions giving rise to 2-imidazoline derivatives **82** (Scheme 4).



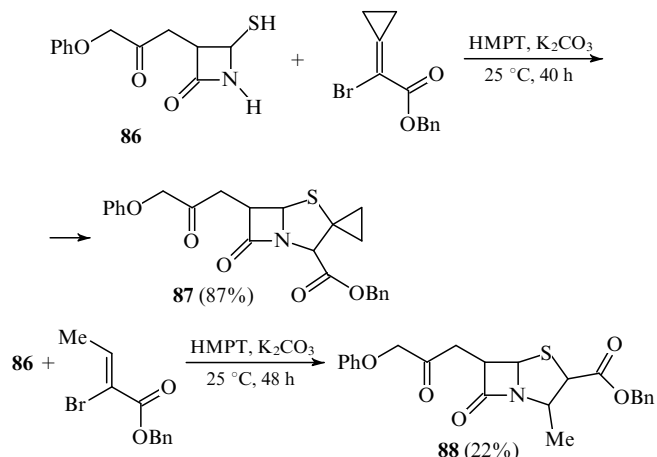
$R^1 = Ph, 4-ClC_6H_4, 4-MeC_6H_4$; $R^2 = H, Me, Bu^t, Ph, OMe, OEt$;
 $R^3 = H, Me, Pr^i, Bn$.

Hydroxylamine reacts with α -bromo- β -glycosyl α,β -unsaturated nitriles **83a** and ketones **83b** as an N,O-binucleophile affording isoxazole derivatives **84a** and isoxazoline derivatives **85b**, respectively (Scheme 5).^{20, 106, 107} The positions of substituents in the N,O-heterocycle make it possible to draw conclusions about the direction of the primary nucleophilic attack. As a rule, the nitrogen atom in N,O-binucleophiles proves to be more nucleophilic. However, rare examples of formation of isoxazoles in which the β -carbon atom of an alkene is bound to the oxygen have also been reported.^{20, 108}



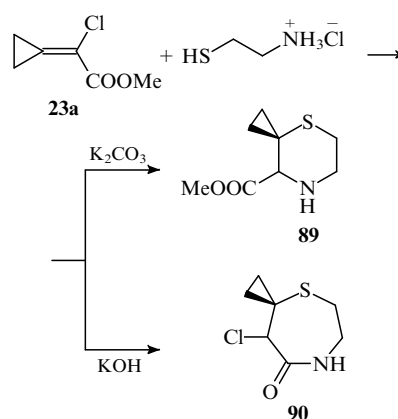
EWG = CN (**a**), Ac (**b**); $R = H, OMe, OBn, CF_3CONH$.

Conversely, in the case of N,S-binucleophiles, the sulfur atom is more nucleophilic and adds at the double bond. The resulting Michael adduct with a free amino group participates in cyclocondensation involving either the α -carbon atom or the activating group.^{52, 109–113} Thus the reaction of 4-sulfanylazetidinone **86** with benzyl 2-bromo(cyclopropylidene)acetate yields a mixture of epimeric cyclopropanespiro-2-bisnorpenicillanates **87**.¹¹³ The formation of the ester **88** from benzyl α -bromocrotonate and the same binucleophile **86** was interpreted¹¹² by assuming isomerisation of the intermediate product of S-addition of the nucleophile.

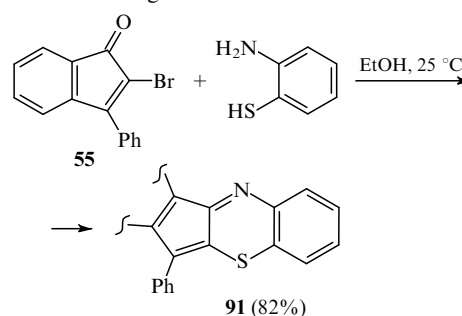


HMPT is hexamethylphosphotriamide.

A clear illustration of the influence of the nature of the base used on the direction of cyclisation has been reported by Wessjohann and de Meijere.⁵² Treatment of α -chloroacrylate **23a** with 2-aminoethanethiol in the presence of K_2CO_3 gives rise to 1,4-thiazine derivative **89**, whereas the use of KOH under the same conditions results in the formation of seven-membered heterocycle **90**.



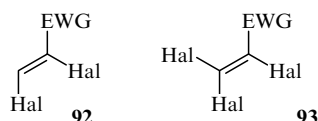
Reactions of N,N-, N,C-, and N,S-binucleophiles with α -halo α,β -unsaturated ketones **1c** begin with halogen substitution, which is followed by intramolecular interaction of the free amino group with the carbonyl carbon atom leading to cyclisation.^{89, 114–118} This route is realised, for example, when *o*-amino-benzenethiol is made to react with 2-bromo-3-phenylindenone **55**; this reaction results in the formation of compound **91** with a 1,4-benzothiazine ring.^{89, 115}



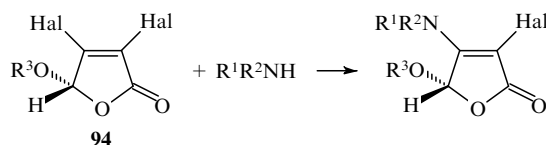
As a rule, reactions of haloalkenes **1** with binucleophiles afford heterocyclic compounds. However, in some cases,^{18, 29, 80, 119} β -aminoalkenes of type **4** have been obtained as the reaction products. This cannot be always explained by steric hindrance at the electrophilic centre of the substrate or by steric inaccessibility of a particular heteroatom in the nucleophile.

IV. Reactions of polyhaloalkenes with N-nucleophiles

Di- and tri-haloalkenes **92** and **93** are even more reactive and are widely used in organic synthesis. The presence of a halogen atom at the β -carbon atom sharply changes the general pattern of interaction of haloalkenes **1a–d** with N-nucleophiles. It is known that a halogen atom located in the β -position in relation to an activating group can be readily substituted. Therefore, compounds of this type have served as the basis for the preparation of various β -functionally substituted α,β -unsaturated carbonyl compounds and their analogues.^{120, 121}

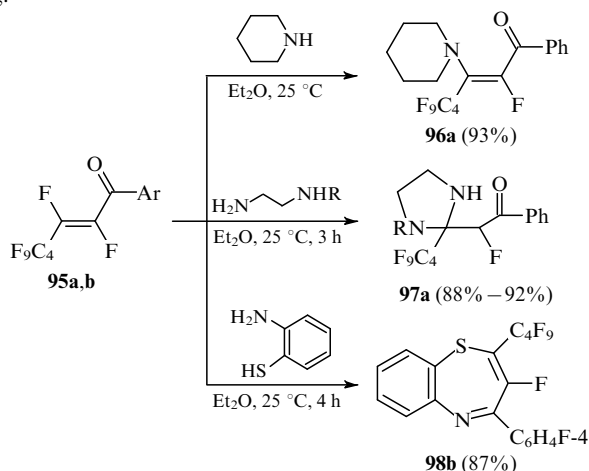


The difference between the reactivities of halogen atoms occupying different positions with respect to an activating group is so great that reactions of N-nucleophiles with α,β -di- (**92**) and α,β,β -tri-haloalkenes **93** involve almost in all cases the β -halogen atom, whereas α -halogen remains absolutely inert. Thus primary and secondary amines enter into a tandem addition–elimination reaction with chiral dihalo(menthyloxy)furanone **94** to replace the β -halogen atom with high enantioselectivity.^{122–124}



Hal = Cl, Br; $\text{R}^1\text{R}^2\text{N} = (\text{CH}_2)_4\text{N}$, $\text{O}(\text{CH}_2\text{CH}_2)_2\text{N}$, BnNH , $\text{PhCH}(\text{Me})\text{NH}$; $\text{R}^3 = 1\text{-menthyl}$.

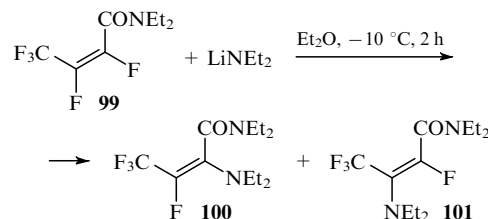
Secondary amines replace only the β -halogen atom in tri-fluoroacrylonitrile under mild conditions.¹²⁵ Of all possible paths of interaction of unsaturated perfluoro ketones **95a,b** with amines or binucleophiles, only chemoselective substitution of the vicinal fluorine atom does occur. The reaction with piperidine results in the formation of product **96a**. In the case of binucleophiles, this is followed by Michael cyclisation yielding imidazolidines **97a**.^{126, 127} The reaction of ketone **95b** with *o*-aminobenzenethiol gives substituted benzothiazepine **98b**. The primary attack by the thiol group in this reaction was confirmed by NMR monitoring.¹²⁷



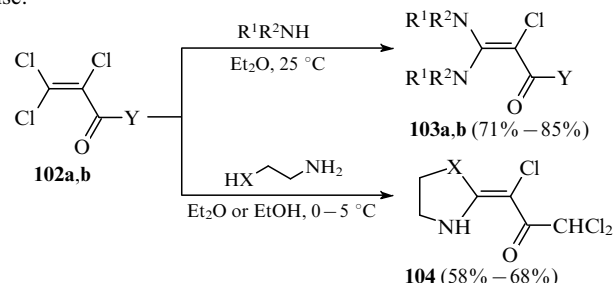
$\text{R} = \text{H}$, Me; $\text{Ar} = \text{Ph}$ (**a**), 4- FC_6H_4 (**b**).

At first glance, these data seem to be at variance with the results obtained by Nguyen *et al.*¹²⁸ The reaction of *N,N*-diethylperfluorocrotonamide **99** with lithium diethylamide under mild conditions gave a mixture of isomeric α - (**100**) and β - (**101**)

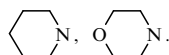
diethylamino-derivatives in $\sim 3:1$ ratio. It is clear that in this case, the regioselectivity of nucleophilic substitution is influenced by the highly electron-withdrawing trifluoromethyl group.



The reactions of primary and secondary amines and also *N,N*- and *N,O*-bidentate nucleophiles with α,β,β -trichloro-substituted unsaturated ketones **102a,b** involve exclusively the β -chlorine atoms and give polyfunctional compounds **103a,b** and **104**.^{129, 130} No trisubstituted products or products of reaction at the carbonyl group are formed even with excess nucleophile. When the nucleophile:substrate ratio is decreased to 1:2, some of the initial ketone is recovered unchanged, but no monosubstituted products arise.¹³⁰

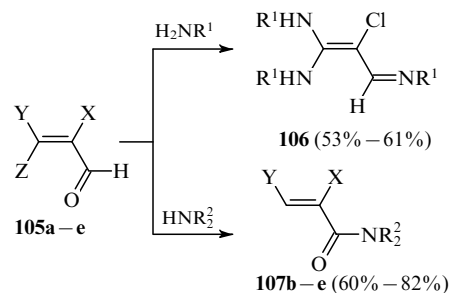


$\text{Y} = \text{CHCl}_2$ (**a**), CF_3 (**b**); $\text{X} = \text{NH}$, O ; $\text{R}^1\text{R}^2\text{N} = \text{PhMeN}$, PhNH , Bu^tNH ,

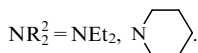


When β -bromo- α,β -dichloroacrolein **105a** is treated with primary amines, the replacement of the β -halogen atoms is accompanied by condensation at the aldehyde group resulting in the formation of 1,1-diamino-2-chloro-3-iminoprop-1-enes **106**.¹³¹ Neither an increase in the excess of amine nor raising the temperature lead to substitution of the α -chlorine atom.

On treatment with secondary amines, trihaloacroleins **105b–e** are unexpectedly converted into dihaloacrylamides **107b–e**.^{132, 133} it was found¹³³ that halogen was eliminated from the β -carbon atom. Based on this conclusion, a possible reaction mechanism was proposed that included primary nucleophilic attack on the carbonyl group of the substrate.

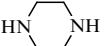
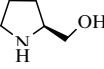
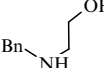


$\text{X} = \text{Y} = \text{Cl}$, $\text{Z} = \text{Br}$ (**a**); $\text{X} = \text{Y} = \text{Z} = \text{Cl}$ (**b**); $\text{X} = \text{Br}$, $\text{Y} = \text{Z} = \text{Cl}$ (**c**); $\text{X} = \text{Cl}$, $\text{Y} = \text{Z} = \text{Br}$ (**d**); $\text{X} = \text{Y} = \text{Z} = \text{Br}$ (**e**); $\text{R}^1 = \text{Ph}$, Bn , 2,4- $\text{Me}_2\text{C}_6\text{H}_3$;

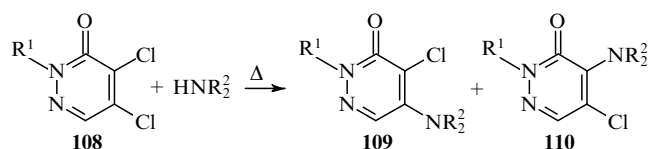


The α -halogen atom in α,β -dihaloalkenes of type **92** can be involved in the reaction only in rare cases. For instance, reaction of 4,5-dichloro-3(2*H*)-pyridazinones **108** with N-nucleophiles affords either the product of substitution of only the β -halogen

Table 1. Reactions of pyridazinones **108** with N-nucleophiles.

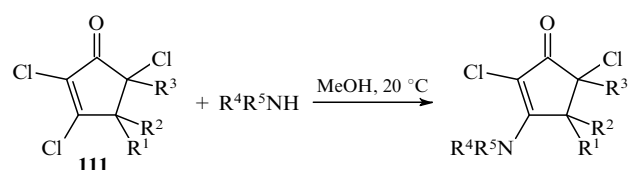
HNR ₂ ²	R ¹	Solvent	t/h	Yield (%)		Ref.
				109	110	
	H	EtOH, Et ₃ N	4	40	—	134
	Me			50	—	
	Ph			50	—	
	H	BuOH	4	60	0	135
	Me	EtOH	4	73	7	135
	BnOCH ₂	H ₂ O	11	41	4	136
		PhMe	11	21	13	136

atom **109**¹³⁴ or a mixture of isomeric α - and β -amino-derivatives **110** and **109**, the latter being formed in substantially (up to 10 : 1) larger amounts (Table 1).^{135, 136}



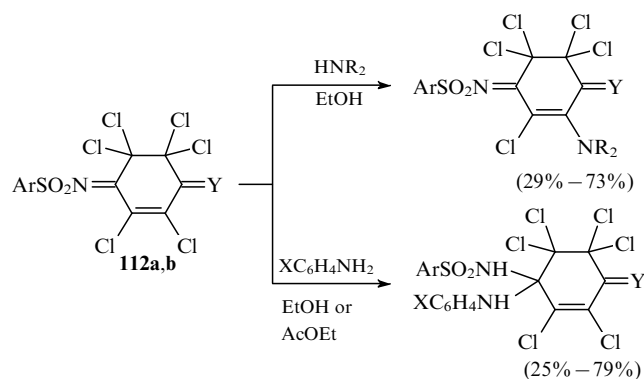
When 5,6-dihalopyrimidines are treated with N-nucleophiles as well as with N,N-, N,O-, and N,S-binucleophiles, both halogen atoms are substituted.^{137–139}

Halogen atoms at a double bond may also remain intact during the reaction of haloalkenes of type **1** with nucleophiles; this is the case when the molecule of the initial substrate contains other, more electrophilic, sites.^{140, 141} It is of interest to consider molecules that contain halogen atoms attached to an *sp*³ hybridised carbon atom in addition to halogen atoms at a double bond. As a rule, the former are replaced much more easily.^{142, 143} Substitution at the vinylic centre requires more drastic conditions. Hence, these two processes can be carried out separately, and different amine fragments can be introduced into the molecule.¹⁴⁴ In some cases, β -halogen atoms can be easily substituted, other centres remaining intact (see, for example, Refs 145–150). Thus the reaction of substituted 2,3,5-trichloro-2-cyclopentenones **111** with various amines occurs smoothly and regioselectively in accordance with the expected *N*-oxovinylolation scheme, the α -chlorine atom at the double bond being inert.



R¹ = R² = OMe; R¹ = OH, R² = Me; R³ = CH₂CH=CH₂, CH=CH=CH₂; R⁴ = Me, R⁵ = H; R⁴ = HO(CH₂)₂, R⁵ = H; R⁴ = R⁵ = Me, Et; R⁴, R⁵ = MeN(CH₂CH₂)₂; R⁴, R⁵ = O(CH₂CH₂)₂; R⁴, R⁵ = (CH₂)₅.

When polychloro-derivatives **112a,b** are made to react with heterocyclic amines (piperidine, morpholine), the chlorine atom at the double bond undergoes nucleophilic substitution.¹⁵¹ The reaction of **112b** with pyridine follows a similar route.¹⁵² Aniline and its derivatives do not form substitution products; instead, they unexpectedly add to the C = N bond.^{151, 153}

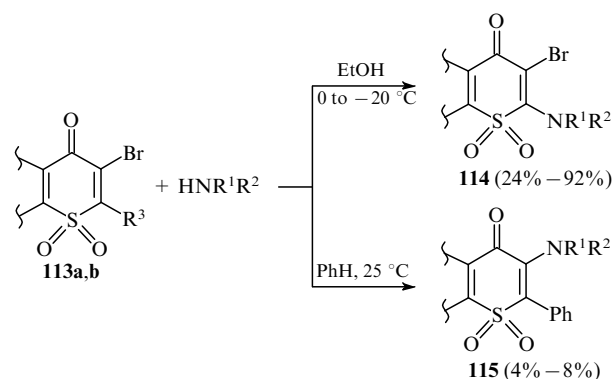


Y = O (**a**), NSO₂Ar (**b**); Ar = 4-MeC₆H₄, 4-ClC₆H₄;

X = H, 4-Me, 3-Me; NR₂ = , .

The reactions of 2,3-dibromo-4*H*-1-benzothiopyran-4-one 1,1-dioxide **113a** with alkylamines, dialkylamines, aniline, and its derivatives afford only products **114** resulting from substitution of bromine that occupies the β -position with respect to the carbonyl group.^{154, 155}

The substitution of bromine in the substrate **113b** results in the formation of compound **115** in a low yield.¹⁵⁶



R³ = Br (**a**), Ph (**b**); R¹ = R² = Me; R¹ = H, R² = Me; Ph, C₆H₄OMe-4.

V. The mechanism of nucleophilic substitution of halogen atoms in *gem*-activated haloalkanes

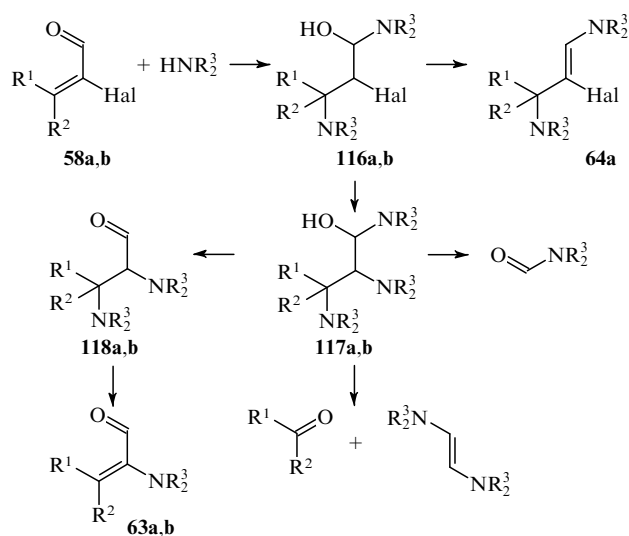
The mechanism of vinylic nucleophilic substitution (S_NVin) in alkenes in which the leaving group is in the β -position in relation to the activating group has been studied fairly comprehensively.¹⁵⁷ About 30 different variants of this reaction have been proposed. However, the mechanism of this reaction for the alkenes in which the leaving and activating groups are attached to the same carbon atom has been much less studied. The diversity of the products of reactions of the haloalkenes **1a–d** with amines indicates unambiguously that it is not a one-step process. The scheme now generally accepted, which permits interpretation of the overwhelming majority of the results obtained, is quite obvious. An amine adds to the double bond of the haloalkene **1a–d** to give the adduct **2a–d** the structure of which is responsible for the direction of subsequent transformations. When primary amines are used, the adducts usually undergo intramolecular substitution of the halogen atom giving rise to aziridines **3a–d**. In the case of secondary amines, the transformations in question occur either as halogen substitution yielding α,β -diamino-derivatives **5a–d** or as dehydrohalogenation to give β -aminoalkenes

4a–d. This scheme was first proposed by Cromwell⁷ as the most probable hypothesis. Subsequently, it was confirmed experimentally and further developed. Strong evidence supporting this scheme has been provided by detection and, in some cases, isolation of the main intermediates. The Michael adducts **2** were isolated for the nitriles **1a**, esters **1b**, and ketones **1c**.^{158–160} The attractive hypothesis of the intermediate formation of an aziridinium salt has been confirmed only after isolation and full spectroscopic identification of this intermediate.^{160, 161} The transformation of the diamino-derivative **5** into the corresponding unsaturated compound **6**, discovered in a number of studies,^{95, 162} has provided final evidence for the reaction mechanism consisting of three successive steps, Ad–S_N–E.

The general scheme of transformations has been recently extended to the most reactive series of substrates **1d**.¹⁶² These compounds differ from all the other haloalkenes activated by geminal substitution in that their activating group does not remain unchanged during the transformations.

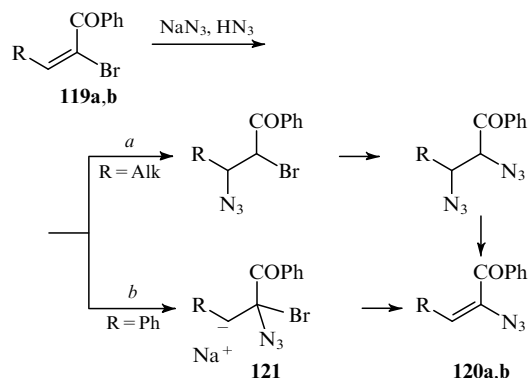
The sequence of transformations of 2-chloroacrolein **58a** and 2-chlorobut-2-enal **58b** on treatment with piperidine has been monitored by NMR spectroscopy. At low temperatures, several main intermediates were detected; they accounted for the formation of all the reaction products. Although the nature of the product resulting from the addition of one equivalent of the amine was not elucidated, some findings as well as the electronic structures of the starting compounds¹⁶³ suggest that the process starts with the 1,4-addition of the nucleophile.

The first intermediate that could be detected in the reaction of the substrate **58b** with piperidine at 5 °C was hemiaminal **116b**. In the presence of excess amine, **116b** readily undergoes bimolecular nucleophilic substitution of the halogen atom being thus converted into triamino-derivative **117b**. When the temperature is increased to 25 °C, the latter participates in several competing reactions, the removal of the hemiaminal protection with regeneration of the aldehyde group being the predominant route. The resulting 2,3-diamino aldehyde **118b** undergoes β-elimination of an amine molecule and is thus converted into the final product **63b**. A similar sequence of transformations is observed when **58a** is used as the substrate in this reaction. However, in this case, the hemiaminal **116a** formed initially is mostly dehydrated yielding the alkene **64a**. The sequence of transformations **116a** → **117a** → **118a** → **63a** is not the prevailing route. In general, the proposed scheme accounts for the diversity of the products obtained from haloalkenes activated by a formyl group. It also explains why transformations of this type do not occur in the series of substrates **1a–c**.

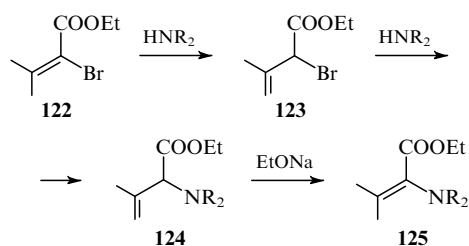


Despite the fact that the multistep scheme of nucleophilic vinylic substitution in these systems is currently generally accepted, in some cases, the possibility of direct substitution also cannot be dismissed.^{164, 165} For example, it is believed that the substitution of bromine in the alkene **119a** by the azide ion occurs as the Ad–S_N–E sequence of steps [Scheme 6, pathway (a)]. However, introduction of a phenyl group into the β-position of the substrate (compound **119b**) enables stabilisation of the negative charge in the β-position of the adduct **121**. Therefore, apart from the multistep substitution [pathway (a)], direct α-addition of the azide ion to the double bond [pathway (b)] resulting in the formation of the same substitution product **120b** also becomes possible.

Scheme 6



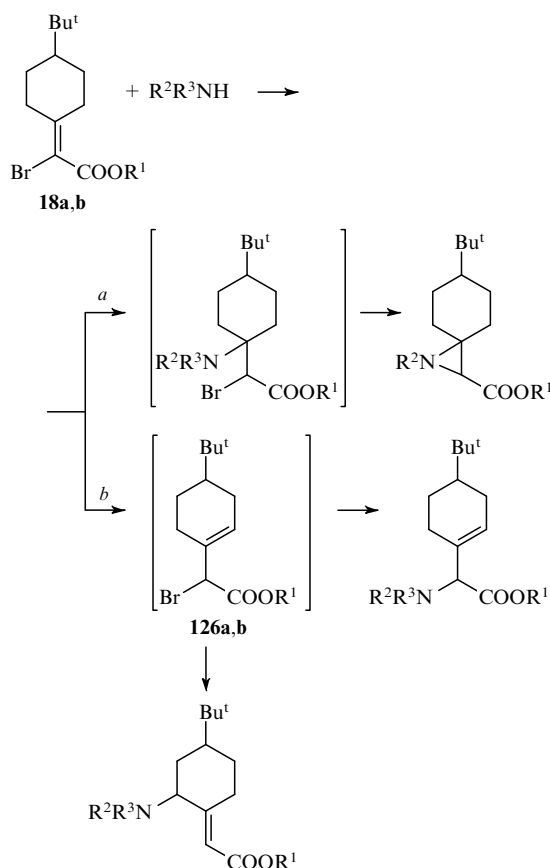
The question arises as to whether nucleophilic substitution in *gem*-activated haloalkenes always includes the step of conjugated addition, or whether another reaction route is also possible in those cases where the β-carbon atom proves to be inaccessible for some reason (mostly steric). The first attempt to answer this question was undertaken as early as the middle 1950s by a group of French chemists.¹⁶⁶ They studied reactions of ethyl 2-bromo-3-methylcrotonate **122** with secondary amines and suggested that the first step of the process is prototropic transformation of the initial α,β-unsaturated carbonyl compound **122** into its β,γ-isomer **123**. The subsequent bimolecular substitution of the allylic halogen atom gives rise to the amino-derivative **124** isomerisation of which induced by a strong base affords the final product **125**.



However, thorough studies¹⁶⁷ made it possible to give preference to the classical Ad–S_N–E mechanism, which includes formation of the ethyleneimmonium intermediate. This is the only possibility that provides a plausible explanation of the migration of the amine fragment from the β-carbon atom, where it is detected initially, to the α-position.

The idea¹⁶⁶ that the reaction might start with the 1,3-shift has later been confirmed for other examples.^{38, 65–68} Thus the diversity of products formed upon interaction of the esters **18a,b** with primary and secondary amines, and also the fact that the spiroaziridine derivative **19a,b** is not transformed into the isomeric ester **20** have led Rulev *et al*³⁸ to the conclusion that the process can occur by different mechanisms, depending on the type of the nucleophile and experimental conditions. The reactions with primary amines carried out at room temperature under an elevated or atmospheric pressure follow the classical Ad–S_N–E

pattern [pathway (a)]. Conversely, for the reactions with secondary amines and also for those with primary amines carried out under reflux, the key stages are isomerisation of the initial ester **18a,b** giving ester **126a,b** with an endocyclic double bond and the subsequent easy substitution of the allylic halogen atom by the amine [pathway (b)]. Examples of such isomerisation in the series of α -halo α,β -unsaturated acids, induced by amines under very mild conditions, have been reported.¹⁶⁸



VI. Conclusion

The high and diverse reactivity of haloalkenes containing an electron-withdrawing group in the α -position is based on the phenomenon, which has been called by Louis Henry 'functional solidarity'.¹⁶⁹ The essence of this phenomenon is the following. When several functional groups are bound to the same carbon atom in a molecule, their mutual influence results in some cases in substantially changed chemical properties, not typical of the same functional groups occurring separately.

Easily accessible *gem*-activated haloalkenes, which are used as polyfunctional building blocks, occupy a prominent place in modern organic synthesis. Analysis of the available data indicates that nucleophilic vinylic substitution in haloalkenes activated by a geminal group differs substantially from related reactions in the series of alkenes with vicinal leaving and activating groups. These reactions have specific features, and it is not always possible to predict the outcome of a particular transformation.

Despite the fact that such polydentate systems are widely used in synthesis, their potential is far from being exhausted. We believe that the synthetic and theoretical aspects of the chemistry of *gem*-activated haloalkenes would remain the focus of the attention of researchers as a part of the chemistry of unsaturated heteroatomic derivatives with a geminal electron-withdrawing group.

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

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

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

^e — *Pharm. Chem. J. (Engl. Transl.)*

Methods of synthesis of nitrogen-containing heterocycles using ureas and related compounds

A A Bakibaev, A Yu Yagovkin, S N Vostretsov

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Abstract. The review surveys numerous experimental data on the application of ureas in the synthesis of mono- and bi-cyclic nitrogen-containing heterocycles with the exception of pyrimidines and hydantoin. The methods of synthesis of phthalocyanines, diazepines, and diazocines from urea and its derivatives are also examined. The bibliography includes 220 references.

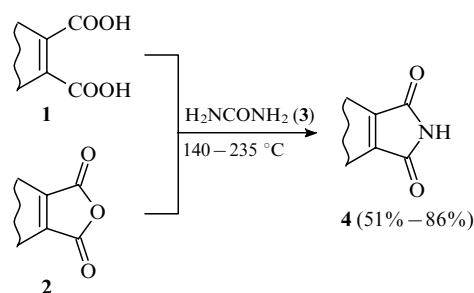
I. Introduction

The procedures of organic chemistry include nowadays a wide range of synthetic methods for the construction of azaheterocycles. Ureas are frequently used as the starting materials for this purpose, but, with the exception of studies describing the methods of synthesis of hydantoin^{1–3} and pyrimidines,^{4–10} there are no reviews in the literature surveying the extensive factual data on the methods of synthesis of nitrogen-containing heterocycles involving ureas. The purpose of the present review is to fill this gap. It does not include the methods of synthesis of hydantoin and pyrimidines except certain compounds of these classes where a non traditional approach to their synthesis has been employed.

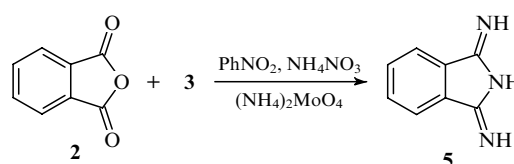
II. Methods of synthesis of monocyclic azaheterocycles

1. Synthesis of heterocycles containing one nitrogen atom

One of the convenient methods for the preparation of the cyclic imides **4** with a wide variety of structures is the pyrolysis of the dicarboxylic acids **1** or their anhydrides **2** in the presence of a slight excess of urea **3**.^{11–16}



The early studies devoted to the synthesis of the imide **4** have been described in a review.¹⁷ Although the pyrolysis of the anhydrides **2** proceeds in the vast majority of cases under milder conditions (140–185 °C) than the pyrolysis of the dicarboxylic acids **1** (185–235 °C), the yields of like imides are comparable. It is generally known that, when dicarboxylic acids are used in these reactions, the anhydrides **2** are formed initially. Under the influence of the products of the thermal decomposition of urea (NH₃ and HNCO), the latter are converted into the target imides **4** via recyclisation–cyclisation stages. In order to increase the effectiveness of the process, it is recommended that the pyrolysis of aromatic dicarboxylic acids **1** be carried out in ethylene glycol,¹⁸ while that of the anhydrides **2** should be performed in xylenes, which readily remove water in the form of an azeotropic mixture.¹⁶ The methods for the aminolysis of the anhydrides **2** by urea are suitable for the synthesis of diimides^{19,20} and 3-dichloromaleimides.²¹ We may note that in the latter case the reaction does not involve the fairly mobile chlorine atoms. (¹⁵N)Homophthalimide has been synthesised by the reaction of (¹⁵N)urea and homophthalic anhydride and was then converted into 1,3-dibromo- (2-¹⁵N)isoquinoline by treatment with PBr₃ and POBr₃ (180 °C, 2 h).²² According to patent data,²³ the interaction of phthalic anhydride **2** with urea in the presence of the (NH₄)₂MoO₄ catalyst at 210 °C leads to a 75% yield of 1,3-diiminoisoindoline **5** after 30 min.

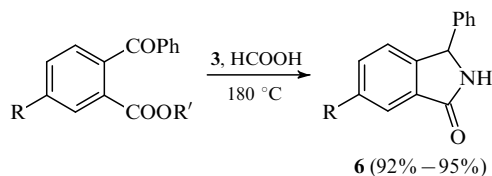


A A Bakibaev, A Yu Yagovkin Tomsk Polytechnic University, prosp. Lenina 30, 634004 Tomsk, Russian Federation. Fax (7-382) 221 90 80. Tel. (7-382) 241 58 61 (A A Bakibaev).
S N Vostretsov Joint-Stock Company 'Organica' 654024 Novokuznetsk, Russian Federation. Tel. (7-384) 337 19 05

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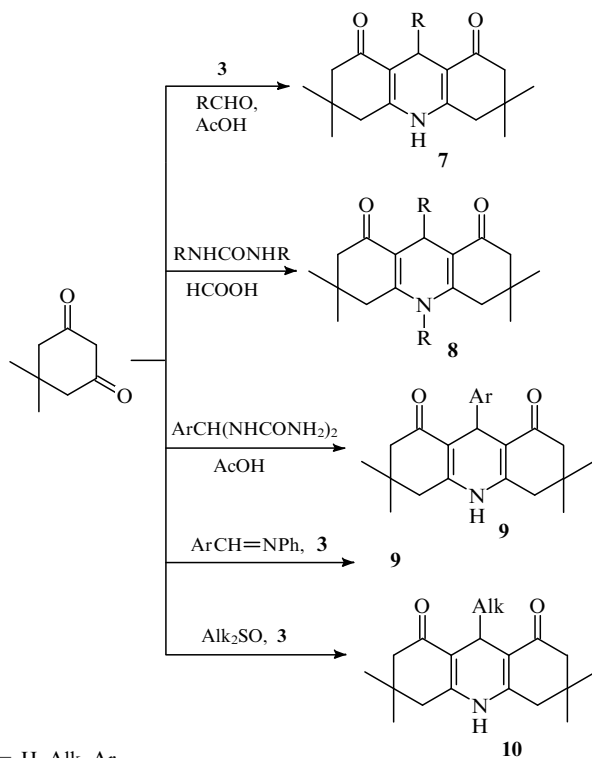
The reductive amination of 2-benzoylbenzoic acids or their esters with urea in formic acid (a modified Leuckart reagent) is completed by the formation of the dihydroisoindolinones **6**, characterised by a broad spectrum of biological activity.²⁴



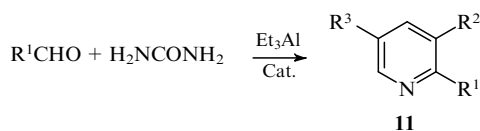
R = H, Cl; R' = H, Me, Et.

The decahydroacridine-1,8-diones **7–10** (Scheme 1) can be readily obtained from 5,5-dimethylcyclohexane-1,3-dione (dime-done) and ureas in formic acid,^{25–27} in acetic acid in the presence of aldehydes,²⁶ in dimethyl sulfoxide (DMSO) in the presence of azomethines,²⁸ with participation of dialkyl sulfoxides,²⁹ or by the reaction of dimedone with arylidenebisureas in glacial acetic acid.³⁰

Scheme 1



R = H, Alk, Ar.



R¹, R², R³ = Alk.

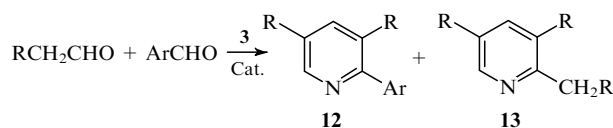
Depending on the structure of the substrates and the ureas, it is possible to obtain with the aid of these reactions the hydrogenated acridine-1,8-diones **7–10** with substituents either in the 9-position (compounds **7**, **9**, and **10**) or in the 9- and 10-positions in the acridine ring (compounds **8**). It had been established^{26, 28} that the reactions of acyclic 1,3-dicarbonyl compounds with urea afford, together with the pyrimidinones which are traditional for reactions of this kind, also 3,5-disubstituted 1,4-dihydropyridines. Under these conditions, dihydropyridines are formed in larger amounts in a neutral or weakly basic medium²⁸ than in an acid medium.²⁶

It has been observed comparatively recently that trisubstituted pyridines **11–13** are formed on liquid-phase condensation of aldehydes with urea in the presence of metal complex cata-

lysts.^{31, 32} Thus, 2,3,5-trisubstituted pyridines **11** have been synthesised on heating aliphatic aldehydes with urea in an autoclave up to 200 °C in the presence of triethylaluminium and cobalt di(2-ethylhexanoate) as the catalyst (see Scheme 1).³¹

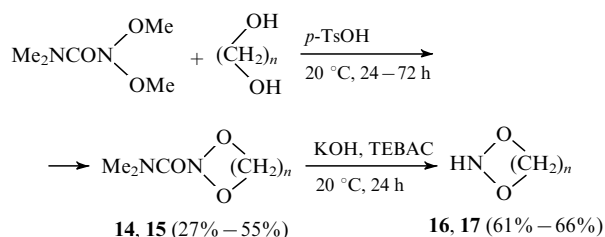
The mixed condensation of benzaldehyde with butyraldehyde and urea under analogous conditions makes it possible to obtain 3,5-diethyl-2-phenylpyridine in ~83% yield and with a high selectivity.³¹

The liquid-phase condensation of aliphatic C₄–C₈ aldehydes with aromatic aldehydes and urea in the presence of metal complex catalysts, obtained by reducing cobalt 2-ethylhexanoate or Co, Al, Ni, V, Cu, Pd, Ti, Zr, *etc.* acetylacetonates with the aid of AlR₃, BR₃, or MgR₂ leads to the aryl- and heteroaryl-substituted pyridines **12** and **13**.³² The composition of the reaction mixture and the yield of the reaction products depend on the structure of the initial aldehydes and the catalyst.



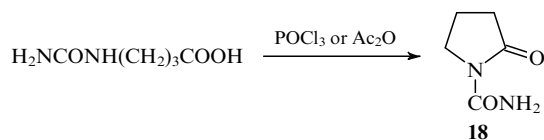
R = Alk; Ar = Ph, 4-NO₂C₆H₄, , , 2-HOC₆H₄, 2-FC₆H₄, 2-MeOC₆H₄.

The reactions of 1,1-dimethoxyureas with ethylene glycol and propane-1,3-diol in the presence of toluene-*p*-sulfonic acid lead to 2,2-dimethylcarbamoyl-1,3,2-dioxazolidine **14** and 2,2-dimethylcarbamoylperhydro-1,3,2-dioxazine **15** respectively. On hydrolysis in the KOH-benzyltriethylammonium system, the latter afford 1,3,2-dioxazolidine **16** and perhydro-1,3,2-dioxazine **17**.³³

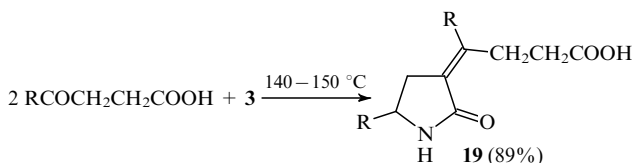


n = 2 (**14**, **16**), 3 (**15**, **17**); TEBAC = Et₃BnN⁺Cl[−].

The cyclisation of 4-ureidobutanoic acid either in the presence of phosphorus oxide chloride under an inert atmosphere^{34, 35} or on treatment with acetic anhydride³⁶ leads to the pyrrolidinone **18**.



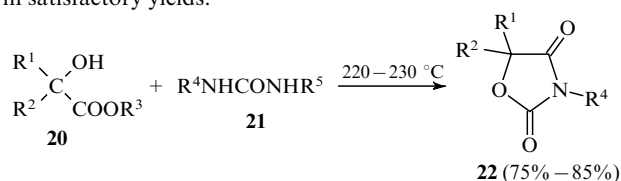
The azacyclisation of β-arypropionic acids on treatment with urea makes it possible to obtain substituted 4-pyrrolidin-2-ones **19** in high yields.³⁷



R = Ph, 4-BrC₆H₄, tetralinyl.

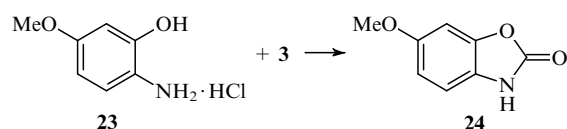
High-temperature (160–230 °C) reactions of ureas with 1,2-bifunctional compounds, one of the functional groups of which is OH, constitute a fairly general method of synthesis of oxazolinones and oxazolidinones. Thus heating of the α-hydroxyesters **20**

with 1,3-disubstituted ureas **21** affords the oxazolidine-2,4-diones **22** in satisfactory yields.³⁸

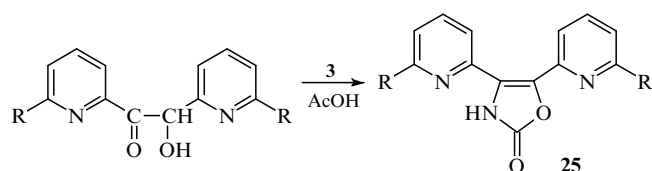


$\text{R}^1, \text{R}^2 = \text{H}, \text{Alk} (\text{C}_1 - \text{C}_4); \text{R}^3 = \text{Alk} (\text{C}_1 - \text{C}_{10}); \text{R}^4 = \text{R}^5 = \text{H}, \text{Ar}.$

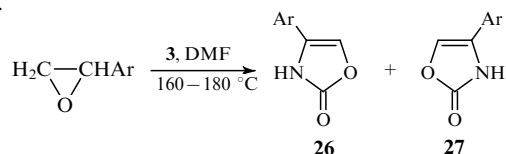
Fusion of 2-amino-5-methoxyphenol hydrochloride **23** with urea leads to 6-methoxybenzoxazolin-2-one **24**.³⁹



In contrast to other acyloins, 1,2-pyridoins afford predominantly substituted 4,5-bis(2-pyridyl)-4-oxazolin-2-ones **25** on heating with urea in glacial acetic acid.⁴⁰



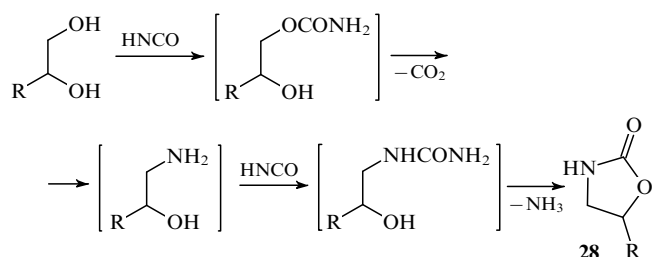
Aryloxiranes undergo interesting reactions on heating with urea without a solvent or in dimethylformamide.⁴¹ The reaction is kinetically controlled: electron-donating substituents in the *ortho*- and *para*-positions of the phenyl group promote the preferential formation of the 5-aryloxazolin-2-ones **27** while electron-accepting substituents promote the formation of 4-aryloxazolin-2-ones **26**.



The reactions of vicinal diols with urea, leading to 5-R-oxazolidin-2-ones **28** have been investigated.^{42–44} Compounds **28** can also be readily obtained from the monoesters of glycerol,^{42,43} 3-aminopropane-1,2-diol,⁴² and 2,3-epoxypropane-1,2-diol.⁴³

The formation of the oxazolidinones **28** from diols and related compounds apparently proceed *via* a series of consecutive stages, presented in Scheme 2.⁴²

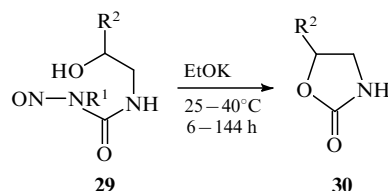
Scheme 2



$\text{R} = \text{ArO}, \text{NH}_2.$

Since these reactions take place above the melting point of urea (under these conditions, it begins to undergo thermal decomposition into NH_3 and isocyanic acid⁴⁵), the nature of the carbamoylating reagent in Scheme 2 is evident. As regards one of the key stages in the Scheme, namely the decarboxylation stage, it too is entirely unambiguous, since the tendency of carbamates to decarboxylate at elevated temperatures is generally known.

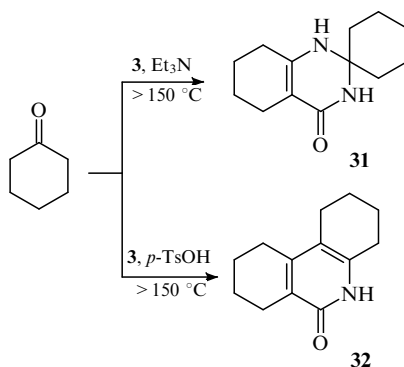
After treatment of 3-(2-hydroxyalkyl)-1-nitrosoalkylureas **29** with bases the oxazolidin-2-ones **30** were isolated in 73%–96% yields.⁴⁶



$\text{R}^1 = \text{Me}, \text{Et}; \text{R}^2 = \text{H}, \text{Me}.$

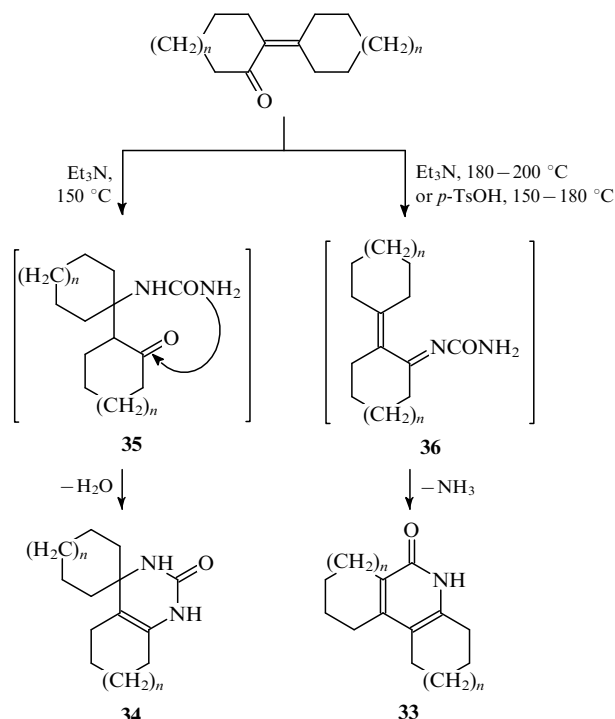
It has been postulated that the reaction begins with the intramolecular nucleophilic attack by the hydroxy-group on the electrophilic carbon atom of the carbonyl group. The intermediate hemiacetal decomposes into the oxazolidinone **30** and the intermediate $\text{R}^1\text{N}=\text{NO} - \text{K}^+$.

The high-temperature reaction of cyclohexanone with urea in triethylamine makes it possible to synthesise the spiro-compound **31**, whilst in the presence of toluene-*p*-sulfonic acid, decahydrophenanthridinone **32** is formed.^{47–49}

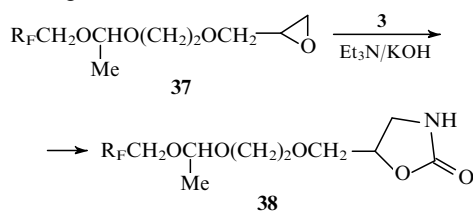


The condensation of urea with α,β -unsaturated ketones in acid (HCl , 60°C) or basic (NEt_3 , 150°C) media leads to substituted 2-oxatetrahydro-pyrimidines.^{50,51} It has been observed⁵² that, on heating of 2-cyclohexylidenecyclohexanone and 2-cyclopentylidenecyclopentanone to 150°C in triethylamine, the pyridinones **33** are formed only in trace amounts. They are the main products when the reaction is carried out at a higher temperature in the presence of NEt_3 or toluene-*p*-sulfonic acid.

The azaheterocycle **33** becomes the main product when the reaction is carried out at higher temperatures ($180-200^\circ\text{C}$) in the presence of triethylamine or toluene-*p*-sulfonic acid. The tetrahydropyrimidinone **34** is formed as a result of the nucleophilic Michael addition of urea to the double bond of the α,β -unsaturated ketone with subsequent dehydration of the alkylurea **35**. On the other hand, the pyridones **33** are apparently formed *via* the deamination of the intermediate **36**.

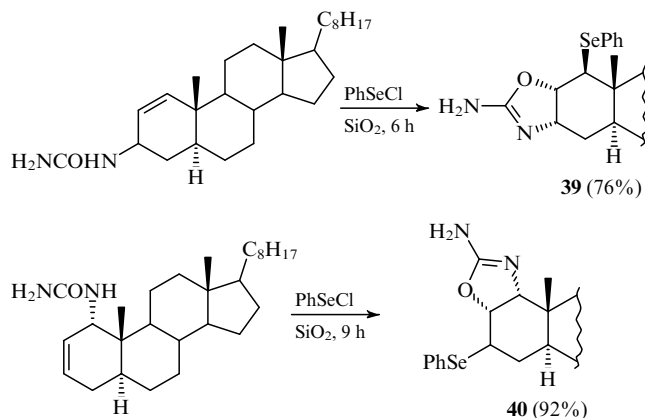


The regioselective opening of the epoxide ring in the epoxide **37**, containing the polyfluoroacetal group, by urea in a basic medium leads to the creation of the oxazolidine ring. Compounds **38**, formed under these conditions, are new functional fluorine-containing monomers.⁵³

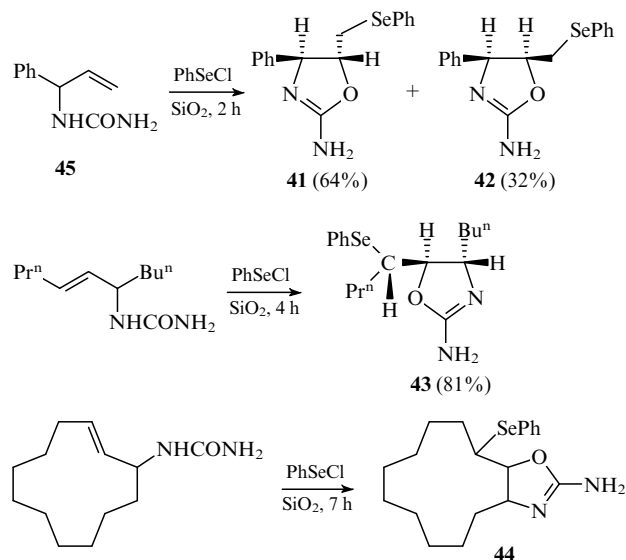


$\text{R}_\text{F} = \text{H}(\text{CF}_2)_n$; $n = 2-8$.

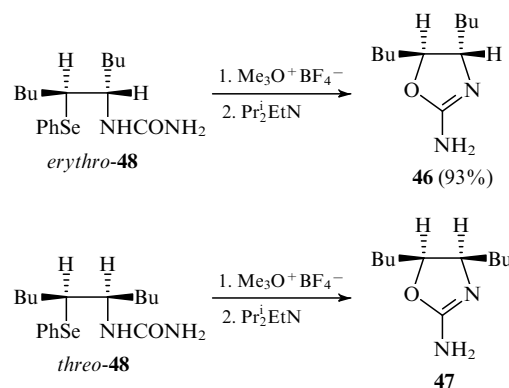
A series of studies⁵⁴⁻⁵⁸ have been devoted to the intramolecular cyclisation of unsaturated ureas initiated by various catalysts. A method of synthesis of 4,5-dihydrooxazoles **39-44** from allylureas by intramolecular heterocyclisation, initiated by phenylselenenyl chloride and catalysed by silica gel under an inert atmosphere, has been described.⁵⁴



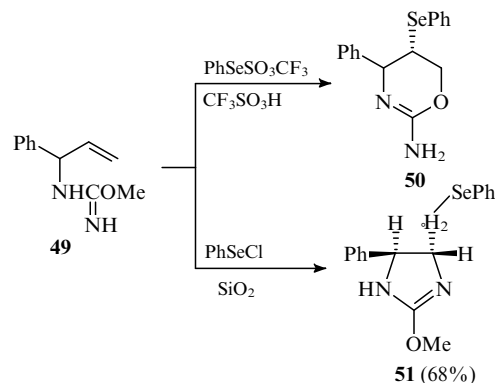
The formation of a mixture of diastereoisomers of the oxazolines **41** and **42** with a twofold excess of the *trans*-isomer **41** is the stereochemical outcome of the intramolecular cyclisation of the terminal alkenylurea **45** with participation of PhSeCl .⁵⁴



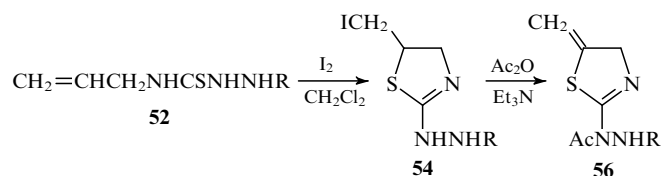
2-Aminooxazolines **46** and **47** are also formed stereospecifically from phenylselenenylurea **48** in the presence of bases. Under these conditions, the *trans*-oxazoline **46** is formed from the *erythro*-isomer, while the analogous treatment of the *threo*-isomer leads to the *cis*-oxazoline **47**.⁵⁴



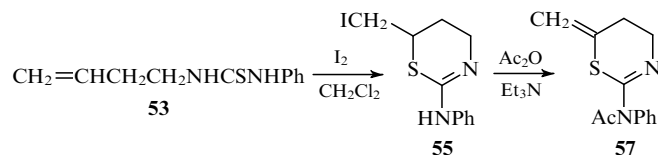
Allylisourea **49** interacts with organic selenium compounds under an inert atmosphere. Depending on the reaction conditions, it cyclises with formation of either the dihydro-1,3-oxazine **50** or the imidazoline **51**.⁵⁵



N-Alkenylthiosemicarbazides **52** and the thioureas **53** readily undergo iodocyclisation to compounds **54** and **55** in methylene chloride. Their subsequent treatment with Ac_2O in triethylamine affords 2-*R*-1,3-thiazolines **56** and 2-(*N*-phenylacetamido)dihydro-1,3-thiazine **57** with an exocyclic methylene group.⁵⁹

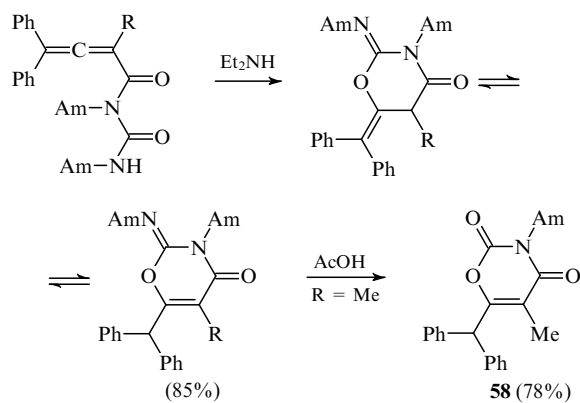


R = H, Ph.



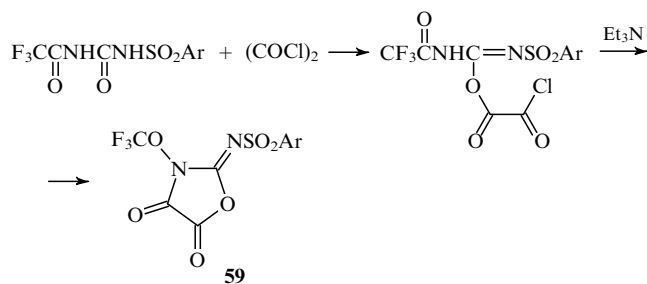
The cyclisation of 1-allyl-3,3-diethylthiourea to 2-diethyl-amino-5-iodomethyl-1,3-thiazoline on treatment with iodonium nitrate in the presence of pyridine proceeds without the retention of the exocyclic methylene group.⁵⁹

The intramolecular cyclisation of allenic acylureas on treatment with diethylamine, *via* a series of intermediate stages, opens a path to tetrahydro-1,3-oxazine-2,4-diones **58** which are difficult to obtain.⁶⁰

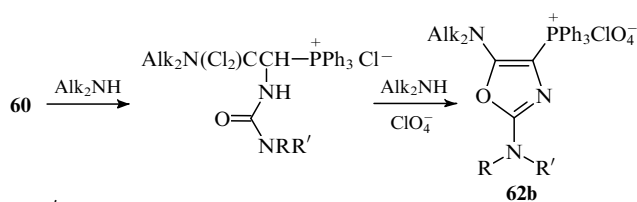
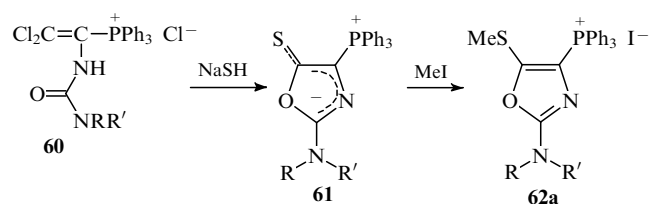


R = Me, Ph; Am = C₅H_{11-n}.

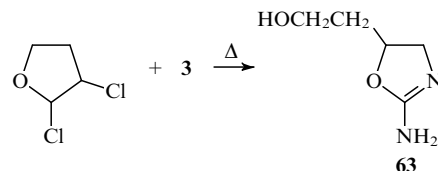
It has been established that the reactions of *N*-arenesulfonyl-*N'*-trifluoroacetylureas and oxalyl chloride under severe conditions in the presence of triethylamine are completed by the formation of 1,3-oxazolidine-4,5-diones **59**.⁶¹



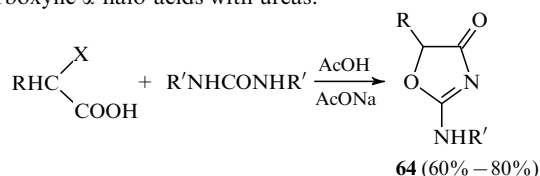
The cyclisation of phosphorylated *N*-(2,2-dichlorovinyl)ureas **60** to phosphorylated mesomeric betaines **61** and oxazoles **62a,b** proceeds in an interesting manner.⁶²


$$R, R' = H, Alk.$$

On heating with urea, 2,3-dichlorotetrahydrofuran gives rise to 2-amino-5-(2-hydroxyethyl)oxazoline **63**.⁶³ The reaction proceeds *via* the opening of the furan ring with subsequent cyclisation of the intermediate substituted urea.

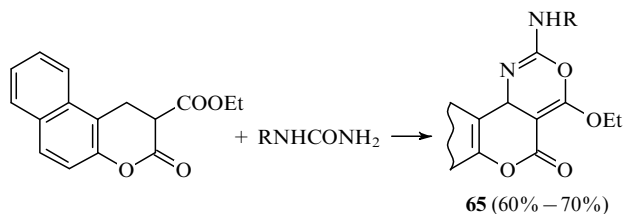


Ureides, which on refluxing in AcOH afford 2-aryl(cycloalkyl)amino-4-oxazolinones **64**, are obtained by the interaction of carboxylic α -halo-acids with ureas.⁶⁴



X = Cl, Br;
R = H, Ph; R' = H, Ar, cyclo-Alk.

The oxazines **65** have been obtained in satisfactory yields in the study of the reactions of 3-ethoxycarbonyl-5,6-benzocoumarin with monosubstituted ureas.⁶⁵



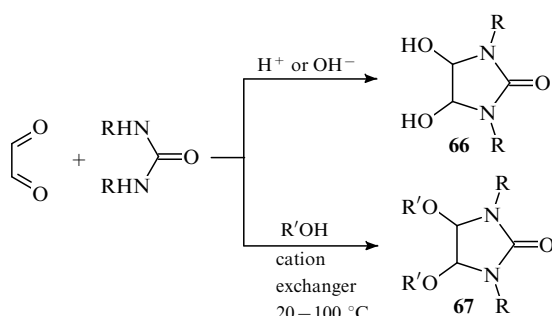
R = H, Alk, Ar.

The photocyclisation of acryloylureas (Hg lamp, 450 W, Pyrex, argon) leads to the formation of *N*-substituted azetidin-2-one derivatives.⁶⁶

2. Synthesis of heterocycles containing two nitrogen atoms

a. Reactions of ureas with 1,2-bifunctional compounds

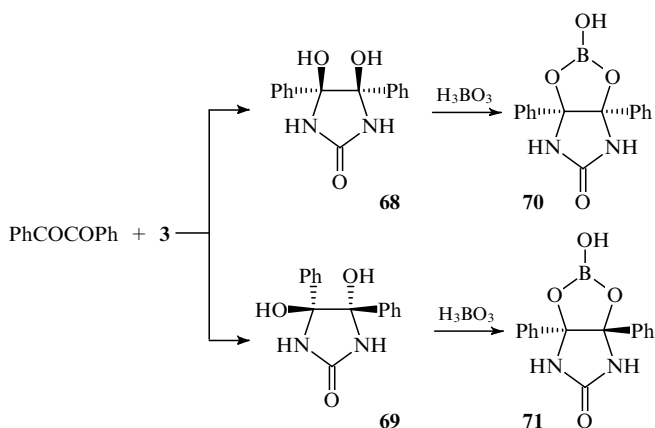
The azaheterocycles containing two nitrogen atoms are represented mainly by imidazole derivatives. The reactions of ureas with 1,2-bifunctional compounds proceed as a rule in polar solvents at temperatures below the decomposition temperature of urea ($< 132.5\text{ }^{\circ}\text{C}$) and afford imidazolidinones (compounds with a carbamide fragment in the ring). Thus the interaction of equimolar amounts of urea and glyoxal in an alkaline or acid medium leads to 4,5-dihydroxyimidazolidin-2-ones **66**.^{67–69} The 4,5-dialkoxy-derivatives **67** are formed in the reactions of ureas with glyoxal in alcoholic solutions in the presence of cation exchangers.⁷⁰



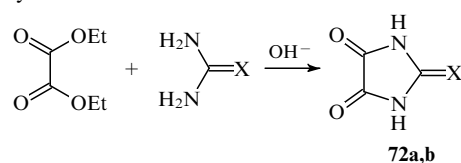
The vicinal diols **66** and their ethers **67** are convenient starting materials for the synthesis of a wide variety of bicyclic hetero-systems and, what is especially important, for the synthesis of bicyclic compounds with an asymmetric structure.⁷¹ In the acid-catalysed reaction with an equimolar amount of ureas, aromatic 1,2-diketones afford 4,5-diaryl-4,5-dihydroxyimidazolidin-2-ones.^{72, 73}

It was later established that a mixture of the *cis*- and *trans*-isomers of 4,5-dihydroxyimidazolidinones **68** and **69** is formed in the reactions of 1,2-dicarbonyl compounds with ureas.⁷⁴

It has been shown on the basis of ¹³C and ¹⁵N NMR spectroscopic and chromatographic data that the interaction of benzil with urea leads to mixture of the *cis*-diols **68** and *trans*-diols **69** in proportions of 65 : 35. The formation of the cyclic boric acid esters **70** and **71** has been used successfully for the separation of the diastereoisomers of such diols.⁷⁵

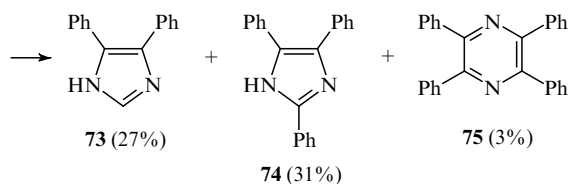
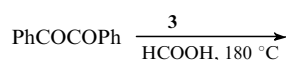


When urea or thiourea is heated with oxalic acid esters, parabanic acid **72a** or its 2-thio-analogue **72b** are formed respectively.⁷⁶

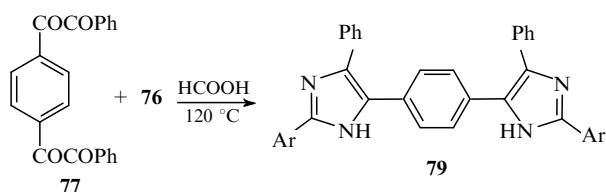
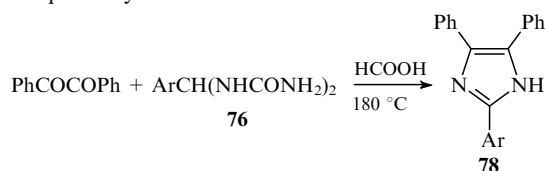


X = O (**a**), S (**b**).

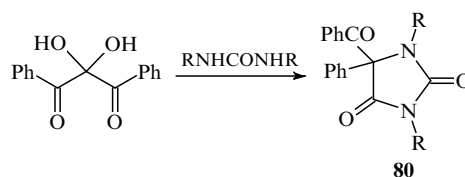
The reaction of benzil with urea in formic acid at a high temperature leads to a mixture of the imidazoles **73** and **74** and tetraphenylpyrazine **75**.⁷⁷



The arylidenebisureas **76**, known as the starting materials for the synthesis of pyrimidines, afford exclusively 2-aryl-4,5-diphenylimidazoles **78** and phenylenebisimidazolines **79** in their reactions with benzil in formic acid or with the tetraketone **77** in acetic acid respectively.^{77, 78}

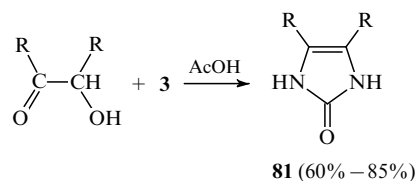


The hydrate of diphenylpropanetrione reacts with ureas in an acid or neutral medium to form the hydantoin derivatives **80**,⁷⁹ although the latter are usually obtained under alkaline conditions.^{1–3}



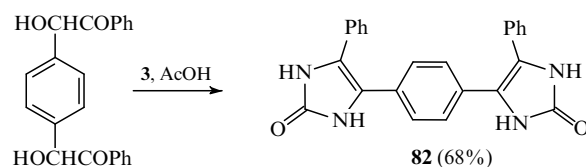
R = H, Alk.

One of the common reactions for the synthesis of imidazolin-2-ones **81** is the cyclisation of acyloins with urea.^{40, 80}



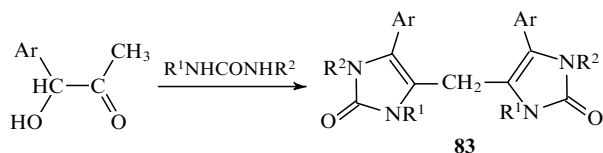
R = Alk, Ar, ArAlk.

Arylenebishydroxyketones react with urea under an argon atmosphere to form arylenebisimidazolinones **82**.⁸¹



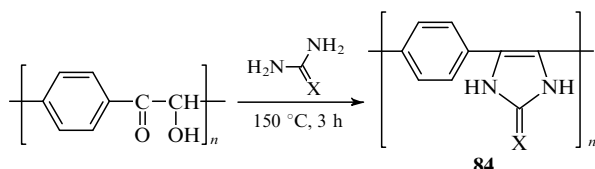
Certain alkylarylacyloins react with urea under the conditions of acid catalysis, affording the methylenebisimidazolinones **83**,⁸² which are formed with participation of the activated CH₃ groups.

Scheme 3



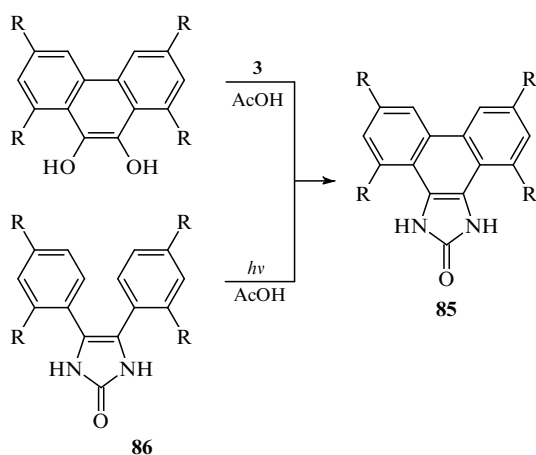
$\text{R}^1 = \text{R}^2 = \text{H, Me.}$

Polyacyloins also react with urea and thiourea, giving rise to polyimidazolinones (thiones) **84**, which are important ingredients of polymeric composite materials.⁸³



$\text{X} = \text{O, S}; n = 15-10000.$

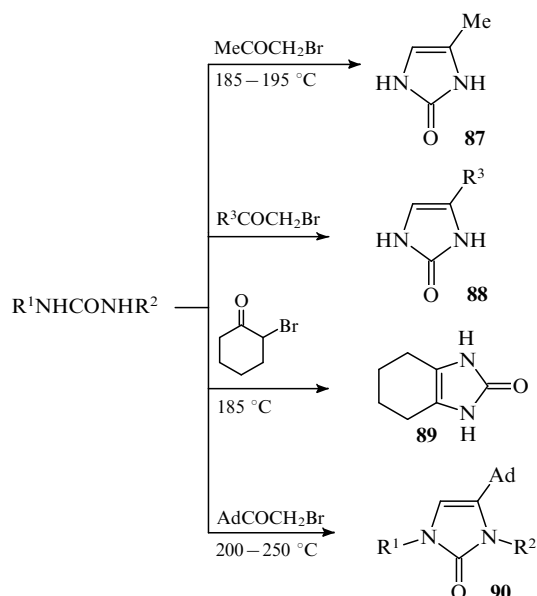
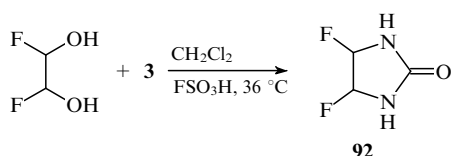
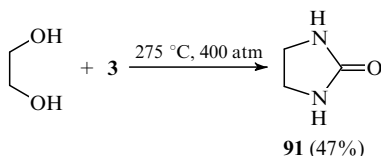
The cyclocondensation of phenanthrene-9,10-diols with urea leads to the phenanthroimidazolinones **85**, the structure of which has been confirmed by specific synthesis — the photolysis of 4,5-diaryl-2-imidazolinones **86** in acetic acid.⁸⁴



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

Aliphatic and alicyclic α -bromo ketones proved to be convenient starting materials for the synthesis of the imidazolin-2-ones **87–90**^{85–90} (Scheme 3). Imidazolinones of type **88** have also been obtained from α -keto alcohols and urea at comparatively low temperatures (125 $^\circ\text{C}$) in the presence of phosphomolybdic acid.⁹¹ The imidazolinones **87** and **88** are intermediates in the synthesis of biotin.

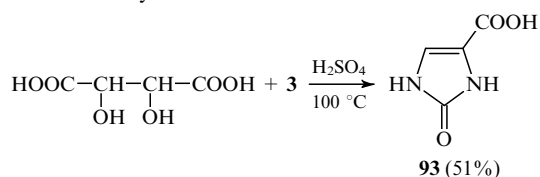
The imidazolidin-2-ones **91** and **92** are obtained as a rule by the condensation of aliphatic 1,2-diols with urea. Thus the interaction of ethylene glycol with urea under fairly severe conditions affords imidazolidin-2-one **91**.⁹²



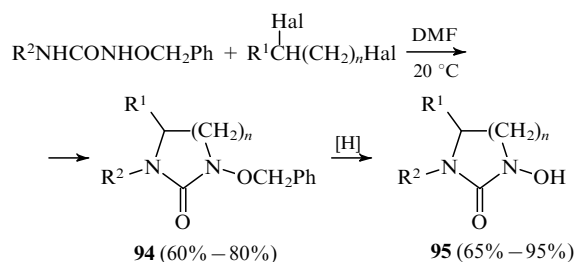
$\text{R}^1 = \text{H, Ph, Ac}; \text{R}^2 = \text{H}; \text{R}^3 = \text{C}_3\text{H}_{11}; \text{Ad} = \text{adamantyl.}$

The presence of a fluorine atom in the 1- and 2-positions in the initial ethylene glycol facilitates significantly the formation of 4,5-difluoroimidazolidin-2-one **92**.⁹³

The cyclisation reaction between tartaric acid and urea **3** in concentrated sulfuric acid proceeds with participation of only the hydroxy-groups and is completed by the formation of 2-oxoimidazoline-4-carboxylic acid **93**.⁹⁴

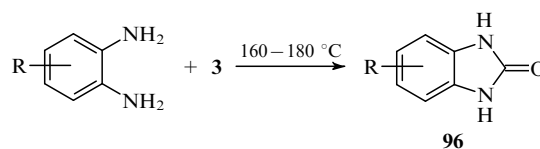


Alkoxyimidazolidin-2-ones **94** ($n = 1$) are obtained by the alkylation of alkoxyureas with dihaloalkanes in DMF. The hydrogenolysis of compounds **94** (HCOONH_4 -Pd/C) leads to the corresponding *N*-hydroxyimidazolidin-2-ones **95** ($n = 1$).⁹⁵



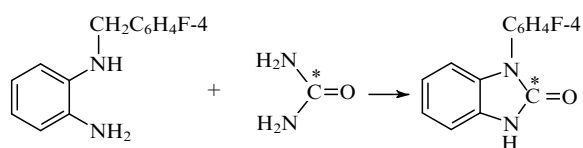
$\text{R}^1 = \text{COOEt, H, CN}; \text{R}^2 = \text{H, Alk}; n = 1, 2.$

The commonest method of synthesis of benzimidazolin-2-ones **96** is perhaps the cyclocondensation of *o*-phenylenediamines with urea **3**.^{96–101}

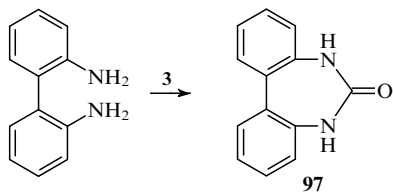


$\text{R} = \text{H, Alk, Ar, Hal, OAlk, COOH, CN.}$

Heterocyclic 1,2-diamines react similarly with urea.¹⁰² It has been shown that the interaction of *N*-(4-fluorobenzyl)-*o*-phenylenediamine with [¹⁴C]urea results in the formation of 2-[¹⁴C]-1-(4-fluorophenyl)-2,3-dihydrobenzimidazolin-2-one.¹⁰³



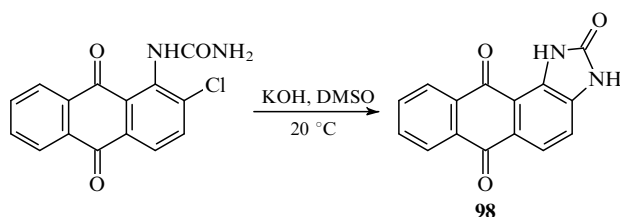
It has been reported¹⁰⁴ that, on refluxing with urea in pentyl alcohol, 2,2'-diaminobiphenyl readily affords dibenzodihydrodi-1,3-azepin-2-one **97**.



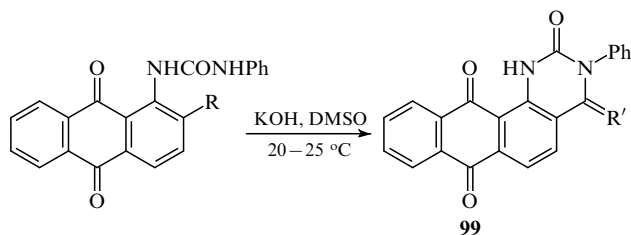
Aliphatic 1,2-diamines condense with urea at 200–260 °C in polar solvents.^{105–107} At a temperature above 180 °C, urea forms cyclic products also with diamines of the type RNH(CH₂)_{*n*}NHR (*n* = 3, 4).¹⁰⁸

b. Intramolecular cyclisation of ureas

Anthraquinonoimidazolinone **98** has been synthesised by intramolecular substitution of the chlorine atom in a superbasic medium.¹⁰⁹

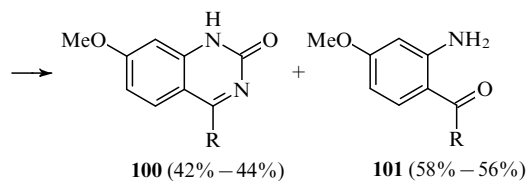
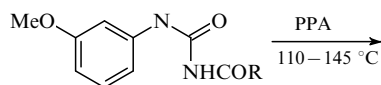


The intramolecular cyclisation of 2-substituted ureidoanthraquinones in a superbasic medium leads to angular condensed heterosystems — derivatives of naphthoquinazoline **99**.¹¹⁰



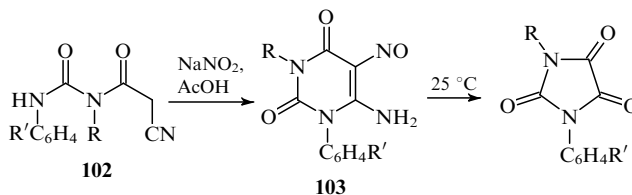
R = C≡CPh, COOH; R' = Z-CHPh (14.5%), E-CHPh (51%), O (27%).

The cyclisation of *N*-acyl-*N'*-(3-methoxyaryl)ureas in the presence of polyphosphoric acid (PPA) affords the dihydroquinazolinones **100** and their hydrolysis products **101**.¹¹¹



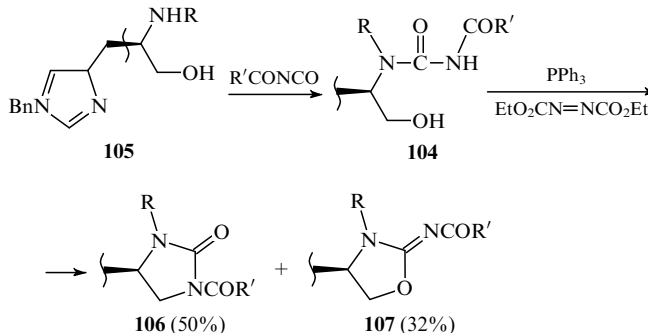
R = Me, Het.

On treatment with sodium nitrite in water in the presence of acetic acid, the cyanoacetylureas **102** are initially converted into the uracil derivatives **103**. However, the latter undergo an unexpected transformation of the pyrimidine heterocycle, whereupon derivatives of parabanic acid are formed.¹¹² The available literature data on the ways in which heterocycles are transformed¹¹³ do not provide a satisfactory mechanism of this reaction.



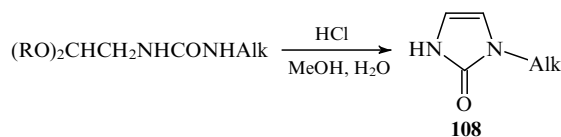
R = H, Me; R' = H, Hal, Me.

The cyclisation of the aroylureas **104**, obtained from the amino alcohols **105** and aroyl isocyanates, leads to a mixture of heterocyclic compounds — the *O*- and *N*-alkylation products **106** and **107**. An important feature is that the configuration of the asymmetric carbon atom is retained.¹¹⁴

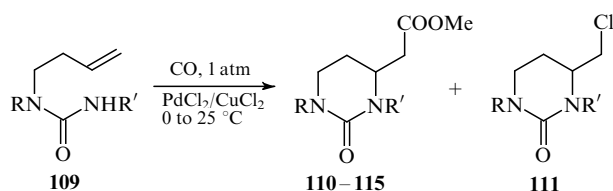


R = Et, Buⁱ; R' = Ph, 4-ClC₆H₄, 2,4-Cl₂C₆H₃, 2-Cl-4-NO₂C₆H₃.

It has been proposed¹¹⁵ that the intramolecular cyclisation of the acetals of aldehydoureas in an acid medium be employed in the synthesis of 1-alkyl-4-imidazolin-2-ones **108**.¹¹⁵

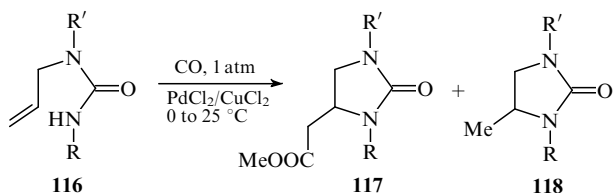


On carbonylation in the presence of PdCl₂/CuCl₂ in methanol at room temperature and atmospheric CO pressure, the unsaturated urea **109** (R = CH₂Ph, R' = Me) gives rise to a mixture of perhydrogenated pyrimidinones **110** and **111** (yields 82% and 14% respectively). Only compound **110** is formed at 0 °C. Compounds **112**–**115** have been obtained under similar conditions.¹¹⁶

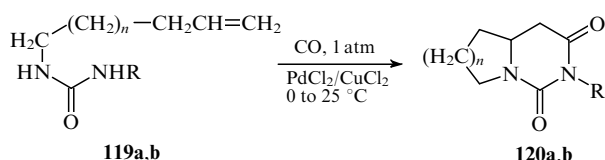


R = CH₂Ph; R' = Me [**110**, (82%)]; Prⁱ, Prⁱ [**112**, (84%)];
Prⁱ, Me [**113**, (82%)]; Bu^t, Me [**114**, (47%)]; Ph, Me [**115**, (58%)].

The pentylureas **116** afford mixtures of the hydrogenated imidazolidinones **117** and **118** under similar conditions.¹¹⁶ 1,3-Diazabicyclo[4.3.0]nonane-2,4-diones **120a** and 1,3-diazabicyclo[4.4.0]decane-2,4-diones **120b** are formed under the same conditions from *N*-penten-4-yl- and *N*-hexen-5-yl-ureas (compounds **119a** and **119b**) respectively.¹¹⁶

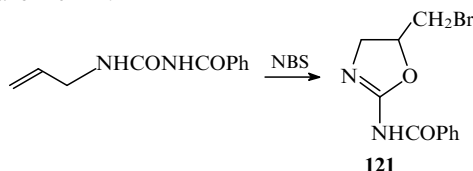


R = Me, Prⁱ; R' = Me, Prⁱ, CH₂Ph.

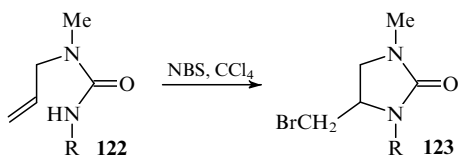


R = Me, Prⁱ, CH₂Ph; *n* = 1(**a**); 2(**b**).

The bromocyclisation of allylbenzoylurea on treatment with *N*-bromosuccinimide proceeds with formation of the substituted oxazoline **121**.⁵⁶

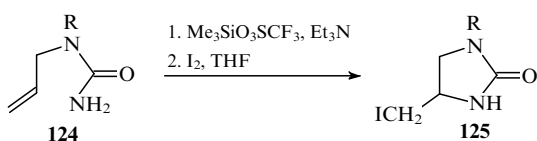


In contrast to this, the halocyclisation of the allylureas **122**, initiated by *N*-bromosuccinimide in CCl₄, leads to the bromomethylimidazolidinones **123**.⁵⁸



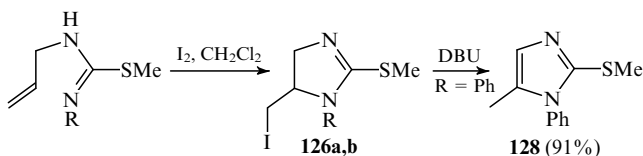
R = Ar, 2-Cl-C₆H₄CO, EtO₂CCH₂.

Preliminary silylation with trimethylsilyl trifluorosulfonate in the presence of NEt₃ in CH₂Cl₂ is necessary for the conversion of the allylureas **124** into the iodoethylimidazolines **125**.⁵⁷

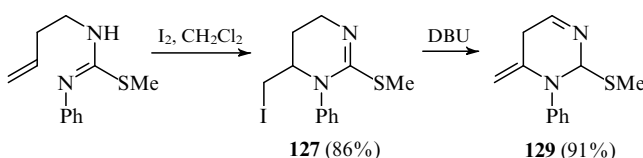


R = Me (83%), PhCH₂ (71%).

Imidazoline derivatives **126** or tetrahydropyrimidine derivatives **127** are formed on iodocyclisation of unsaturated isothio-ureas. After treatment with diazabicycloundecane, they are converted into compounds **128** and **129** respectively.⁵⁷

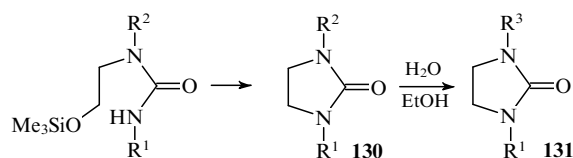


R = Ph [**126a**, (89%)], Ac [**126b**, (77%)].



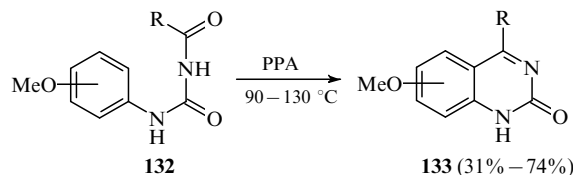
DBU = diazabicycloundecene.

After prolonged storage in the light in the absence of contact with air, intramolecular cyclocondensation of substituted 2-trimethylsilyloxy ethylureas takes place and leads to the imidazolidinones **130**. Their subsequent hydrolysis affords the imidazolidin-2-ones **131**.¹¹⁷



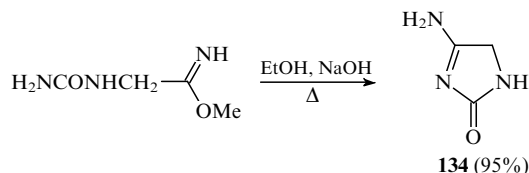
R¹ = Alk, R² = Me₃Si, Me₃SiOCH₂CH₂, R³ = H, CH₂CH₂OH.

The heterocyclisation of *N*-acyl-*N'*-arylureas **132** on treatment with polyphosphoric acid leads to 4-substituted quinazolin-2-ones **133**, which are believed to be formed as a result of a reaction of the Bischler–Napieralski type.¹¹⁸



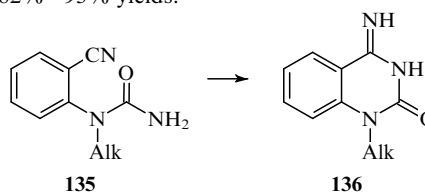
R = Alk, Ph.

According to patent data,¹¹⁹ the refluxing of the iminoester of ureidoacetic acid with alkali in aqueous alcohol leads to 4-amino-Δ³-imidazolin-2-one **134** in a high yield.

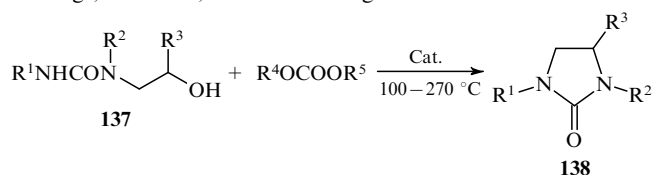


134 (95%)

It has been established¹²⁰ that, on exposure to ultrasound in the presence of baker's yeast, *ortho*-substituted carbamide derivatives of benzonitrile **135** cyclise to the 4-iminoquinazolinones **136** in 82%–93% yields.



The cyclisation reaction between β -hydroxyethyl(propyl)-ureas **137** and carbonic acid esters, catalysed by Group I–IV metal halides, is completed by the formation of substituted imidazolidin-2-ones **138** in yields up to 60%. They are of interest as monomers and comonomers for the manufacture of plastics, coatings, varnishes, and ion-exchange resins.¹²¹

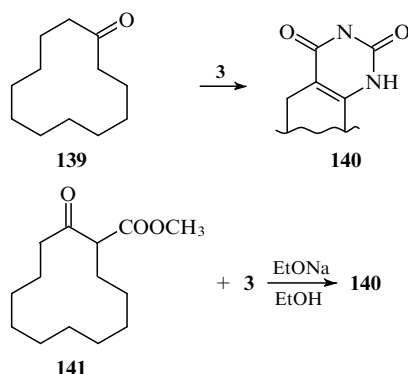


$\text{R}^1 = \text{R}^2 = \text{Cl, Br, NO}_2, \text{CF}_3, \text{Alk}(\text{C}_1\text{--C}_4)\text{O, Ar; R}^3 = \text{H, Me; R}^4, \text{R}^5 = \text{Alk}(\text{C}_1\text{--C}_4);$

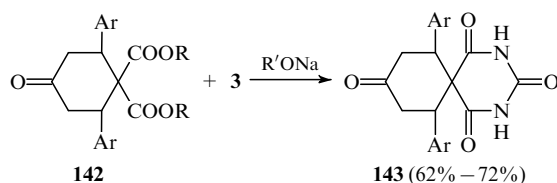
c. Other methods of synthesis

An erroneous structure was initially attributed to the compound obtained by the condensation of cyclohexanone with urea on refluxing in *o*-xylene.¹²² It was later established that⁴⁷ it is 5,6,7,8-tetrahydrospiro[cyclohexane-1,2'-(1*H*)-quinazoline]-4'-(3'*H*)-one. In contrast to cyclohexanone, the high-temperature condensation of cyclododecanone **139** with urea at 280 °C¹²³ or on refluxing in *o*-xylene in the presence of *p*-TsOH (150 °C, 8 h)¹²³ leads to the condensed pyrimidine (1*H*,3*H*)-2,4-dione **140**.

Compound **140** has also been obtained by an independent synthesis from methyl 2-oxocyclododecanecarboxylate **141** and urea in the presence of sodium ethoxide.¹²³

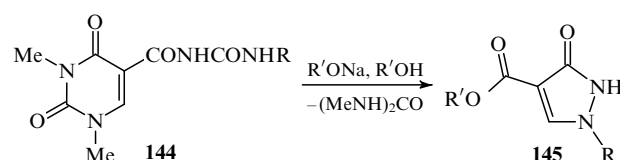


The spiro-compounds **143** have been synthesised in satisfactory yields by the cyclocondensation of the dialkyl esters of 2,6-diaryl-4-oxocyclohexane-1,1-dicarboxylic acids **142** with urea in the presence of sodium alkoxides.¹²⁴



$\text{R} = \text{R}' = \text{Me, Et.}$

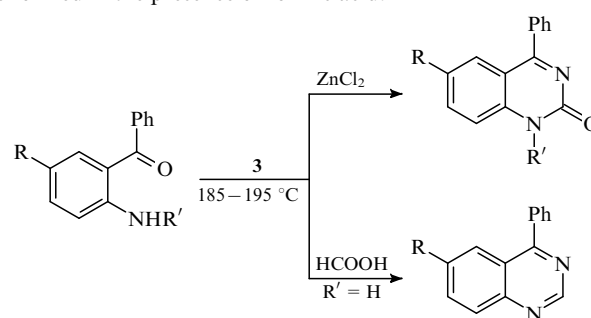
A remarkable example of the intramolecular rearrangement of the uracil derivatives **144** to the pyrazolones **145** has been described.¹²⁵ Thus the refluxing of the ureides **144** in EtOH or MeOH in the presence of sodium alkoxides affords the pyrazolones **145** and the symmetrical dimethylurea as a result of the intramolecular rearrangement of the ureides **144** and the attack by the alkoxy-group on the carbonyl C(6) atom.¹²⁵



$\text{R} = \text{H, Me; R}' = \text{Me, Et.}$

2-Aminobenzophenones are key compounds for the synthesis of tranquilisers of the 1,4-benzodiazepine series. The heterocyclisation reaction between 2-aminobenzophenones and urea **3** leads to quinazoline derivatives.^{126–129}

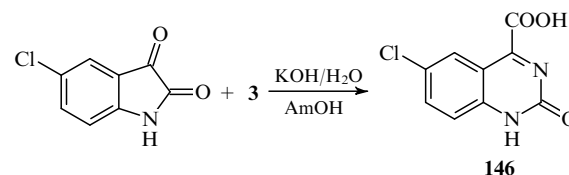
The cyclisation in the presence of ZnCl_2 affords 1- R' -6- R -4-phenylquinazolin-2-ones,^{128–130} while 6- R -4-phenylquinazolines are formed in the presence of formic acid.^{131, 132}



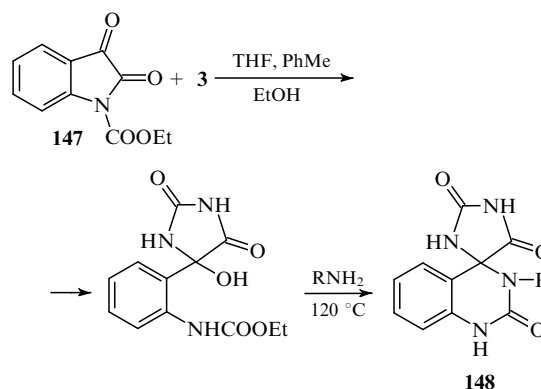
$\text{R} = \text{H, Cl; R}' = \text{H, Me.}$

It has been shown that *N*-allyl-*N*-nitroso-urea is converted into pyrazole in 18% yield *via* the intermediate vinyldiazomethane.¹²⁵

6-Chloro-2-quinazoline-4-carboxylic acid **146** has been synthesised by condensing 5-chloroisatin with urea in 1-pentanol in the presence of aqueous KOH.¹³¹

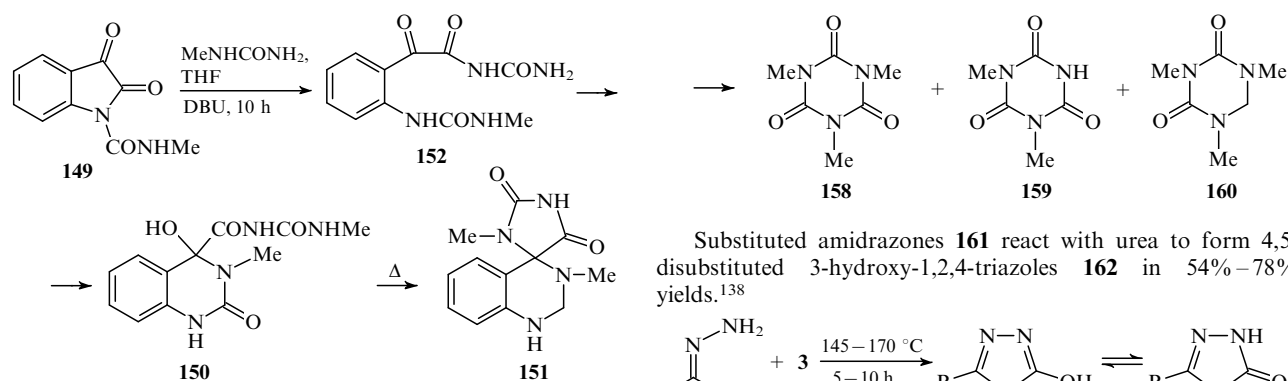


It has been established that, on heating in a sealed tube with ammonia, hydrazine, or hydroxylamine, *N*-ethoxycarbonylisatin **147** and urea afford spiro[imidazolidine-4,4'-(1*H*)-quinazoline]-2,2',5(3*H*) triones **148** after 4 h at 120 °C.¹³²



R [yield (%): H(59), NH_2 (57), OH(15).

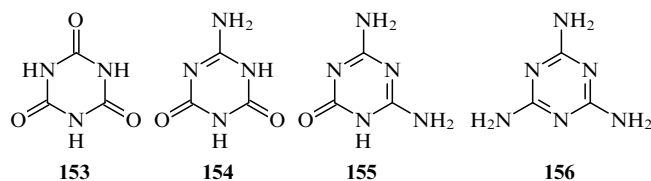
On interaction with methylurea in boiling THF, *N*-methylcarbamoylisatin **149** recycles to the ureidoquinazolin-2-one derivative **150** in 29% yield after 5 h in the presence of diazabicycloundecene. On refluxing in 1,2-dichlorobenzene, compound **150** is converted into the spiro-compound **151** in 97% yield.¹³²



According to the data of Yamagishi *et al.*,¹³³ the ureidoquinazolinone **150** is formed from *N*-methylcarbamoylisatin **149** and methylurea *via* the acyclic intermediate **152**.

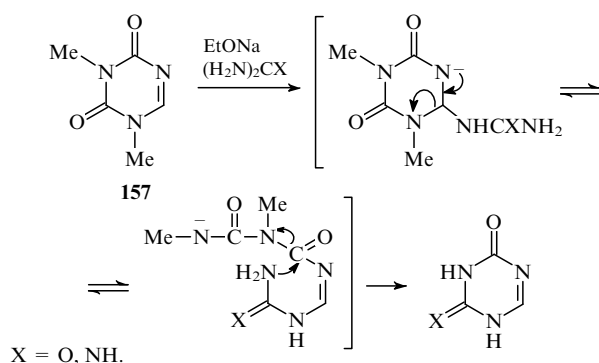
3. Syntheses of heterocycles containing three nitrogen atoms

Cyanuric acid — 1,3,5-triazine-2,4,6-trione **153** — is perhaps the main representative of azaheterocycles containing three nitrogen atoms. As a consequence of its unique properties, it has found application in various branches of industry.¹³⁴ Cyanuric acid is obtained mainly by the pyrolysis of urea in organic solvents in a fluidised bed on the surface of metals.¹³⁴ However, the pyrolysis affords, together with cyanuric acid, also related triazines — ammelide **154**, ammeline **155**, and melamine **156** — the products of the amination of cyanuric acid which are of independent practical interest.^{134, 135}

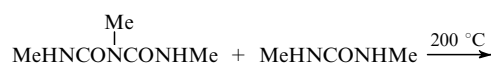


All these heterocycles are products of the cyclotrimerisation of isocyanic acid and/or cyanamide.

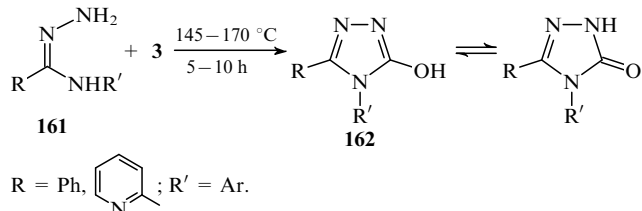
The recyclisation–cyclisation of 1,3-dimethyl-1,3,5-triazine-2,4-dione **157** on treatment with urea or guanidine in DMF in the presence of bases has been observed recently.¹³⁶



The interaction of 1,3,5-trimethylbiuret with 1,3-dimethylurea in chloroform at 200 °C leads to a mixture of the triazinones **158**–**160**.¹³⁷

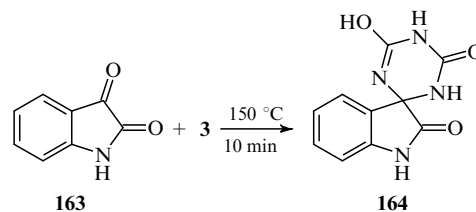


Substituted amidrazones **161** react with urea to form 4,5-disubstituted 3-hydroxy-1,2,4-triazoles **162** in 54%–78% yields.¹³⁸

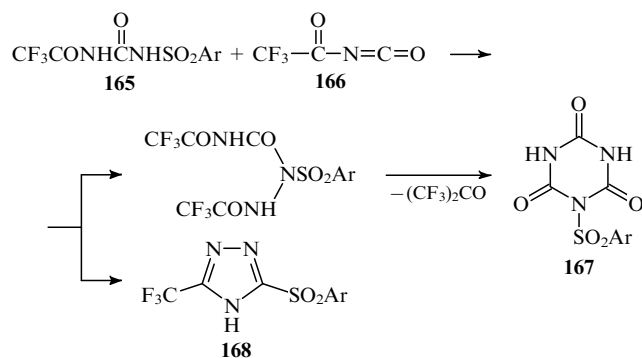


3-Hydroxy-*sym*-triazolo[4,3-*a*]pyridine and 3-hydroxy-*sym*-triazolo[4,3-*a*]phthalazine are formed on interaction with 2-hydrazinopyridine¹³⁹ or 1-hydrazino-phthalazine¹⁴⁰ respectively with urea.

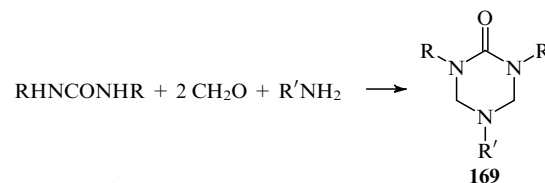
The reaction of isatin **163** with urea is rapid and leads to the formation of 2-oxoindolinyl-3-spiro-2'-(6'-hydroxy-4'-oxo-2',3',4',5'-tetrahydro-*sym*-triazine) **164** in 34% yield.¹⁴¹



The presence of a mobile hydrogen atom in *N*-acyl-*N'*-arenesulfonylureas **165** and their tendency to undergo tautomeric transformations in reactions with acyl isocyanates **166** promotes the formation of the *sym*-triazine (compounds **167**)^{58–61} or triazole (compounds **168**) rings.¹⁴²

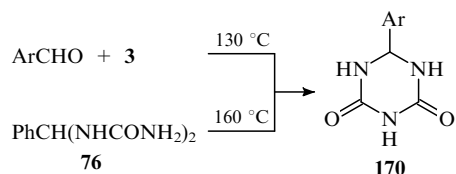


Urea or its mono- and *sym*-di-substituted derivatives react with 2 equivalents of formaldehyde and 1 equivalent of a primary amine to form 5-alkyl-2-oxotetrahydro-1,3,5-triazines **169**.¹⁴³ Glycylglycine enters into a similar reaction.¹⁴⁴

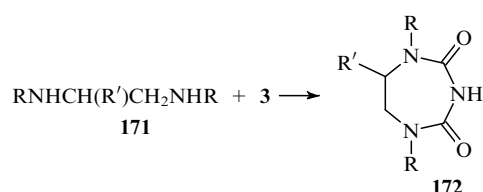


$\text{R} = \text{H}, \text{Alk}; \text{R}' = \text{Alk}$.

Perhydro-4-aryl-1,3,5-triazine-2,4-diones **170** can be synthesised either by the direct condensation of the corresponding substituted benzaldehydes with urea^{145, 146} or by the intermolecular cyclisation of benzyldienebisurea **76** in DMSO.¹⁴⁷



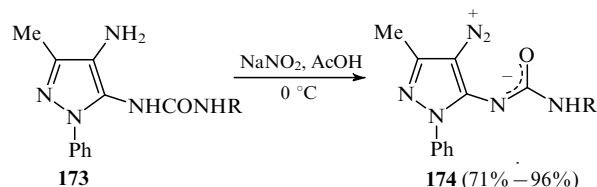
2-Ary(heteroaryl)-1,2,3-triazoles, which have the properties of optical bleaching agents, are synthesised by the interaction of compounds of the type $\text{A}[\text{NHN}=\text{C}(\text{Alk}, \text{Ar})\text{C}=\text{NOH}]_n$ (where A = aromatic or heterocyclic residue) with an excess of urea in water.¹⁴⁸ According to patent data,¹⁴⁹ the hydroxyalkyl derivatives of 1,3,5-triazacycloheptane-2,4-dione **172** have been obtained by the reaction of the diamines **171** with urea **3** or biuret at 100–150 °C in DMSO or DMF.



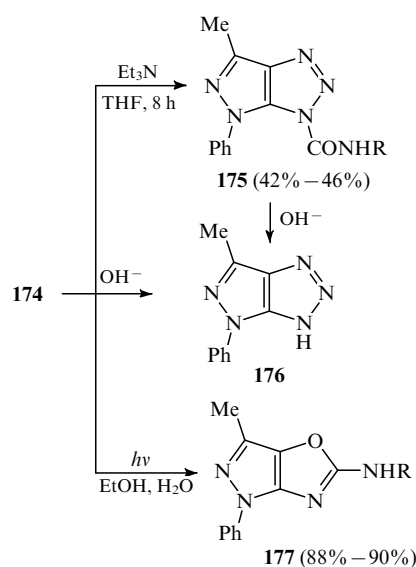
R = CH₂CH₂OH; R' = H, Alk.

4-Diazopyrazoles **173**, obtained by the diazotisation of *N*-alkyl-*N'*-(4-amino-5-pyrazolyl)ureas **174**, proved to be convenient synthons for the construction of various heterocyclic compounds of types **175–177**¹⁵⁰ (Scheme 4).

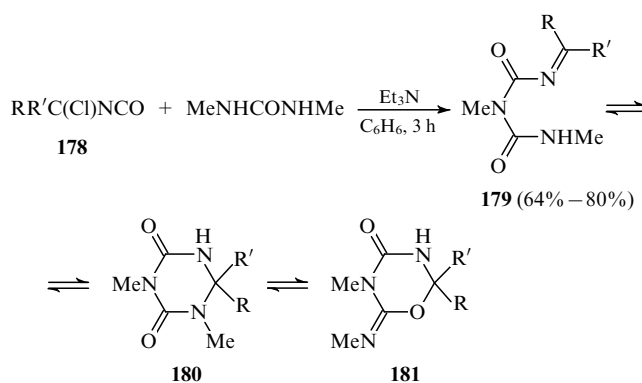
Scheme 4



R = Me, CH₂Ph.



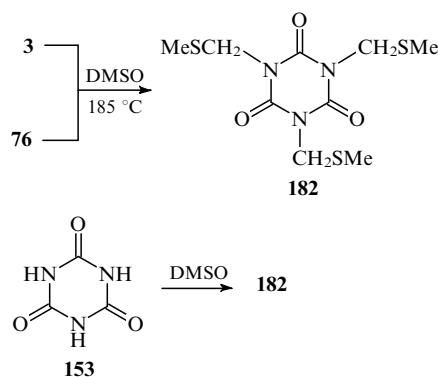
The interaction of 1-chloroisocyanates **178** with 1,3-dimethylurea involves *N*-acylation with formation of the corresponding *N*-alkylideneaminocarbonylurea **179**.¹⁵¹



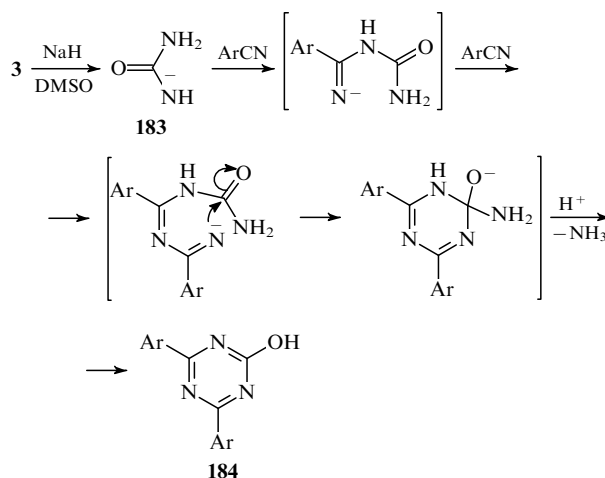
R = H, CF₃; R' = Ar, P(O)(OEt)₂.

Analysis of NMR spectroscopic data in polar solvents led to the observation that *N*-alkylideneureas **179** contain up to 13% of compounds **180** and **181**, formed as a result of intramolecular cyclisation.

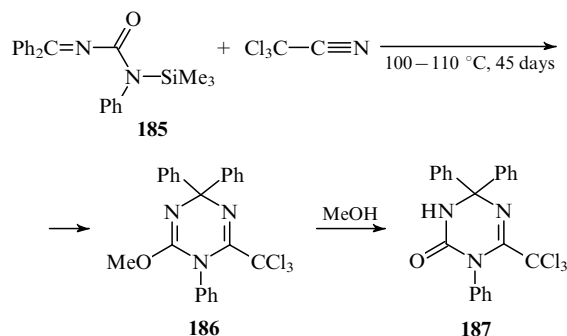
The high-temperature reaction of ureas **3** or benzyldienebisurea **76** with DMSO constitutes a single-stage method of synthesis of 1,3,5-tris(methylthiomethyl)-1,3,5-triazine-2,4,6-trione **182**.¹⁵² The reaction of cyanuric acid **153** with DMSO also leads to compound **182**. On this basis, it has been concluded that cyanuric acid is an intermediate in the synthesis of the triazine **182** from ureas.



The interaction of the anion **183**, obtained from urea **3** by treatment with NaH in DMSO, with aromatic nitriles¹²³ leads to 4,6-diaryl-2-hydroxy-*sym*-triazines **184**. It has been suggested that the reaction is a two-stage process.



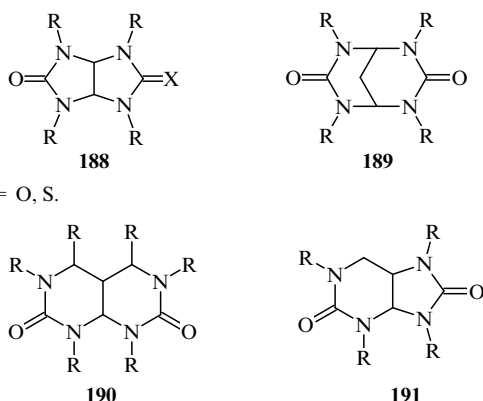
As a result of its reaction with trichloroacetonitrile in benzene in a sealed tube and subsequent treatment of the reaction product **186** with methanol, the arylideneurea derivative **185** affords the *sym*-triazinone **187**.¹⁵⁴



III. Methods of synthesis of bicyclic azaheterocycles

Bicyclic bisureas (BBU) have been known since the end of the past century. The principal methods of their synthesis, described in the literature up to 1972, have been surveyed.¹⁵⁵ By virtue of the valuable properties of the BBU, the methods of their synthesis using ureas are being constantly improved.

The most successful classification of the BBU, represented by structures of the type **188–191** which differ in the size of the rings and the ways in which they are joined together, has been proposed in Ref. 156.



X = O, S.

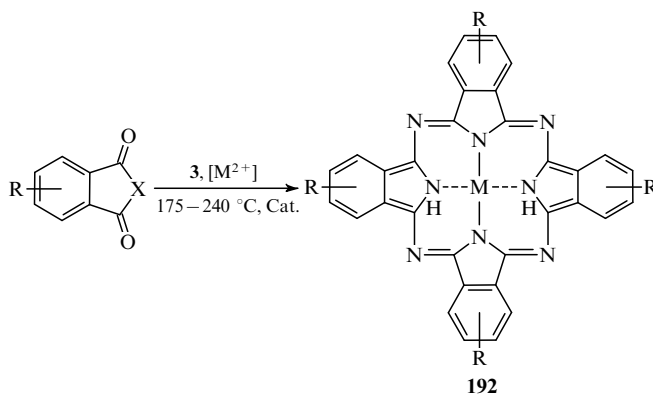
Since fundamentally new approaches to the synthesis of the BBU have not been developed in recent years, we shall confine ourselves to reactions by means of which the BBU are obtained. Furthermore, we shall present data which appeared in the literature after the publication of the review in Ref. 155.

The BBU of the bicyclooctane series **188** are synthesised by the reactions of 1,2-diketones,^{77, 78, 157–163} α -hydroxy ketone,^{81, 82} α -ketomonooximes, and α -isonitroso ketones¹⁶⁴ with ureas, predominantly under the conditions of acid catalysis. The type **188** BBU can be obtained stepwise. 4,5-Dihydroxyimidazolidin-2-ones are synthesised initially from the corresponding 1,2-bifunctional compounds and ureas and are then cyclocondensed with ureas and thioureas to compounds **188**.⁷¹ An advantage of the stepwise synthesis of the BBU is that this approach makes it possible to obtain BBU with an asymmetric structure. The BBU of the bicyclononane series **189** are synthesised by the reactions of 1,3-dicarbonyl compounds or their analogues with ureas.^{155, 165–167} The BBU of the bicyclodecane series **190** and compounds of type **191** are as a rule synthesised from ureidopyrimidines prepared beforehand^{155, 168} or by the interaction of the latter with aldehydes.

The kinetics of the reactions of carbonyl compounds with ureas have been investigated and the mechanisms of the formation of the BBU have been proposed in a series of studies.^{77, 78, 158, 159, 161–163, 167} The main requirement for the successful synthesis of the BBU **188–191** is the creation of conditions under which urea would not decompose.

IV. Methods of synthesis of phthalocyanines, diazepines, and diazocines

The decomposition of urea with elimination of ammonia at high temperatures has been used successfully in the amination of various organic substrates. One of the main synthetic applications of urea as an aminating agent is the preparation of phthalo- and naphthalo-cyanines. Phthalocyanines **192** are obtained from phthalic acids.¹⁶⁸ However, the main synthesis is from their anhydrides and imides^{168–172} or from phthalodinitrile¹⁷³ on interaction with urea **3** in the melt in the presence of transition metal (Cu,^{168–171, 174} Ni or Co^{172, 173}) compounds and a catalyst. The synthesis is sometimes carried out in high-boiling solvents.



R = H, NO₂, Alk, Ar, NH₂;

X = NH, O; M²⁺ = Cu, Ni, Co.

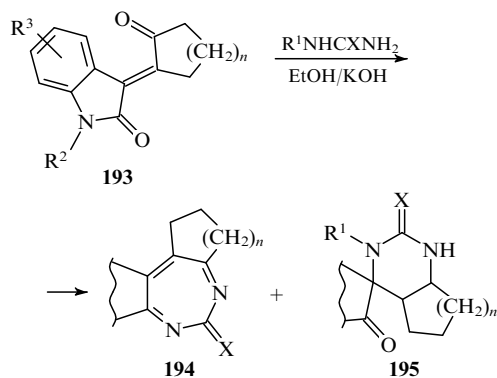
Molybdenum compounds and more rarely titanium or zirconium salts are used as catalysts for the synthesis of phthalocyanines.¹⁶⁸

Substituted phthalocyanines and their complexes with vanadium oxide are obtained in high yields by the high-temperature reaction of 4,5-dichloro-3,6-di(phenylthio)phthalic anhydride with urea in the presence of ammonium molybdate and VOCl in trichlorobenzene on heating.¹⁷⁵ Naphthalocyanines are synthesised similarly from derivatives of naphthalene-2,3-dicarboxylic acids and urea. The latter is used as the aminating agent.^{172, 176–178} Macrocyclic phthalocyanines and naphthalocyanines have found wide applications as optical, recording, and photosensitive materials.

The polymeric platinum-phthalocyanine is obtained by the reaction of pyromellitonitrile, PtCl₂, and urea and is used as the catalyst in the formation of indole from *N*-ethylaniline.¹⁷⁹

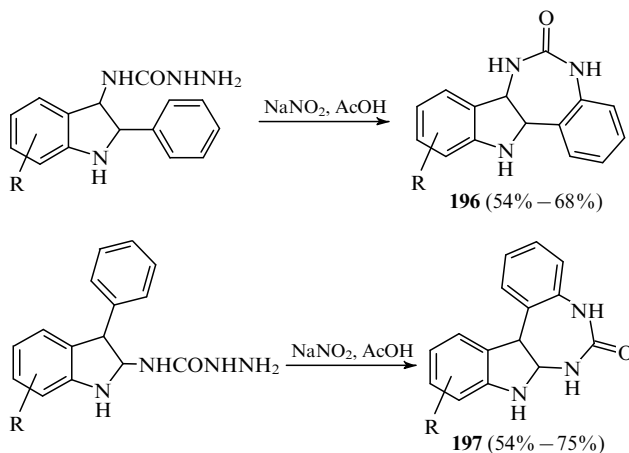
Tetrafluorinated¹⁸⁰ or tetrasulfonated¹⁸¹ phthalocyanines have been obtained by the reaction of the corresponding anhydrides or ammonium salts with urea in the presence of suitable metal salts.

It has been shown in a number of studies^{182–184} that urea can be used in the synthesis of benzodiazepine derivatives, which are of independent interest for pharmacology. Thus the interaction of 3-(2-oxocycloalkylidene)indolin-2-ones **193** with urea or thiourea in an alcoholic KOH solution leads to a mixture of reaction products: a tetracyclic system comprising indolodiazepinones (thiones) **194** and spiro-2-indolinones **195**. The yields of the reaction products were 30%–35% for **194** and 40%–50% for **195** respectively.¹⁸²



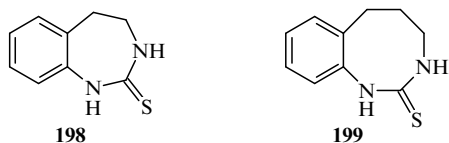
$R^1 = \text{H, Ar; } R^2 = \text{H, Me, Ac; } R^3 = \text{H, F, CF}_3$;
 $X = \text{O, S; } n = 1, 2$.

Cyclic ureas of the indolo[3,2-*d*]benzo[1,3]diazepin-2-one **196** and indolo[2,3-*d*]benzo[1,3]diazepin-2-one **197** series are formed when 2-phenylindolyl-3-semicarbazides or 3-phenylindolyl-2-semicarbazides are treated with sodium nitrite in acetic acid.¹⁸³

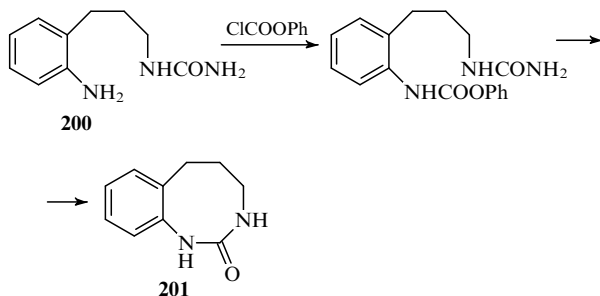


$R = 5\text{-Me, 5-Cl, H, 6,7-CH=CHCH=CH}$.

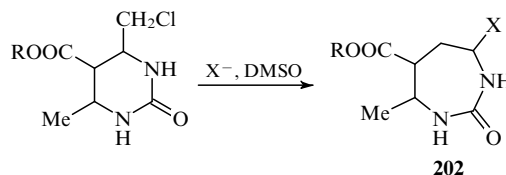
Examples of the formation of the diazepine and diazocine rings from ureas and 1,4- or 1,5-diamines respectively have been published.¹⁸⁴ For example, 1,3,4,5-tetrahydro-2*H*-benzo-1,3-diazepine-2-thione **198** and 1,2,3,4,5,6-hexahydrobenzo-1,3-diazocine-2-thione **199** have been synthesised from the corresponding diamines and thiourea.



Benzo-1,3-diazocin-2-one **201** is synthesised from 1,4- and 1,5-diamines *via* a series of intermediate stages leading to the *N*-substituted urea **200**.¹⁸⁴

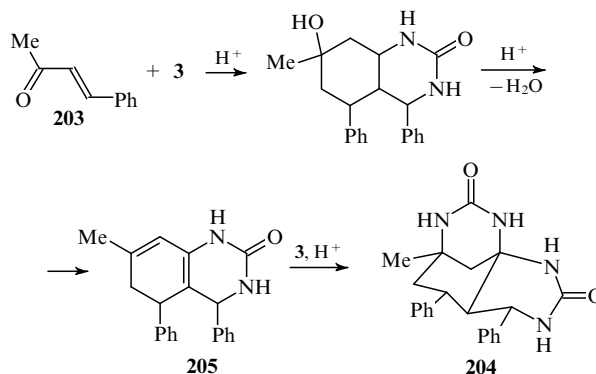


On treatment with nucleophiles, 4-chloromethyltetrahydropyrimidin-2-ones undergo ring expansion, which leads to the 1,3-diazepinone derivatives **202**.¹⁸⁵



$R = \text{Me, Et; } X = \text{CN, SH, OEt, OMe, SO}_2\text{H, H, NR}_2$.

The interaction of 4-phenylbut-3-en-2-one **203** with urea in ethanol in the presence of an acid leads to the pyrimido[4,5-*d*]-1,3-diazocinedione **204** after 24 h at 50 °C.¹⁸⁶

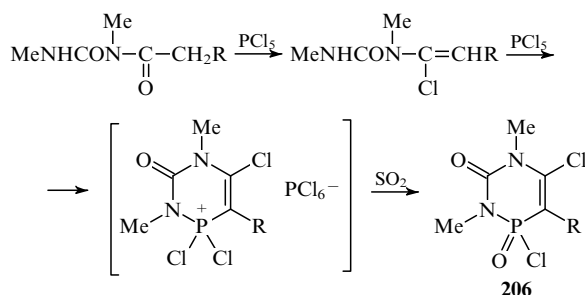


It has been suggested that the quinazolinone **205** is an intermediate in the synthesis of the diazocinedione **204**. Its formation may be represented as a synchronous reaction of two molecules of the phenylbutenone **203** with urea.

V. Synthesis of azaheterocycles containing other elements

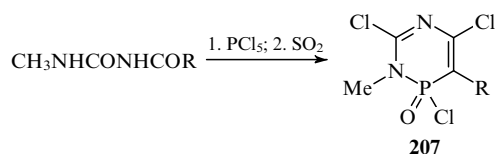
1. Phosphorus-containing heterocycles

The presence of a series of nucleophilic reaction centres in the carbamide fragment of *N*-acylureas promotes the heterocyclisation of the latter on treatment with phosphorylating agents. Thus the interaction of *N,N'*-dimethylacylureas with PCl_5 in proportions of 1:5 results in the formation of diazaphosphorinones, which are converted *in situ*, on treatment with SO_2 , into 4,6-dichloro-1,3-dimethyl-5-*R*-2,4-dioxo-1,3,4-diazaphosphorines **206**.¹⁸⁷



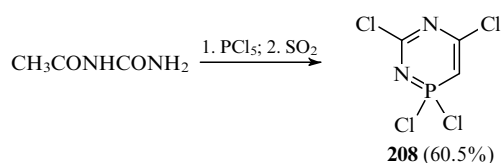
$R = \text{H, Me}$.

In contrast to dimethylacylureas, the reaction of monomethylacylureas with phosphorus pentachloride is completed mainly by the formation of a compound of the type $[\text{Cl}_3\text{P}=\text{NC}(\text{Cl})=\text{CHPCl}_3]^+\text{PCl}_6^-$ and a small amount (8.5%) of 2,2,4,6-tetrachloro-1-methyl-1,2-dihydro-1,5,2-diazaphosphorinonium hexachlorophosphate. On treatment with SO_2 , the latter is readily converted into 2,4,6-trichloro-3-methyl-4-oxo-3,4-dihydro-1,3,4-diazaphosphorine **207**.¹⁸⁸

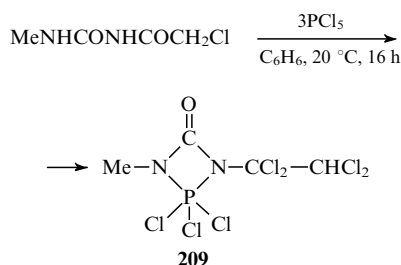


R = H, Me.

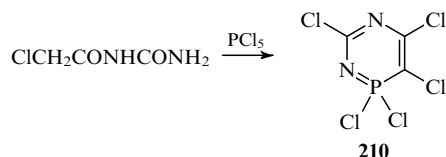
It has been shown^{189–191} that the phosphorylation of *N*-acetylurea with a fivefold excess of PCl_5 proceeds with participation of the acetyl and free amino-groups with formation of 2,4,4,6-tetrachloro-1,3,4-diazaphosphorine **208** in a satisfactory yield.



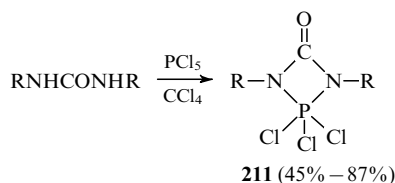
Treatment of *N*-chloroacetyl-*N*'-methylurea with phosphorus pentachloride results in the formation of the substituted 1,3,2-diazaphosphetidin-4-one **209**.^{192, 193}



On the other hand, heating of chloroacetylurea with PCl_5 leads to 2,4,4,5,6-pentachloro-1,3,4-diazaphosphorine **210**.¹⁹⁴

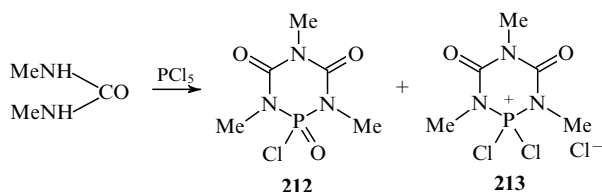


1,3-Dialkyl(alkylaryl)-2,2,2-trichloro-1,3,2-diazaphosphetidin-4-ones **211** are obtained by the reaction of equimolar amounts of PCl_5 and *N,N'*-dialkyl-(alkylaryl)ureas.¹⁹⁵ When an excess of PCl_5 is employed, the carbonyl group is chlorinated.¹⁹⁶

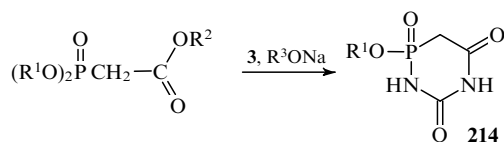


R = Alk ($\text{C}_1\text{--C}_4$).

The 1,3,5,2-triazaphosphorines **212** and **213** are obtained by the interaction of PCl_5 with *sym*-dimethylurea.¹⁹⁷

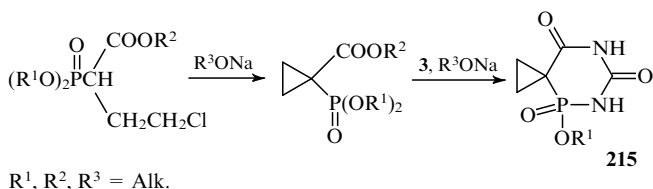


The phosphorus analogues of barbituric acid **214** are formed on condensation of phosphonoacetic acid esters with urea **3** in the presence of sodium alkoxide.¹⁹⁸



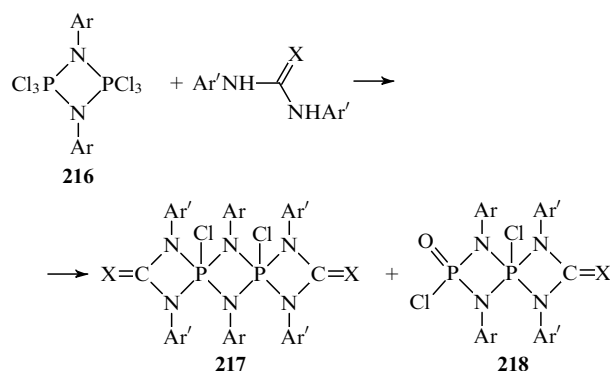
$\text{R}^1, \text{R}^2, \text{R}^3 = \text{Alk.}$

The condensation of 4-chloro-2-dialkoxyphosphorylbutyric acid esters with urea in the presence of sodium alkoxides (1 : 2) leads to spirocyclopropanediazaphosphorinones **215** via intermediate cyclopropane derivatives.¹⁹⁹



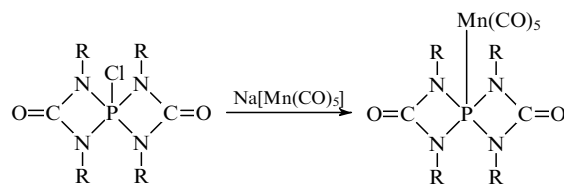
$\text{R}^1, \text{R}^2, \text{R}^3 = \text{Alk.}$

Aryl- and *sym*-diaryl-ureas and -thioureas readily afford the spiro-compounds **217** and **218** after 30 min on interaction with hexachlorodiazaphosphetidine **216** in acetonitrile.¹⁹⁹



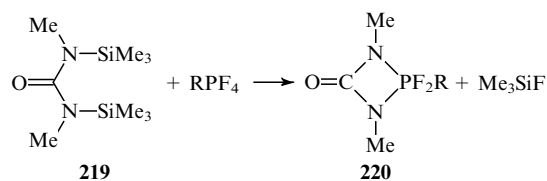
X = O, S.

It has been shown²⁰⁰ that the chlorine atom in compounds of this type is substituted by pentacarbonylmanganese. The reaction is carried out under an inert atmosphere.



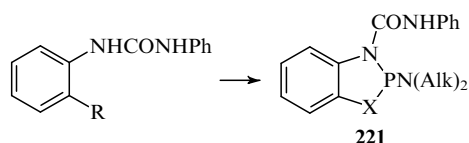
R = Alk, Ar.

Treatment of symmetrical dimethylsilylureas **219** with alkyl or aryl-fluorophosphanes results in cyclisation with the cleavage of the Si–C bond and the formation of the fluorophosphadiazetines **220**.²⁰¹



R = Alk, Ar.

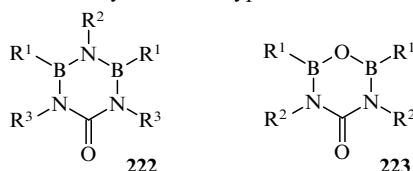
The condensation of *o*-amino- or *o*-hydroxy-diphenylureas with tris(dialkylamino)phosphine afforded a series of the corresponding substituted 1,3,2-oxaza- or diaza-benzophospholenes **221**.²⁰²



R = NH₂, OH; X = O, NP(NAlk₂)₂.

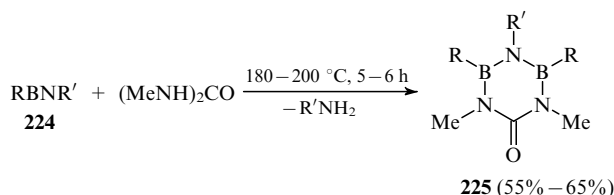
2. Boron-containing heterocycles

On heating with N-substituted ureas, haloorganylboranes give rise to heterocycles of the type **222** and **223**.^{203–205}



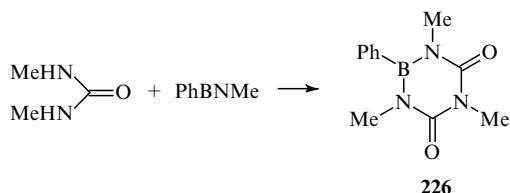
R¹, R², R³ = Alk.

The reaction of the borazines **224** with dimethylurea results in the formation of 1,3,5-triaza-2,4-diboracyclohexan-6-ones **225**.²⁰⁶

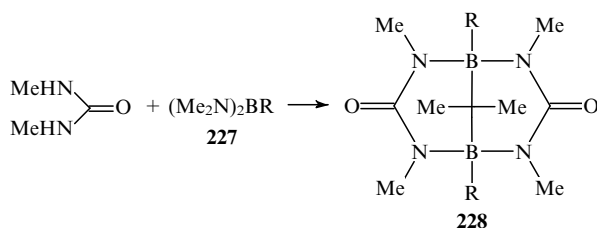


R, R' = Alk.

The interaction of dimethylurea with borazine yields triaza-boracyclohexane-4,6-dione **226** after 10 min.²⁰⁶ It has been shown that the reaction proceeds *via* the intermediate formation of *N,N',N''*-trimethylbiuret.

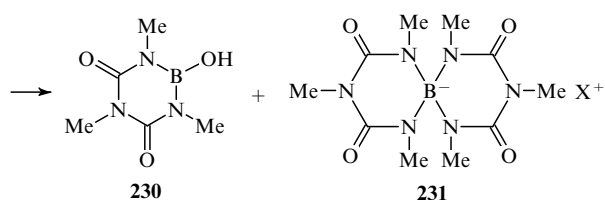
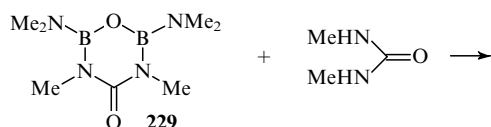


Refluxing of dimethylurea with the borazines **227** in toluene leads to the bicyclic borazinones **228** after 9–10 h.²⁰⁶



R = Alk, Ph.

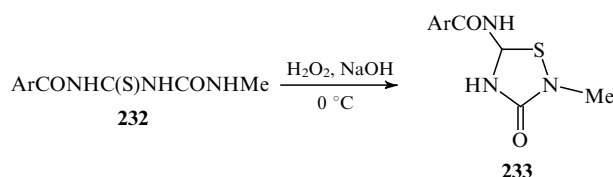
The interaction of compound **229** with dimethylurea is used to synthesise the corresponding 1,3,5-triaza-2-boracyclohexane-4,6-diones **230** and a mixture of the ammonium salts of the spirane borates **231**.²⁰⁷



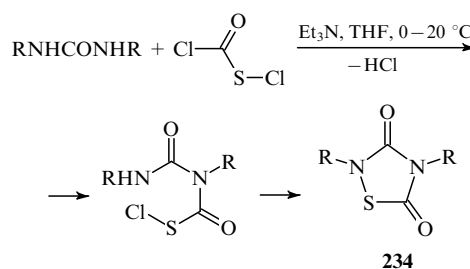
X = Me₂NH₂, MeNH.

3. Sulfur-containing heterocycles

Aroylthiobiurets **232**, which readily undergo oxidative cyclisation to 5-arylamino-2-methyl-(2*H*)-1,2,4-thiadiazol-3-ones **233** (yield 31%–85%), have been obtained by the interaction of aroyl isothiocyanates with *N*-methylurea.²⁰⁸

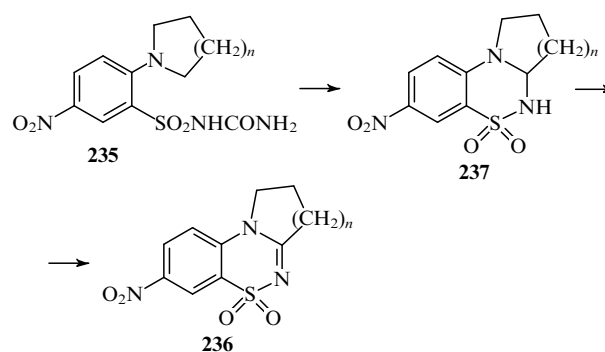


Preparative methods of synthesis have been developed²⁰⁹ for thiadiazolodiones **234** on the basis of the reaction of chlorocarbonylsulfenyl chloride with ureas.



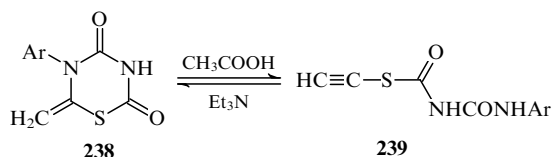
R = Me, MeOCH₂, cyclo-C₆H₁₁, Ar.

It has been established²¹⁰ that, on treatment with a 1:1 mixture of HgO and the disodium salt of ethylenediaminetetraacetic acid, aryl-substituted benzenesulfonylureas **235** cyclise to the sulfonylamidines **236** *via* a stage involving the formation of the sulfonylaminals **237**.



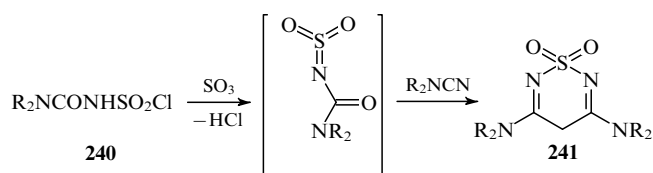
n = 1–3.

On treatment with catalytic amounts of HCl or CF₃COOH, the thiadiazinediones **238** are capable of undergoing reversible ring cleavage to ethynylthiocarbonylureas **239**. Subsequent treatment of the resulting solutions with an organic base is accompanied by complete displacement of the equilibrium towards the cyclic form **238**.²¹¹



According to Vovk,²¹¹ the transformation **238** $\rightleftharpoons$ **239** is an example of a new type of ring–chain enamidine tautomerism.

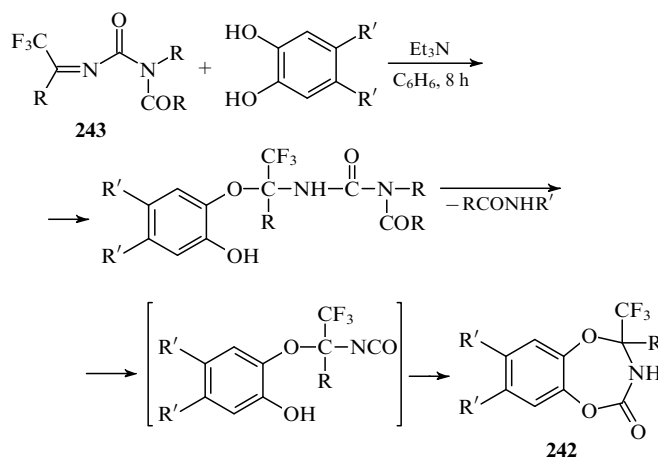
The interaction of chlorosulfonylureas **240** with sulfur trioxide and cyanamides entails the formation of 1,4,3,5-oxathiadiazine 4,4-dioxides **241**.^{212, 213}



R = H, Alk.

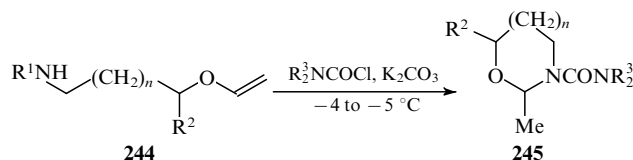
4. Oxygen-containing heterocycles

We examined the methods of synthesis of oxazole derivatives using ureas in the previous Sections of this review. The methods of synthesis of compounds with a larger ring size are described here. Thus a series of 1,5,3-benzodioxazepinones **242** have been synthesised in 64%–82% yields by refluxing *N*-alkylidene-*N'*-acylureas **243** with catechol and its derivatives.²¹⁴



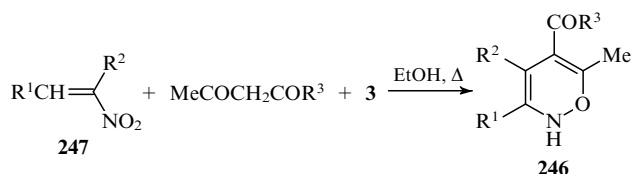
R = Ar; R' = H, Cl, Br.

The vinyl ethers of the aminoalcohols **244** give rise to the cyclic carbamides **245** on treatment with *N,N'*-dialkylcarbamoyl chlorides in the presence of potassium carbonate and in the absence of steric hindrance to cyclisation.²¹⁵

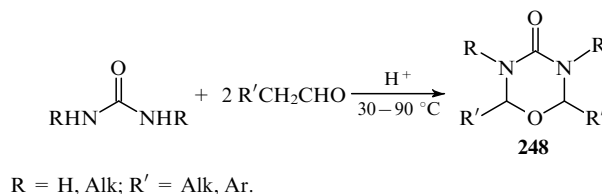


R¹, R² = H, Me, Bu, CH₂Ph, cyclo-C₆H₁₁;
R³ = Me, Et, Bu, C₁₂H₂₅, C₁₈H₃₇;
n = 0, 1.

The substituted 1,2-oxazines **246** have been obtained by a three-component reaction of nitroalkenes **247** with 1,3-dicarbonyl compounds and urea **3**.²¹⁶

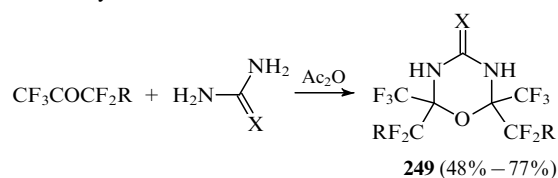


The interaction of unsubstituted urea and of its 1,3-disubstituted derivatives with aldehydes in the presence of acid catalysts results in the formation of 4-oxotetrahydro-1,3,5-oxadiazines **248**.^{217, 218}



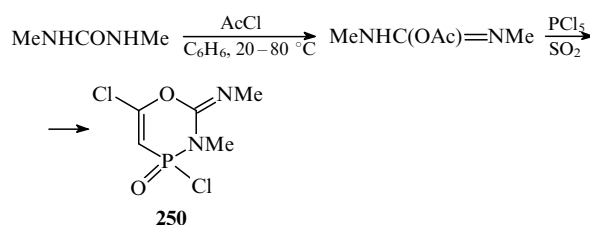
R = H, Alk; R' = Alk, Ar.

The stable tetrahydro-1,3,5-oxadiazines **249** have been obtained by condensing ureas (thioureas) with polyfluoro ketones in acetic anhydride.²¹⁹



R = F, NO₂; X = O, S.

4,6-Dichloro-2-(*N*-methylimino)-3-methyl-4-oxo-1,3,4-oxazaphosphorine **250** has been synthesised by acetylating dimethylureas and subsequent treatment of the intermediate with PCl₅ and SO₂.²²⁰



VI. Conclusion

The data presented demonstrate the extensive possibilities for the employment of ureas and related compounds in the synthesis of azaheterocycles with a wide variety of structures — oxazoles, imidazoles, pyridines, phthalocyanines, triazines, and many others. The advances in the practical application of the compounds obtained using ureas, particularly in medicine and biochemistry, are so numerous that they require an independent survey.

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Radiation-chemical degradation of cellulose and other polysaccharides

B G Ershov

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Abstract. Results of studies on the radiation-chemical transformations of cellulose, its ethers, and some other polysaccharides (xylan, starch, dextran, chitin, chitosan, and heparin) are discussed. Ionising radiation causes the degradation of these compounds accompanied by decomposition of the pyranose ring and formation of compounds with carbonyl and carboxy groups, as well as formation of hydrogen, carbon dioxide, and carbon monoxide. The efficiency of degradation increases considerably with temperature and depends on the structure of the polysaccharide and the nature of its substituents. A mechanism of the radiation-chemical transformations of cellulose and other polysaccharides is suggested. The prospects of using radiation-chemical methods for processing of cellulose and other polysaccharides in industry and agriculture are considered. The bibliography includes 213 references.

I. Introduction

Cellulose is the most widespread natural polymer, the main component of plants. Products based on cellulose are widely used in everyday life. In many technological processes, cellulose undergoes radiation treatment. They include: sterilisation of cellulose-based dressings; degradation of plant raw materials aimed at the intensification of industrial hydrolysis of raw materials and production of foodstuff, forage, and technical products (alcohols, furfural, *etc.*); preliminary treatment of cellulose for subsequent production of its various derivatives (nitrates, xanthates, *etc.*), and a number of other processes.

The prospects for the successful adoption of radiation technology for preliminary cellulose treatment stem from the possibility of replacing ecologically hazardous chemical steps by pure

treatment with ionising radiation, reduction of the number of technological stages, and decrease in energy consumption. These factors encourage the studies in the field of radiation chemistry of cellulose and related compounds, in particular, on the elucidation of the detailed mechanism of radiation-induced chemical transformations. Furthermore, depending on the area of cellulose application, opposite problems are targeted: on the one hand, increase in the radiation stability of cellulose, and on the other hand, intensification of its degradation.

Preliminary destructive treatment of cellulose by ionising radiation may turn out to be particularly important for the industrial production of viscose and nitrate esters. The manufacture of these compounds generally includes a preliminary stage of cellulose treatment in order to decrease its molecular mass. Radiation treatment can eliminate this stage or simplify it considerably. In addition, radiation-induced degradation of cellulose-containing plant materials favours their subsequent acid hydrolysis, which is particularly important for the intensification of industry based on hydrolysis. It has also to be taken into consideration that cellulose and a number of other polysaccharides (chitin, starch, *etc.*) are the constituents of biological structures. Therefore, systems based on these polysaccharides are rather convenient models for studying the effect of radiation on biological structures.

We discussed the problems of the radiation chemistry of cellulose in a previous review¹ in which the results published before 1984 were systematised. Since that time, new experimental results on the mechanism of cellulose radiation-induced degradation have been obtained. This mechanism has the form of a local explosion of the pyranose ring in the polymeric chain, which results in its scission with formation of diverse products. To date, quantitative relationships for the radiation-chemical yields of degradation and major products[†] have been determined and ways for intensifying the degradation of cellulose and plant

B G Ershov Institute of Physical Chemistry, Russian Academy of Sciences, Leninskii prosp. 31, 117915 Moscow, Russian Federation.
Fax (7–095) 335 17 78. E-mail ershov@ipc.rssi.ru

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[†] The radiation-chemical yields refer to 100 eV of energy absorbed. For example, the yield of degradation is the number of bonds cleaved per 100 eV of energy absorbed, the yield of gaseous products is the number of gas molecules per 100 eV of energy absorbed, the yield of the oxidised groups is the number of these groups per 100 eV of energy absorbed, *etc.*

materials by combined ionising radiation and thermal treatment as well as by mechanical treatment (grinding) have been established. The present review includes data on the radiation-induced degradation and chemical transformations of other polysaccharides (starch, xylan, chitin, *etc.*), which make it possible to reveal general regularities of the interaction of ionising radiation with this important class of natural compounds.

II. Random degradation of polymers

The main result of the action of ionising radiation on cellulose (as well as on other polysaccharides) is scission of the polymeric chain, *i.e.* the degradation changing the physicochemical properties of the polymer (structural state, mechanical strength, solubility in different media, reactivity, *etc.*).¹

Let us consider degradation in which a macromolecule undergoes random scission without cross-linking.^{2–5} It will be shown below that this process predominates on irradiation of cellulose and other polysaccharides.

The degradation of polymers is described using the statistical method. If the initial molecular-mass distribution (MMD) of the polymer is the most probable one and the chain scission occurs randomly, the MMD will be maintained with a decrease in the average molecular mass of the fragments. The following equation relating the number of scissions (S) per initial polymeric molecule to the number-average (P_n) and weight-average (P_w) degrees of polymerisation is valid

$$S = \frac{P_n^0 - P_n}{P_n} = \frac{P_w^0 - P_w}{P_w}, \quad (1)$$

where P_n^0 and P_w^0 are the starting number-average and weight-average degrees of polymerisation, respectively. For the most probable distribution, $P_w = 2P_n$.

The number of scissions can also be calculated from the radiation-chemical yield of degradation according to the following equation:

$$S = \frac{DP_n^0 m G^0}{10^2 N_A}, \quad (2)$$

where D is the absorbed dose, eV; m is the molecular mass of a polymer monomeric unit (which equals 162 for cellulose); and N_A is the Avogadro number.

Combining Eqns (1) and (2) we obtain the dependence of the number-average (or weight-average) degree of polymerisation on the absorbed dose of ionising radiation

$$\frac{1}{P_n} - \frac{1}{P_n^0} = \frac{G^0 m D}{10^2 N_A}. \quad (3)$$

Thus, the quantitative determination of the efficiency of radiation-chemical degradation of cellulose expressed through the yield G^0 is reduced to finding the dependence of P_n or P_w on the absorbed dose according to Eqn (3).

Experimental determination of the number-average degree of polymerisation P_n of cellulose is carried out rarely. This is usually performed using osmometry, which gives a considerable error. In practice, the degree of polymerisation of cellulose is most commonly determined by measuring the viscosity of its dilute solutions. The empirical Mark–Kuhn–Houwink equation, which relates the characteristic viscosity of a solution $[\eta]$ to the viscosity-average degree of polymerisation P_v , is valid in this case:

$$[\eta] = K P_v^\alpha. \quad (4)$$

For a given polymer, the K and α coefficients are constants provided the measurement conditions and solvents are the same. The dependence of P_v on P_n is given by the equation³

$$P_v = P_n[(\alpha + 1)\Gamma(\alpha + 1)]^{1/\alpha} = P_n^0 k, \quad (5)$$

where $\Gamma(\alpha + 1)$ is the gamma-function of α and k is a coefficient. Depending on the shape of the polymer macromolecule in solution and the character of the solvent effect, the value of $1/\alpha$ varies from 0.6 to 1.0, which corresponds to a variation of the term in brackets in Eqn (5) just from 1.82 to 2.0.³ Thus, one can determine the yield of polymer degradation G^0 from the experimental values of P_v using the equation

$$\frac{1}{P_v} - \frac{1}{P_v^0} = \frac{G^0 m D}{10^2 N_A k}, \quad (6)$$

where the k coefficient takes account of the actual ratio of P_v and P_n determined from Eqn (5).

In determination of the radiation-chemical yield of cellulose degradation, one makes certain assumptions on the character of its molecular-mass distribution and the random chain scission; also, one takes into consideration the use of different experimental methods for the measurement of its molecular mass with different inherent errors. The degradation of cellulose has been dealt with in a number of studies.^{6–24} The yields of degradation have a considerable scatter from 1.8–2.0 (see Refs 6 and 7) to 25 (see Ref. 8). Let us consider in more detail the effect of the main factors on the determination of the radiation-chemical yield of cellulose degradation.

Molecular-mass distribution factor. Equations (3) and (6) were obtained for the most probable molecular-mass distribution. However, this is generally not the case for the MMD of the original celluloses. One cannot state *a priori* that radiation-induced degradation results in the most probable distribution. Therefore, it is necessary to follow the changes of cellulose MMD during irradiation and to find the relationship between P_n and P_v . If the MMD differs from the most probable one, the k coefficient in Eqn (6) should differ from the value corresponding to the most probable distribution (~ 2). However, it was assumed groundlessly that $P_n = P_v$.^{6, 7, 9–14, 17–19} The radiation-chemical yield was generally close to 3.

This approach is based on the assumption on the monodisperse MMD and its retention during the irradiation, *i.e.* it is assumed that the radiation-induced cleavage of polymer chain bonds is not random. Then it should follow that the yield of degradation is underestimated considerably. If this process is random and the cellulose MMD is nonuniform before the irradiation, it will tend to reach uniformity during the irradiation. It will be shown below that the ratio $P_v \simeq 2P_n$ is established in the case of uniform MMD. Therefore, the yield of degradation should be twice as high as that measured under the assumption that $P_n = P_v$.

Assuming a random character of cellulose degradation, it is easy to show that with virtually any initial MMD, the most probable distribution is reached during the irradiation. The dose required for this may vary from 30 to 80 kGy depending on the initial MMD. For the first time, this conclusion seems to have been confirmed experimentally by Kusama *et al.*²⁰ It was shown that during γ -irradiation of cotton cellulose whose initial MMD was close to the monodisperse one ($P_v/P_n = 1.26$), the most probable distribution was reached at an absorbed dose of 30–50 kGy ($P_v/P_n = 2.0 \pm 0.1$). Hence, when the molecular mass of cellulose is determined by viscosimetry, the use of Eqn (6) for the description of degradation is justified at doses exceeding the above value.

Chemical stability of irradiated cellulose in different solvents. In early studies, the viscosity of cellulose was measured mostly in aqueous solutions of copper complexes with ammonia or ethylenediamine.^{6, 7, 9–12, 14, 16, 21–24} In some cases, the radiation-chemical yields of degradation differed considerably. As to the yield of carbonyl groups, it was unreasonably high (*e.g.*, 58 in Ref. 22). This fact may be regarded as an indication of the chain character of degradation. However, it became clear later that cellulose in the presence of bivalent copper underwent spontaneous oxidative alkaline degradation. This process was initiated

by the existing terminal carbonyl groups,²⁵ whose concentration in cellulose increases significantly after irradiation. Therefore, one has to consider critically the results obtained without taking account of the possible spontaneous alkaline degradation of cellulose in the solvents specified above.

A quantitative estimate of possible errors resulting from the use of alkaline solutions of copper complexes with ammonia or ethylenediamine for the analysis of cellulose was made in by Sakurada *et al.*¹³ As shown in later studies, the optimum solvent for cellulose is cadoxen, *i.e.* an aqueous solution containing cadmium oxide and ethylenediamine.^{26–28} In this solvent, cellulose undergoes no noticeable spontaneous degradation. It was extensively used in studies of the radiation-induced degradation of cellulose. In some cases, cellulose was nitrated first, and the viscosity of the resulting nitrates was then measured in acetone.^{13, 15, 20} All these methods made it possible to avoid the errors caused by the chemical degradation of irradiated cellulose during the preparation of its dilute solutions.

III. Radiation-chemical degradation of cellulose

The radiation-chemical degradation of cellulose of different origins in different solvents has been studied.^{16, 20, 29, 30} Changes in the degree of polymerisation of cotton cellulose upon γ -irradiation as measured by viscosimetry in cadoxen were shown to be a function of the absorbed dose.²⁹

Dose /kGy	0	5	10	32	170	480	680	800	1680
P_v	2537	827	723	314	138	32	30	28	14

It is seen that the degree of polymerisation decreases with an increase in the dose, *i.e.* cellulose undergoes degradation. It was noted²⁹ that the crystallinity index remains virtually unchanged at all absorbed doses and equals 73%. The amount of the fraction soluble in ethanol increases from 10.3% in non-irradiated cellulose to 43.7% at an absorbed dose of 1680 kGy. Figure 1 presents the dependence of $1/P_v - 1/P_v^0$ on the absorbed dose. Unless specified otherwise, it was dry cellulose that was subject to γ -irradiation *in vacuo* or in an inert gas. The cellulose was dried at 105 °C over P_2O_5 .

The characteristic viscosity of cotton cellulose has been measured in a solution of copper–ethylenediamine complex.¹⁶ Freshly prepared solutions were used, and the possible spontaneous alkaline degradation of cellulose was taken into account. In another study,³⁰ the sulfite cellulose with an initial degree of polymerisation of 920 was used; the characteristic viscosity was measured in cadoxen solutions. Finally, Kusama *et al.*²⁰ studied Mexican cotton with an initial degree of polymerisation of 3265,

whose characteristic viscosity was measured in acetone following nitration of the irradiated material.

At doses above ~ 50 kGy, all experimental data from these works^{16, 20, 29, 30} fit on a linear plot, which passes through the origin. Hence, Eqn (6) actually gives a good quantitative description of the dependence of the degree of polymerisation on the absorbed dose for celluloses from various sources. It turned out to be insignificant in practice what solvent was used for the determination of the characteristic viscosity of dilute cellulose solutions and what kind of cellulose was used. A detailed analysis of data for doses below 50 kGy showed some deviations of the $(1/P_v - 1/P_v^0) - D$ dependence from linearity, which is due to nonuniform MMD of the starting celluloses and to the fact that the most probable distribution is reached at doses above 50 kGy.

Thus, the validity of Eqn (6) confirms the random character of degradation and the attainment of the most probable molecular-mass distribution. When determining the radiation-chemical yield of degradation, one has to take into account the relationship between the viscosity-average and number-average degrees of polymerisation as a function of the α factor involved in Eqn (5). For cadoxen, the α factor is 0.94 (see Refs 26–28), and the corresponding relationship is $P_v = 1.96P_n$. For a copper–ethylenediamine complex solution, the α factor is considered to be 0.9 (see Ref. 16), and $P_v = 1.9P_n$. Finally, for solutions of nitrocellulose in acetone, the α factor is considered to be 1 (see Ref. 20), and $P_v = 2P_n$. Taking the errors inherent in the viscosimetric method into account, one has grounds to assume that the following relationships are valid for all of the solvents mentioned: $P_v = 2P_n$ and $P_v = P_w$. Hence, the k coefficient in Eqn (6) may be considered to be ~ 2 . Given the slope of the linear plot in Fig. 1, one can find the yield of cellulose degradation from Eqn (6); it equals 6.0 ± 1.0 . In Refs 16, 20, and 30, whose experimental data we used for the determination of the degradation yield, it was assumed that $P_v = P_n$. The yield determined under this assumption was about two times smaller than that determined by us.

It was noted¹² that the yield of degradation of various kinds of cellulose materials changed from 7.6 to 3.1 with an increase in the absorbed dose from 12 to 120 kGy. The yields were calculated assuming that $P_n = P_v$. This dependence of the yield on the dose can be explained as follows. At small doses, uniform MMD is not established yet, hence it is improper to use Eqn (6) for calculation of the yield. At large doses, uniform MMD is reached, so it is necessary to bear in mind that $P_v = 2P_n$. In this case, we find that the yield of degradation is 6.2, *i.e.* it agrees with the value determined above.

The viscosimetric method in copper–ammonia solutions was used to measure the degradation yields, which were found to be 4.5 (Ref. 24) and 5.0 (Refs 3 and 21), account being taken of the partial degradation of cellulose. The actual dependences of P_n and P_v on the characteristic viscosity according to Eqns (4) and (5) were used in these calculations. The P_n values of nitrocelluloses were determined by the osmometric method, and the degradation yields were calculated to be 3.3 (Ref. 13) and 2.9 (Ref. 15). These low yields might be due to the low accuracy of the method used and the small absorbed doses at which the uniform MMD was not achieved.

The discrepancies between the literature data for the radiation-chemical yields of cellulose degradation are explained by different interpretations of viscosimetric data for the molecular mass determination and by differences in the absorbed doses. Given a random pattern of radiation-induced degradation, it is only at a certain absorbed dose that the most probable distribution is reached, where $P_v = 2P_n$. In this case, Eqn (6) can be used for the yield determination. Analysis of experimental data from numerous works shows that, taking account of the factors specified above, the yields are very similar and are equal to 6.0 ± 1.0 .

Cellulose materials differ markedly in their initial molecular masses and in the MMD.^{31–34} For instance, the weight-average degree of polymerisation (P_w) changes from several thousand for

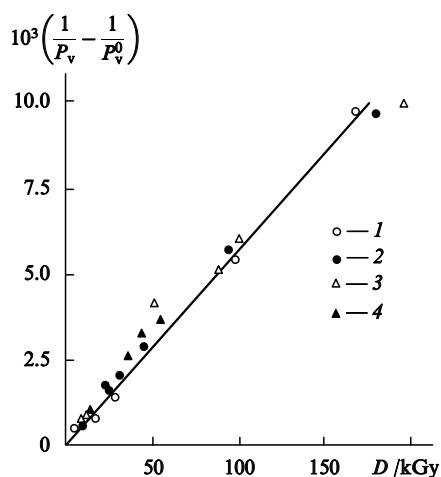


Figure 1. Dependence of $1/P_v - 1/P_v^0$ in cellulose on the absorbed dose; (1–4) data from Refs 29, 16, 30, and 20, respectively.

cotton linter to ~ 400 for viscose fibres.³⁴ As a rule, the MMD differs noticeably from the most probable distribution, and the non-uniformity factor $U = P_w/P_n$ for the majority of natural and industrial celluloses varies over the range 1.2–3.0.³³

Let us evaluate the effect of the MMD non-uniformity factor of the starting cellulose on the dependence of $1/P_v$ on the absorbed dose assuming a random degradation pattern. At absorbed doses D_c where the most probable distribution is reached, the following equation is valid:

$$\frac{1}{P_v} = \frac{G^0 m D_c}{10^2 N_A k} + \frac{U^0}{2P_v^0},$$

where $U^0 = P_w^0/P_n^0$.

According to this equation, the radiation-chemical yield of degradation can be calculated from the slope of the plot of $1/P_v$ versus the absorbed dose, while the intercept with the y-axis allows one to determine U^0 . This approach was used in a study of the radiation-induced degradation of wood and cotton cellulose.³⁵ The yield of degradation was 5.6 for both celluloses. The calculated U^0 value was in good agreement with the measured one.

Fractionation was used^{35,36} to determine the MMDs of various types of intact and irradiated celluloses, and the values of P_w and P_n were calculated. The integral MMD curves prior to and after irradiation are shown in Fig. 2. After irradiation, the integral MMD curve becomes considerably narrower and is shifted toward smaller P_w . For example, the major part of macromolecules in non-irradiated cellulose has P_w values in the region from 600 to 1500, whereas after irradiation to the absorbed dose of 40 kGy, more than 90% of the macromolecules have P_w from 250 to 400. The percentage of the α -fraction measured by the solubility of cellulose in a 17.5% alkali solution decreases as the absorbed dose increases, hence the content of a low-molecular-weight fraction having enhanced solubility increases. The results of mathematical treatment of the integral MMD curves are presented in Table 1. It is seen that both the number-average and weight-average degrees of polymerisation decrease as the dose increases, while the non-uniformity factor increases after irradiation to reach the value of ~ 2 , which corresponds to the most probable distribution. The pattern of U variation is similar to that found by Kusama *et al.*²⁰ who used gel permeation chromatography. The most probable MMD was observed²⁰ at somewhat smaller doses. This difference is probably due to the fact that the fractionation of irradiated celluloses results in a loss of some portion of the low-molecular-weight fraction, which in turn affects the P_w/P_n ratio.

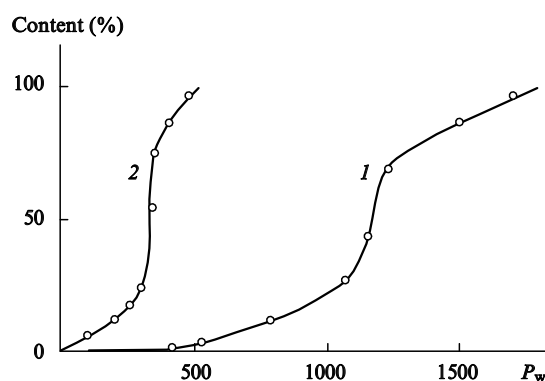


Figure 2. Integral MMD curves for cotton cellulose.^{35,36} (1) before irradiation, (2) after irradiation; the absorbed dose was 40 kGy.

Thus, the experimental data from many studies on cellulose degradation are described satisfactorily by equations derived assuming a random cleavage of the polymeric chain. As a result of irradiation, the most probable MMD is attained. The average

Table 1. Molecular-weight characteristics of celluloses exposed to γ -irradiation.^{35,36}

Dose / kGy	P_v	P_w	P_n	P_w/P_n
Wood cellulose				
0	974	987	700	1.41
50	302	300	195	1.55
100	196	197	96	2.05
150	150	185	87	2.13
Cotton cellulose				
0	1220	1160	1060	1.1
40	330	340	240	1.4
100	190	182	124	2.0

radiation-chemical yield of degradation is generally 6.0 ± 1.0 . This yield is virtually independent of the dose rate of γ -irradiation or accelerated electrons, on the initial degree of polymerisation, and on whether the irradiation was carried out in a vacuum, in an inert gas, or in air. The absence of a noticeable effect of air on the degradation efficiency is most probably due to the dense crystalline packing of cellulose, which hinders the diffusion of oxygen to the reaction centres. Oxygen has only a slight effect on the formation of carbonyl and carboxy groups, which should be due to the partial radiation-induced oxidation of the surface layer of the material. Special studies showed that the presence of moisture has a slight inhibiting effect on the cellulose degradation.²⁰

The degradation of cellulose is well described by Eqn (6) up to an absorbed dose of ~ 200 kGy. At higher doses, $1/P_v - 1/P_v^0$ tends to a steady value. Since

$$\frac{1}{P_v} - \frac{1}{P_v^0} = \frac{1}{P_v^0} \left(\frac{P_v^0}{P_v} - 1 \right) = \frac{S}{P_v^0},$$

where S is the number of bonds cleaved in one macromolecule, the rate of accumulation of cleaved bonds decreases, *i.e.* the efficiency of degradation decreases. This phenomenon, which is rather common for radiation-chemical processes, results from the accumulation of radiolysis products with an increase in the absorbed dose; these products then accept the energy of the ionising radiation. For cellulose, this phenomenon may be due to the fact that the cleavage of bonds in macromolecules is accompanied by the formation and accumulation of radicals stable at room temperature and new functional groups. Compounds with carbonyl and carboxy groups are, along with radicals, efficient acceptors of electrons and excited species formed upon irradiation. Therefore, the accumulation of these compounds during radiolysis hinders subsequent degradation of cellulose. In fact, the degradation of cellulose-based materials containing carboxy groups (monocarboxylcellulose) is much slower.³⁷ It should be noted that up to very large absorbed doses (> 1000 kGy), the degradation of cellulose can be described by an empirical equation similar to Eqn (6) in which the value of D has an exponent q equal to 0.83 (see Refs 16 and 19) or 0.73 (see Ref. 12).

IV. Products of radiation-chemical transformations of cellulose

The action of ionising radiation on cellulose results in profound chemical transformations and produces carbonyl and carboxy groups at the sites of bond cleavage and gases, namely, H_2 , CO_2 , and CO .^{38–42} The dependences presented in Fig. 3 demonstrate the change in the content of $>C=O$ and $-COOH$ groups in the γ -irradiation of cotton cellulose at room temperature. The yields of formation of these groups are 6.5 ± 0.5 and 1.8 ± 0.2 , respectively. Hence, the process of cellulose degradation is accompanied by preferential formation of compounds with carbonyl groups. The yields presented here are in good agreement with the values found by Imamura *et al.*¹⁶ The yields of formation of the carboxy

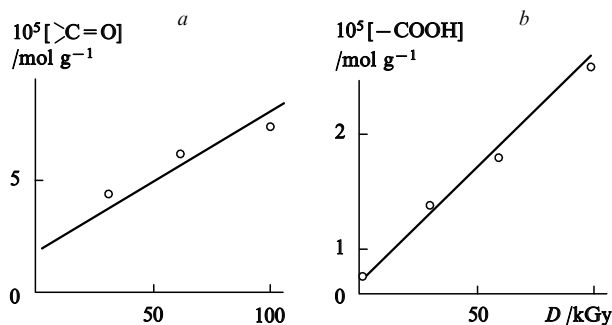


Figure 3. Dependence of the accumulation of carbonyl (a) and carboxy (b) groups in cellulose on the absorbed dose.⁴²

group^{10, 12, 22, 23, 43–46} range from 0.9 to 1.4. Commercial brands of cellulose differ in the content of carbonyl and carboxy groups. However, this does not affect markedly the yields of these groups under γ -irradiation. Irradiation of cellulose increases their content in comparison with the initial concentrations (Table 2). To decrease the degree of polymerisation of commercial celluloses to ~ 300 – 400 , which is an optimum value for their conversion into viscose, nitrate esters, and other products, an irradiation dose of ~ 50 kGy is required. Such an absorbed dose produces ~ 3 mmol of carbonyl groups and 1 mmol of carboxy groups per 100 g of cellulose.

Table 2. Initial concentrations and radiation-chemical yields of oxidised groups upon γ -irradiation of cellulose.^{35, 36}

Cellulose	Concentration /mmol per 100 g		Yield /mmol per 100 eV	
	–CHO	–COOH	–CHO	–COOH
Sulfite wood	0.13	0.24	6.0	2.0
Sulfite wood, high viscosity	0.53	3.16	5.4	1.8
Cotton	0.10	0.45	5.9	2.5

In the initial stage of γ -irradiation, the dependence of the accumulation of carbonyl and carboxy groups in cellulose on the absorbed dose is linear (see Fig. 3). At greater doses, the concentration (c) of these groups increases with the absorbed dose according to the equation

$$c = BD^q,$$

i.e. it obeys the same law as the degradation of cellulose at similar doses. The B coefficient is 6.8×10^{-7} and 1.8×10^{-7} mol (g kGy) $^{-1}$ for carbonyl and carboxy groups, respectively.¹⁶ The q exponent was found to be ~ 0.5 for both groups. In a discussion of data by Blouin and Arthur¹⁰ for the accumulation of carboxy groups,¹² the q exponent was determined to be 0.69. Obviously, as in the case of degradation, the existence of a limiting concentration of functional groups in cellulose is explained by their involvement in radiation-chemical transformations.

The gaseous products of cellulose radiolysis were studied by several authors.^{22, 23, 47–50} The yields of hydrogen, carbon dioxide, and carbon monoxide measured in a vacuum in the γ -irradiation of cellulose were 1.3, 1.6, and 0.8, respectively.^{22, 23} Carbon dioxide predominates in the products of radiation-chemical transformations of cellulose. A systematic study of gas formation in the irradiation of cellulose in vacuum has been carried out.^{40, 42} Linear dependences of the H_2 , CO_2 , and CO accumulation on the absorbed dose were found up to doses of ~ 300 kGy. The yields determined from these linear plots were 3.2 (H_2), 6.0 (CO_2), and

0.9 (CO). In addition to the gases mentioned, a trace amount of methane was also detected. The reported yields and ratio of the gases formed agree with other data.⁴⁹

Because of the high molecular mass of macromolecules of cellulose and other polysaccharides, the use of traditional analytical methods such as chromatography and mass spectrometry for the determination of the final products of their radiation-chemical transformations is virtually impossible. It was noted^{48, 51, 52} that irradiated cellulose contains water-soluble and water-insoluble fractions. Components that dissolve well in ethanol can be isolated from the water-soluble fraction. They include cellobiose, glucose, arabinose, glyoxal, 2-oxogluconic acid, and a number of other acids.⁴⁸ Hydrolysis of the water-soluble fraction results in xylose, arabinose, glucuronic and formic acids, and malondialdehyde.^{43–45, 53} The following radiation-chemical yields were determined for some of these compounds: 48.7 ± 2.4 for glucose, 10.1 ± 2.0 for xylose, 2.3 ± 0.2 for formic acid, and 0.016 for malondialdehyde.⁴⁴ The formation of pentosans upon irradiation of cellulose was also reported.¹⁶

V. The nature of radical products in cellulose

There are plenty of data on free radicals formed under the action of ionising radiation on cellulose.^{54–64} However, the generally accepted concept of their nature has been settled only after a series of publications.^{65–69} Figure 4 shows the ESR spectra of several types of cellulose (absolutely dry, moistened with H_2O , and moistened with D_2O) γ -irradiated at 77 K. All of the irradiated samples are blue (the dry cellulose is weakly coloured, while the colour of moist samples is rather intense) and decolourise upon illumination. This is accompanied by disappearance of narrow singlet signals of ~ 1.0 – 1.2 mT (in the case of H_2O) or 0.3–0.5 mT (D_2O) widths in the central part of ESR spectra of moistened celluloses. In the spectrum of dry cellulose, the signal intensity is much lower, and photobleaching does not change noticeably the ESR spectrum. These singlets are due to captured electrons.^{66, 70}

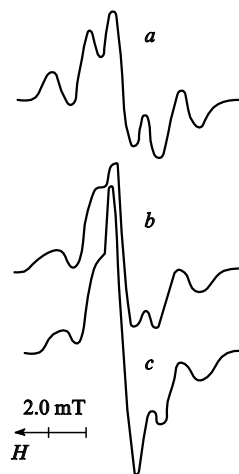


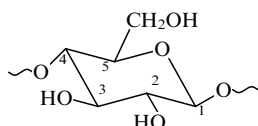
Figure 4. ESR spectra of cellulose γ -irradiated at 77 K;⁷⁰ (a) absolutely dry cellulose; (b) moistened with H_2O (40%); (c) moistened with D_2O (40%).

After photoannealing of the captured electrons by visible light, the ESR spectra of dry and moistened celluloses become identical with the spectrum shown in Fig. 4a. The latter is a superposition of a triplet signal, in which the intensity ratio of the components is 1 : 2 : 1 and the splitting is 3.0 ± 0.2 mT, with a doublet signal with 2.6 ± 0.1 mT splitting (Fig. 4a shows the hyperfine structure of ESR signals of the radicals). The triplet and doublet signals are due to radicals in which the unpaired electron interacts with β -protons, viz. with one proton to form a doublet

and with two protons to form a triplet. The doublet signal can belong only to the radical formed upon abstraction of a hydrogen atom from the C(1) atom of the glucopyranose ring, while the triplet signal can be identified with any radical containing an unpaired electron at positions C(2), C(3), or C(4). Such interpretation of ESR spectra of irradiated cellulose has been suggested in a series of publications.^{65–69}

Subsequent analysis of the radical centre conformations made it possible to draw a fundamental conclusion that the radicals with doublet and triplet hyperfine structures (HFS) are terminal and appear due to the cleavage of the glucosidic bond in the polymeric chain of cellulose.⁷⁰

Let us discuss this approach in more detail. The monomer units of cellulose consist of pyranose rings in the chair conformation with axial hydrogen atoms.



The polymer and its fragments are characterised by high rigidity, which restricts considerably the conformational transitions.

In valence-saturated organic compounds, the carbon atom has four sp^3 -hybrid orbitals. Cleavage of one C–H bond results in sp^2 -hybridisation, while the unpaired electron in the radical centre occupies a $2p_z$ orbital perpendicular to the plane of the three sp^2 -orbitals. In this arrangement, it interacts efficiently with the β -protons. It is obvious that such radical centres at positions C(1) and C(4) of the pyranose ring cannot be obtained without cleavage of the polymeric chain of cellulose. The HFS coupling constants indicate that terminal radicals are formed. This conclusion is supported by calculations of HFS constants for “cellulose” radicals carried out with the assumption of complete sp^2 -hybridisation.⁷⁰ Figure 5 shows a projection of a radical fragment.

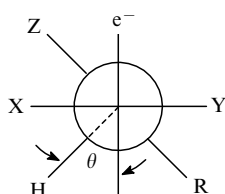


Figure 5. Frontal projection of the C_α – C_β radical fragment. X, Y, Z, and R are substituents. The angle θ between the axis of the $2p_z$ orbital of the unpaired electron and the projection of the C_α –H on the plane perpendicular to the C_α – C_β bond characterises the conformation of the radical centre.

The dependence of the HFS coupling constant for β -protons, a_H , on the angle of rotation around the C_α – C_β bond is expressed by the equation⁷¹

$$a_H = Q_\beta \rho_x \cos^2 \theta,$$

where Q_β is a constant equal to 5.86 mT for alkyl-substituted radicals,⁷² and ρ_x is a coefficient that takes into account the change in the spin density of the unpaired electron at the α -carbon atom caused by substituents. In radicals of the X–C–Y type, the value of ρ_x is calculated by the formula^{72, 73}

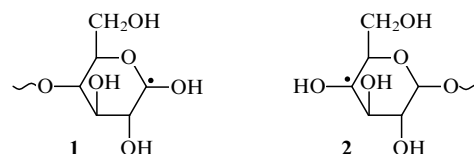
$$\rho_x = (1 - \Delta x)(1 - \Delta y)(1 - \Delta z).$$

The Δx , Δy , and Δz values show the fraction of spin density withdrawn by the X, Y, and Z substituents, respectively. The coupling constants of radical centres in cellulose were calculated with the use of data for substituents that best match the actual ones in the radicals in question. It was found that the calculated constants (2.72 mT for the triplet and 3.04 mT for the doublet) fit

those observed experimentally (2.6 and 3.0 mT, respectively) if one assumes that the θ angle for the axial β -hydrogen atoms with respect to the C(1) and C(4) atoms is 30° . This value agrees with that expected for the actual structure of the radical centres where they are localised at these positions of the pyranose ring at the ends of the polymeric chain.

Calculations for the radical centres at positions C(2) and C(3) with the expected triplet structures can be carried out less accurately due to the absence of data on the electronegativity of the closest substituents. Nevertheless, it is believed that the coupling constants for them (triplets) would also be close to the experimental value of 2.6 mT. Therefore, it cannot be ruled out that radicals with an unpaired electron at the C(2) or C(3) atoms also appear on irradiation of cellulose. However, the fact that the C(1)–H and C(4)–H bonds are the weakest makes them most susceptible to hydrogen abstraction.

The conclusion on the formation of radicals at these positions of the pyranose ring due to the polymeric chain cleavage is in good agreement with data on chain degradation and formation of products of radiation-chemical transformations. Moreover, considering the rigid structure of cellulose, sp^2 -hybridisation could be formed only due to the cleavage of the glucosidic bonds. Otherwise, due to the strong dependence of a_H on the angle θ , one could expect a considerable deviation of the HFS coupling constants from those found experimentally. Thus, the radical states in irradiated cellulose are localised in the terminal fragments of the polymeric chain.



An estimate⁷⁰ shows that the yields of radicals **1** and **2** are approximately the same, *i.e.* the radiation-induced cleavage of the C(1)–H and C(4)–H bonds occurs with about the same probability even at the liquid nitrogen temperature.

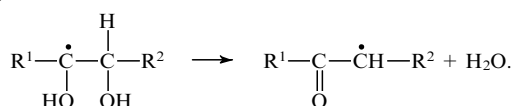
When a considerable amount of water (up to 50 mass%) was present in cellulose samples, an ESR signal was found in the temperature range corresponding to unfreezing of the vibrational-rotational mobility of the pyranose ring fragments. This signal is a triplet (2.5–2.7 mT splitting) of quadruplets (0.5–0.7 mT splitting).⁷⁴ It belongs to the radical **2**, whose ESR spectrum displays the hyperfine coupling on γ -protons at C(6) and C(2) due to the narrowing of the triplet signal components.

As mentioned above, γ -irradiation of cellulose at the liquid nitrogen temperature results in the formation of trapped electrons with low yield; which cause the blue colour of the samples.^{66, 67, 70} The colour intensity increases with the humidity of the samples. If heavy water is used, the ESR signal of trapped electrons becomes much narrower, and its intensity increases (Fig. 4*b,c*). The reason is that the stabilisation of electrons occurs in intermolecular traps in the field of oriented dipoles of water molecules.⁷⁵ The ESR signal of trapped electrons is an envelope of unresolved HFS due to the coupling of an unpaired electron with the closest protons (deuterons in the case of heavy water). The magnetic moment of the deuteron is *ca.* three times smaller than that of the proton, hence the HFS constant decreases, and narrowing of the ESR signal occurs.

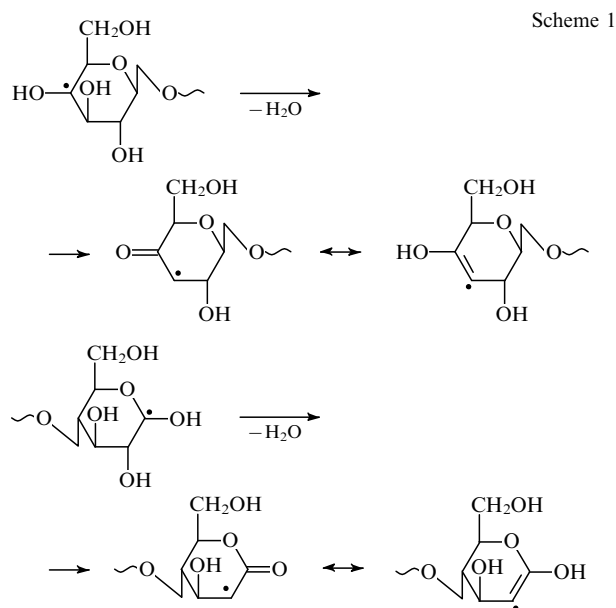
The stabilisation of electrons occurs most efficiently in hydrated cellulose, which contains much more water than natural and industrial celluloses. Due to the transparency of the material, it was possible to record the optical spectrum of the trapped electrons. It is a single wide band with a maximum at 540 nm and a half-height width of ~ 1.3 eV,⁶⁶ which are close to the parameters of optical spectra of trapped electrons in glassy polyatomic alcohols^{76–78} and in concentrated aqueous solutions of carbohydrates.^{79, 80} However, even in hydrated cellulose, the yield of electrons was estimated to be only ~ 0.3 . In cotton and industrial

celluloses, this yield is even smaller, specifically only a few per cent of the overall yield of radicals. Thus, the stabilisation of electrons preferentially occurs in the water microphase. Efficient stabilisation takes place if a system has a glassy (amorphous) structure.^{74, 81} It may therefore be believed that the water present in cellulose exists in the glassy state when it is frozen.

The presence of moisture and ammonia in cellulose accelerates the thermal decay of radicals after γ -irradiation at 77 K.^{22, 55–58, 63, 68} Most probably, this is due to the plasticising effect of the admixtures that weaken the intermolecular bonds in the polymer.⁶⁸ It was noted⁷⁰ that radicals in which the unpaired electron is located at position C(1) (the doublet signal in the ESR spectrum) have the lowest thermal stability. In dry cellulose, such radicals gradually disappear at temperatures above 233 K. The disappearance of doublet and triplet signals occurs at 320–370 K, and a new doublet signal with a 1.4 ± 0.1 mT splitting becomes distinct in the ESR spectrum. Such a coupling constant is characteristic of allylic-type radicals in which the unpaired electron forms a conjugated structure with π -electrons of a double bond.⁸² Radicals of this type are formed in the dehydration of polyatomic alcohols,^{83, 84} mono- and poly-saccharides⁸⁵ according to the reaction



Obviously, dehydration of radicals in the irradiated cellulose (Scheme 1) is also the main process in thermal transformations.



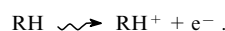
Because of the distortion of the pyranose ring conformation and the decrease in the spin density ρ_z , hyperfine coupling with β -protons is not detected ($a_{\text{H}} < 0.8$ mT). Admixtures of lignin in the irradiated cellulose can cause a new signal to appear in the ESR spectrum (a symmetrical singlet with a width of ~ 1.0 mT).⁶⁷ No $\text{RO}^\bullet$ -type radicals have been detected in the irradiated cellulose.⁷⁴

The irradiation of cellulose at room temperature produces the same radicals as the irradiation at the liquid nitrogen temperature does. However, the concentration ratio of different radicals changes somewhat (the proportion of more thermally stable radicals with a triplet HFS increases). The yield of radicals is ~ 3.0 – 4.0 . The yield increases approximately twofold if the irradiation is carried out at room temperature.⁶³ The kinetics of the accumulation⁶³ and thermal decay⁶⁸ of radicals as a function of the accumulated dose were considered. The observed polychromatic kinetics of radical decay is caused by the physical non-

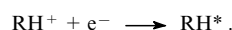
uniformity of the polymeric matrix. Therefore, the chemically identical processes occurring in the matrix have different rate constants of their limiting steps, *i.e.* a distribution of rate constants over the activation energy exists. The diffusion mobility of macroradicals increases by several orders when a polymer is plasticised with water. The elementary act of their diffusion apparently includes the migration of the pyranose unit, in which the radical is localised, relative to other polymer units. The presence of water weakens the bonds between the polymer chain segments.

VI. Mechanism of radiation-chemical transformations of cellulose

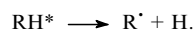
The first step of action of an ionising radiation on a material, *e.g.*, on cellulose (RH), is reduced to ionisation of its components



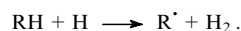
The Coulomb interaction of the electrons kicked out by irradiation and the parent positive ions after their thermalisation leads eventually to their recombination



This process is favoured considerably by a crystal-like and rigid structure of the polymer. The recombination of opposite charges formed in the physical step of the interaction of the irradiation with cellulose predominates, as follows from the extremely low yield of stabilised electrons, which does not exceed 5% of the overall yield of radicals after γ -irradiation at 77 K.⁷⁰ Recombination is probably preceded by charge migration, which is completed on defects of the crystal structure (mainly in amorphous regions). As a result, excited fragments of the polymer are formed. These fragments decompose with preferential cleavage of the C(1)–H and C(4)–H bonds of the glucopyranose ring



The hydrogen atoms formed abstract hydrogen from other carbon atoms at the corresponding positions



The resulting $\text{R}^\bullet$ radicals are unstable. Because their structures are strained, they decompose with the cleavage of the glucosidic bond to give radicals **1** and **2** and with scission of the glucopyranose ring (Scheme 2).

In our opinion, the available data do not make it possible to infer the detailed mechanism of intermediate reactions. Probably, a substantial role in the radiation-induced decomposition of cellulose belongs to the excited states. The scission of the glucopyranose ring results in CO_2 (or CO) and polymeric compounds containing terminal carbonyl or carboxy groups. Some possible ways for the chemical transformation of irradiated cellulose have been reviewed in detail.¹

According to the general scheme suggested for the radiation-chemical transformations of cellulose, the following ratio of yields of the main products should be expected:

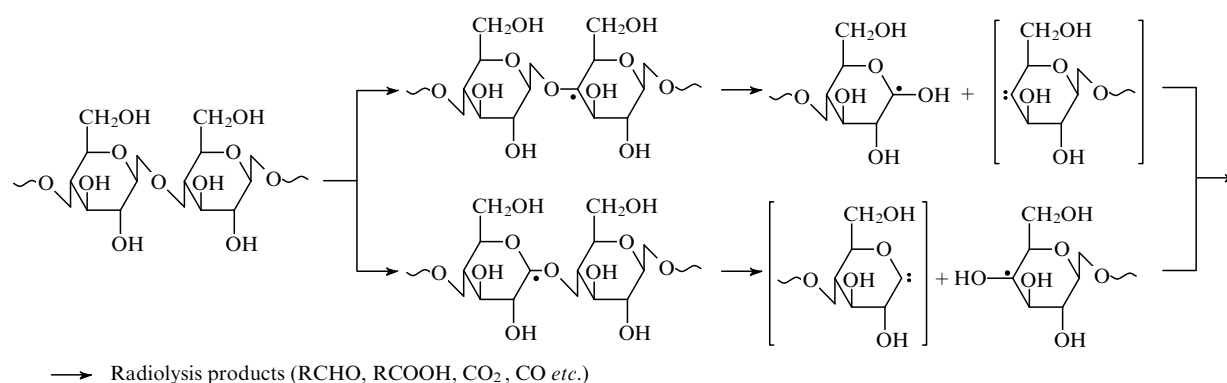
$$2G_{\text{H}_2} = G_{\text{d}} \simeq G_{\text{RCHO}} \simeq G_{\text{CO}_2} + G_{\text{CO}},$$

where G_{d} is the degradation yield.

In fact, this ratio is fulfilled well in the γ -irradiation of celluloses at room temperature. This can be regarded as a confirmation of the general scheme suggested for the initial step of the radiation-induced degradation of cellulose. The yield of carbonyl groups is quite close to the degradation yield and the yield of carbon dioxide, *i.e.* each act of cleavage of the polymeric chain is accompanied by the formation of one CO_2 molecule and one carbonyl group.

It was found^{40, 42} that the degradation of cellulose in the γ -irradiation at the liquid nitrogen temperature is described by the same equations as at room temperature. However, the degradation yield decreases from 6.0 to 3.4. The yields of carbonyl and

Scheme 2



carboxy groups decrease from 6.5 and 1.8 to 3.3 and 1.3, respectively, while the yield of carbon dioxide decreases from 6.0 to 3.1. The yield of molecular hydrogen is about the same as that at room temperature.

Since the yield of hydrogen is used as a measure of the efficiency of radiation-induced cleavage of the C—H bonds in the polymer, it can be concluded that this process is not affected considerably by a decrease in temperature. The formation of CO₂ shows that deep radiation-chemical transformations of cellulose occur which lead to decomposition of the glucopyranose ring. The decrease in the CO₂ yield indicates that this process is hampered as the temperature is decreased. It should be emphasised that the gas analysis^{40, 42} has been carried out after the temperature was increased to 210 or 300 K. This was done in order to ascertain the role of radicals in the formation of CO₂ since the primary radicals partially disappear only at temperatures above 233 K.

The yields of gases were found to be independent of the temperature used for the determination of the gaseous products. Hence, the formation of CO₂ does not result from secondary reactions of radicals. Most likely, it is formed even at the liquid nitrogen temperature through decomposition of the glucopyranose ring in a single process, which involves the formation of radicals and cleavage of the glucosidic bond. This also occurs with the same ratio of yields of the main products ($G_d \approx G_{CO_2} \approx G_{RCHO}$) determined for the irradiation at room temperature and confirming that the acts of degradation and formation of carbon dioxide and carbonyl groups occur simultaneously. The decrease in the yields of cellulose degradation on passing from room temperature to liquid nitrogen temperature is probably due to the hindrance of intramolecular mobility at lower temperatures causing a decrease in the efficiency of degradation of the pyranose ring.

We have already mentioned the difficulties inherent in the determination of the yield of cellulose degradation by viscosimetry. This yield is calculated with a number of assumptions, such as the Gaussian distribution of molecular masses, the known dependence of viscosity on the degree of polymerisation, account of chemical reactions in the dissolution of cellulose, etc. Therefore, it is necessary to measure this most important characteristic of the efficiency of radiation-chemical transformation of the polymer by additional, independent methods. The formation of CO₂ and CO in the irradiated cellulose suggests that scission of the glucose fragment occurs. The overall yield of CO₂ and CO determines the yield of polymer degradation by this mechanism. Within the experimental error, the yield of gases coincides with the degradation yield found by viscosimetry. On the one hand, this confirms that the degradation of cellulose mainly involves the degradation of the glucose unit, and, on the other hand, this justifies the applicability of the viscosimetric method for characterisation of cellulose degradation.

The mechanism of formation and chemical transformations of radicals in cellulose can be determined more accurately by using the data available for similar processes in cellobiose.⁸⁶ Cellobiose

is a structural element of cellulose and is used in studies of model reactions of hydrogen atoms with carbohydrates and polysaccharides.^{87, 88} Analysis of these reactions indicates that degradation of polysaccharides can involve not only the glucosidic bond, but also the C—O bond in the pyranose ring. Pentoses (arabinose, xylose, etc.) were found among the hydrolysis products of radiation-chemical transformations of cellulose.^{44–46, 52} The suggested radiolysis scheme shows that they are formed through removal of one carbon atom as CO₂ and CO from the glucose fragment. Deeper degradation of the glucopyranose ring gives low-molecular-weight products (formaldehyde, formic acid, malondialdehyde, and others). Deoxy- and deoxyoxo-sugars (hexoses) are probably formed through disproportionation of the radicals **1** and **2**.

VII. Degradation of cellulose in plant tissues

Preliminary irradiation of plant raw materials (e.g., wood) changes its properties substantially: it increases the solubility in various media of the constituent cellulose, and, most importantly, enhances its ability to undergo acid hydrolysis.^{89–96} It is natural to relate the latter property to the degradation of cellulose in plant tissues, which contain 60%–80% of cellulose. Studies of the effect of irradiation on the physicochemical state of a lignin–carbohydrate complex from plant materials have confirmed this conclusion. They also demonstrated that the efficiency of cellulose degradation *in situ* is much lower than that in the pure state.^{97–99} This is due to the presence of lignin in plant tissues, which protects cellulose from the radiation-induced degradation.

Systematic studies of the degradation of cellulose within plant tissues have been carried out for aspen wood.^{100, 101} It was found that the yield of cellulose degradation *in situ* is actually about half that of cellulose isolated from this source and subjected to irradiation. However, this comparison is insufficient to draw a final conclusion on the effect of lignin on the efficiency of radiation-induced degradation of cellulose in plant tissues, because the approach used^{100, 101} for the yield determination did not take into account the possible additional hydrolytic degradation of cellulose during its isolation from the plant material. The degree of such degradation is the larger the higher the absorbed dose.

The hydrolytic degradation of cellulose in acidic media depends on the content of carbonyl and carboxy groups, which affect the hydrolysis rate. Therefore, cellulose degradation was studied in the course of its one-step delignification¹⁰² carried out according to Seifert.¹⁰³ The latter method involves treatment of a plant material with a solution containing acetylacetone, dioxane, and aqueous hydrochloric acid. It was shown that the dependence of $1/P_v$ on the duration of treatment with the delignifying solution is described by a first-order equation.^{104, 105} The rate constants of hydrolysis calculated from the slope of the $1/P_v - \tau$ plot increase with the absorbed dose (Table 3). Extrapolation of the kinetic straight line to the ordinate axis (*i.e.* to $\tau = 0$) makes it possible to

determine the degree of cellulose polymerisation in the plant tissue after irradiation, but before its isolation by the delignification process. As noted above, the latter process leads to additional hydrolysis of cellulose. The P_v values obtained are listed in Table 3. The dependence of $1/P_v$ on the absorbed dose is described well by Eqn (6). The degradation yield of aspen wood cellulose was calculated to be 1.8 ± 0.2 , *i.e.* one-third that for pure cellulose. The yield of CO_2 in the radiolysis of aspen wood, which can be related to the degradation of the constituent cellulose, is ~ 2.0 . Hence, like in the irradiation of pure cellulose, aspen wood decomposition also involves the degradation of glucopyranose rings.

Table 3. Change in viscosity-average degree of polymerisation of cellulose isolated from irradiated wood on the duration of delignification.¹⁰²

Dose /kGy	Degree of polymerisation at τ /min			
	30	40	50	60
0	360	350	340	330
50	200	180	165	150
100	160	150	140	120
150	135	120	110	100

Thus, cellulose irradiated *in situ* is decomposed to a much lesser extent than pure cellulose due to the protective effect of lignin. This effect is probably due to the transfer of the excitation energy from the cellulose complex to lignin. Lignin contains complex aromatic groups, which are known^{106,107} to act as protectors in the radiolysis in a mixture with other organic compounds.

The protective effect of lignin in the radiation-induced degradation of cellulose as a component of wood is detected when analysing the quantitative and qualitative composition of radicals at 77 and 300 K. It was shown that the same cellulose radicals **1** and **2** are formed as from pure cellulose, along with a lignin-type radical. The latter is observed in the ESR spectrum as a narrow symmetrical singlet with a g -factor 2.003 and a width 1.0 ± 0.1 mT.¹⁰¹ It was assumed that this is a phenoxyl radical formed upon cleavage of the ether lignin–carbohydrate bond. Analysis of the ESR spectrum of this radical in the 2-mm region confirmed the above assignment.⁷⁴ At absorbed doses < 60 kGy, the signal of the lignin radical predominates in the ESR spectrum, although the content of carbohydrates (cellulose and hemicellulose) is $\sim 70\%$ of the plant tissue weight. The yield of formation of cellulose radicals upon γ -irradiation of aspen wood at 77 K was found to be 0.8. In pure cellulose, this yield is 2.7. The yield of lignin radicals is 1.7.

Thus, the efficiency of *in situ* degradation of cellulose changes noticeably over a wide temperature range in which the plant tissue is irradiated; this can be explained by the protective effect of lignin present in it.

VIII. Radiation-thermal degradation of cellulose

Cellulose processing, primarily the manufacture of esters (viscose, nitrates, *etc.*), is preceded by a stage of its preliminary degradation in order to achieve the required average molecular mass and the optimum MMD. This is commonly done by hydrolysis or thermal treatment. Acidic or alkaline hydrolysis of cellulose makes it possible to achieve this goal. However, the disadvantages of this method (it is laborious, involves inevitable and considerable losses of material, and requires chemicals hazardous to the environment) necessitate the search for alternative ways for decreasing the molecular mass of cellulose. Thermolysis of the polymer also results in its degradation. The degree of polymerisation achievable by this method is limited to ~ 200 –250. Subsequent treatment leads only to pyrolysis with the formation of gaseous products,

levoglucosan, and resins.^{108, 109} Comparison of the above methods with radiation-induced degradation shows the attractiveness of the latter for industrial application. Such treatment of cellulose results in its deep and bulk-uniform degradation to the required and controlled molecular masses without using chemical reagents and without considerable decomposition. Combination of the radiation and thermal treatments makes it possible to decrease the energy consumption for cellulose degradation.

The radiation-induced degradation of cellulose is accelerated markedly with temperature.³⁸ The decrease in the degree of polymerisation in the γ -irradiation is more significant the higher the temperature. The dependence of P_v on the absorbed dose is well described in the coordinates of Eqn (6). Figure 6 demonstrates the dependence of the calculated yields of degradation on temperature in the Arrhenius equation coordinates; Table 4 lists the yields of degradation and the yields of the carbonyl and carboxy groups in the temperature range from 303 to 463 K. It is seen that two temperature ranges of the radiation-induced degradation of cellulose exist: < 380 K, where the yields do not change much, and > 380 K, where the yields increase markedly with temperature. It should be noted specially that the contribution of thermal degradation in the γ -irradiation was taken into account in the calculation of the yields, although it is insignificant.

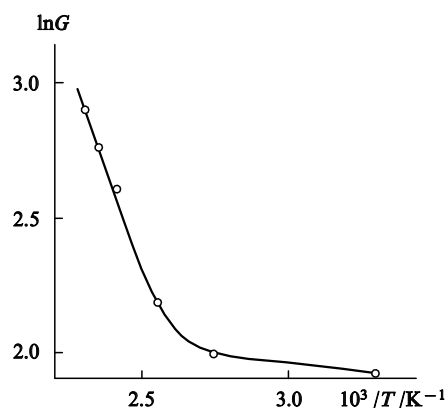


Figure 6. Dependence of the yield of cellulose degradation (bonds per 100 eV of absorbed energy) on temperature in the Arrhenius equation coordinates.³⁸

The activation energy determined in the second temperature range is 23.4 ± 1.6 kJ mol⁻¹. It is most probable that the activation energy corresponds to the diffusion of radicals in the polymer. An increase in temperature initiates the transfer of the radical state to the nearest polymeric chain and causes its degradation. This explanation is based on the fact that the activation energy measured corresponds to the energy of conformational vibrations of the glucopyranose ring.¹⁰⁹ One can see from Table 4 that the degradation yield coincides with the yield of formation of carbonyl groups. It was also found³⁸ that the

Table 4. Yields of products upon radiation-thermal degradation of cellulose.³⁸

T/K	G_d	G_{CHO}	G_{COOH}
303	5.1	5.4	1.8
363	6.0	5.8	1.8
393	7.4	7.1	1.8
413	10.7	11.1	1.9
423	11.4	—	—
433	16.8	17.1	2.3
443	18.1	—	—
463	27.7	26.0	3.3

radiation-induced degradation at high temperatures is accompanied by the formation of hydrogen and carbon dioxide. The yield of the latter is about two times higher.

These facts indicate that the radiation-induced degradation of cellulose at temperatures above 380 K occurs by a chain mechanism, which is initiated by radicals formed upon irradiation. The ratio of the yields of the main products is the same as that in the irradiation under ordinary conditions. This indicates the similarity of processes of radiation-induced degradation occurring in different temperature ranges that are accompanied by degradation of glucopyranose rings with evolution of carbon dioxide and formation of compounds with carbonyl groups.

IX. Degradation of cellulose upon sequential irradiation and thermal treatment

Takeshi and Shosaki¹¹⁰ were the first to observe that degradation of cellulose exposed to γ -irradiation and thermal treatment depends considerably on the ordering of these processes. After irradiation or thermal treatment, the degree of polymerisation of cellulose decreases, while the amount of reducing sugar obtained on its acid hydrolysis increases (Table 5). In the heating–irradiation mode, the increase in the amount of reducing sugar is approximately the sum of the increments corresponding to each of the effects. When treatment is carried out in the irradiation–heating mode, a different picture is observed: the increase in the amount of reducing sugar is markedly greater than that expected for the additive degradation processes. A similar situation was observed when analysing the changes in the number of chain scissions (S). It was found that the total number of bond scissions ($S_{\gamma T}$) in a macromolecule upon consecutive γ -irradiation of cellulose (S_γ) and heating (S_T) can be represented as follows:^{40, 111–113}

$$S_{\gamma T} = S_\gamma + S_T + \beta D,$$

where β is a coefficient which takes account of the increase in the cellulose thermal degradation and D is the absorbed dose. It was also shown that the result of thermal treatment followed by irradiation is additive, *i.e.* the number of chain scissions observed ($S_{\gamma T}$) equals the sum of scissions obtained separately, *i.e.* S_γ and S_T .

Figure 7 shows plots of the number of bond scissions in wood cellulose as a function of the absorbed dose for different modes of irradiation and thermal treatment. In all cases, the dependence of $1/P_v$ on the absorbed dose is described by the simple Eqn (6). The slopes of straight lines 1 and 2 characterising the efficiency of degradation are the same, which confirms the above fact that preliminary thermal treatment does not affect the efficiency of subsequent radiation-induced degradation. On the other hand, the higher slope for consecutive radiation and thermal treatment corresponds to the more efficient polymer degradation. The β

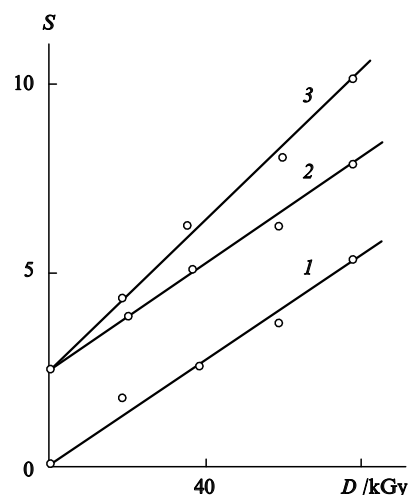


Figure 7. Dependence of the number of bond scissions (S) in wood cellulose on the absorbed dose;¹¹² (1) radiation treatment; (2) successive thermal and radiation treatment; (3) successive radiation and thermal treatment. In all cases, the thermal treatment was carried out at 463 K for 3 h to reach a steady state.

factor is determined from the difference between the slopes of dependences of $1/P_v$ vs. the absorbed dose for each temperature. It is equal to 0.4×10^{-2} , 2.0×10^{-2} , and 3.8×10^{-2} scissions per 1 kGy at 423, 443, and 463 K, respectively.^{40, 112}

Hence, the efficiency of degradation of irradiated cellulose increases with temperature. Enhancement of degradation in the irradiation–heating mode probably results from the formation of defects such as weakened bonds, reactive groups, and radicals in cellulose upon irradiation. On heating, these defects activate scission of the polymeric chain. The Arrhenius-type dependence of the β factor on temperature made it possible to determine the activation energy, which is about 96 kJ mol^{−1}. This value corresponds to the activation energy of super-slow transmolecular motion of the cellulose macromolecule on its thermal treatment.⁶⁸

Thus, combination of irradiation and heating can lead to much deeper degradation of cellulose than that resulting from irradiation or thermal treatment separately. The most energetically favourable mode is the simultaneous action of irradiation and heat or successive irradiation and heating. It was shown^{114, 115} that electron accelerators can be used to implement successfully the destructive treatment of cellulose without the application of additional heating devices. Because of the very poor heat transfer properties of cellulose materials, their intense radiation-induced heating occurs on irradiation with accelerated electrons with dose intensity > 0.4 kGy s^{−1}. Under convective heat exchange conditions, the temperature increased nonuniformly across the depth and reached 430 K, thus providing an efficient degradation mode. Under these conditions, radiolysis products formed in cellulose impregnated with iron salts efficiently reduce the metal ions to produce pyrophoric compounds.^{116, 117}

Table 5. Viscosity-average degrees of polymerisation (P_v) and amount of reducing sugar in cellulose after different types of treatment.¹¹⁰

Treatment	P_v	$P_v/P_v^0 - 1$	Total sugar ^a	Increase in sugar content ^a
Without treatment	408	—	130	—
Irradiation (100 kGy)	71	4.7	167	37
Heating (473 K, 1 h)	190	1.1	155	25
Heating and irradiation	62	5.6	184	54
Irradiation and heating	43	8.5	311	181

^a In mg of sugar per 1 g of cellulose.

X. Radiation-chemical transformations of polysaccharides

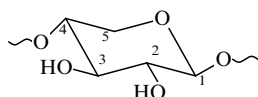
In addition to cellulose, plant materials include other polysaccharides, such as starch and xylan. A number of physicochemical properties and the biological role of cellulose and chitin are similar. Like cellulose, chitin is among the most abundant natural polymers. It constitutes the basis of the outside skeleton (cuticle) of insects, crustaceans, and other Arthropoda, and is a substitute of cellulose in lower plants (*e.g.*, in fungi). Deacetylation of chitin gives chitosan. In recent years, the radiation-chemical transformations of the above polysaccharides have been studied inten-

sively. Below, we discuss the results of the relevant studies and compare these with the data for cellulose.

1. Radiation-chemical transformations of xylans

The study of xylans has received much less attention than that of cellulose.^{118–123} It was reported^{118–120} that irradiation of xylan results in transformations that decrease the viscosity of its solutions and give products with carbonyl and carboxy groups. The degradation of xylans and the nature of the resultant radicals and final products have been studied systematically.^{121–123} 4-*O*-Methylglucuronoxylan isolated from beech holocellulose by extraction with 10% alkali was used. This compound contains 4-*O*-methyl-D-glucuronic acid residues glycosidically linked at position O(2) of about every eighth xylose unit.

The ESR spectra of xylan γ -irradiated at 77 K¹²¹ are shown in Fig. 8 for different absorbed doses. It is seen that the shape of the spectrum changes as the dose increases, which indicates that several types of radicals are formed, which accumulate at different rates. In the initial stage, a narrow singlet signal of trapped electrons predominates. At higher absorbed doses, two signals predominate in the spectrum: a triplet with 2.6 mT splitting and a doublet with 3.0 mT splitting, *i.e.* almost the same signals as those observed in irradiated cellulose. The doublet signal can belong only to the radical formed on abstraction of the hydrogen atom from position C(1) followed by cleavage of the glycosidic bond. The triplet signal can belong to any of the radicals formed upon abstraction of hydrogen from positions C(2), C(3), or C(4).



For positions C(2) and C(3), both β -protons are equivalent, which explains the observed structure of the ESR signal. When the radical state is localised at C(4), the two β -protons at C(5) are nonequivalent. The coupling constants with one of the β -protons at C(5) and with the β -proton at C(3) are approximately the same, while that with the other β -proton at C(5) is much smaller. In this case, a triplet ESR signal can be expected, and its components can be further sub-split into doublets due to the weaker coupling with one of the β -protons at C(5). However, considering that the C(1)–H and C(4)–H bonds are the weakest, it may be assumed that the formation of radicals in γ -irradiated xylan is due to the localisation of the unpaired electron at positions C(1) and C(4) and cleavage of the glycosidic bond. Hence, radicals of the same type as in the case of cellulose are formed.

Theoretical analysis of the ESR spectra¹²¹ agrees with this interpretation. The spin densities for radicals with localisation of

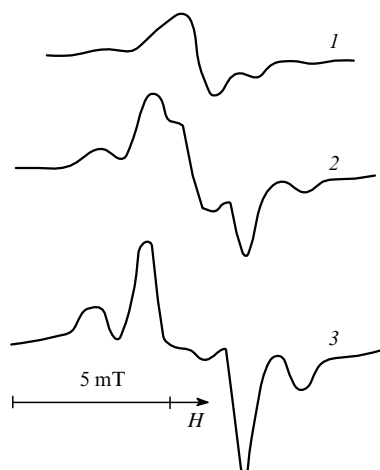


Figure 8. ESR spectra of xylan γ -irradiated at 77 K.¹²¹ Absorbed dose /kGy: (1) 10; (2) 30; (3) 240.

the unpaired electron at positions C(1) and C(4) are 0.696 and 0.619, and the coupling constants are 3.04 and 2.72 mT, respectively. The role of the glucuronic acid residue was found to be insignificant and not to affect significantly the nature of radicals formed. The radicals are accumulated linearly up to an absorbed dose of 300 kGy. The overall yield of radicals measured in this range is ~ 4.0 .

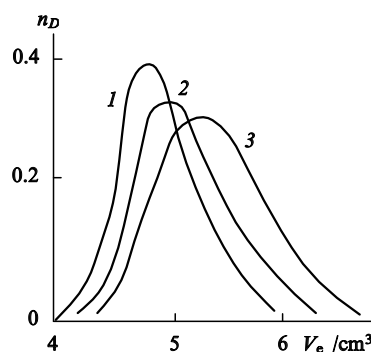


Figure 9. Gel-permeation chromatograms of xylan;¹²³ (1) original sample; absorbed dose /kGy: (2) 50; (3) 125.

The irradiation of xylan is accompanied by its intense degradation.^{122, 123} Figure 9 shows the gel-filtration curves of xylans γ -irradiated to different doses (the molecular-mass characteristics were monitored with a refractometer). It is seen that the peak height decreases, while the distribution curve broadens. Table 6 lists the experimental molecular masses M_v and the calculated number-average M_n and weight-average M_w molecular masses. The decrease in the molecular mass with an increase in the absorbed dose is the consequence of the radiation-induced degradation of the polysaccharide. This fact was pointed out by Beinart *et al.*,¹¹⁸ who also observed a noticeable decrease in the viscosity-average degree of polymerisation of glucuronoxylan after γ -irradiation and an increase in its solubility in water. In fact, the content of a water-soluble fraction in xylan increased from 35.7% to 54.5% at an absorbed dose 125 kGy (see Table 6). The degradation of xylan occurs in a random way, which follows from the change in the M_w/M_n ratio from 1.53 in the starting sample to 1.9 after irradiation to a 125 kGy dose. The latter ratio is close to 2.0, which corresponds to the most probable molecular-mass distribution of polymers. As indicated above, such MMD can result from random scissions of an infinite polymeric chain. This allows the use of Eqn (6) for the determination of the degradation yield. In fact, the dose dependence of $1/M_n$ (or $1/P_n$) predicted by this equation is linear in the high dose region, and the calculated degradation yield is 8 ± 1 .

It was also found that xylan, like cellulose, produces hydrogen and carbon dioxide, whose radiation-chemical yields are 2.8 and 4.4.^{122, 123} The presence of carbon dioxide indicates that the formation of radicals actually does not occur directly upon cleavage of the glycosidic bond but involves rupture of the

Table 6. Molecular-weight characteristics and solubility of irradiated xylan.¹²³

Dose /kGy	Extraction with water (%)	$10^{-3}M_w$	$10^{-3}M_n$	$10^{-3}M_v$	M_w/M_n
0	35.7	22.1	14.4	21.8	1.53
12.5	40.7	20.1	12.6	19.8	1.59
25	51.2	18.5	11.2	18.2	1.65
50	49.6	16.0	9.4	15.8	1.70
87.5	49.1	12.7	7.2	12.5	1.76
125	54.5	12.2	6.6	12.0	1.90

pyranose ring resulting in the formation of a carbon dioxide molecule. Hence, the mechanisms of radiation-induced degradation of xylan and cellulose are fairly similar.

2. Radiation-chemical transformations of chitin and chitosan

Chitin is a polysaccharide built of 1,4-linked 2-acetamido-2-deoxy- β -D-glucose moieties. It can be regarded as cellulose in which the OH groups at C(2) are replaced by acetamido groups. Deacetylation of chitin produces chitosan. The difficulty of studying the radiation-chemical transformations of chitin is due to its extraordinary chemical stability: γ -irradiation of chitin with even rather high doses does not cause a noticeable change in the IR spectra and is not accompanied by a decrease in the adsorption properties toward metal ions from aqueous solutions.^{124–127} The conclusion made as to the high radiation stability can hardly be considered proven because of the inadequacy of the methods used in the study. These methods are too insensitive to determine the destructive role of the ionising radiation. Moreover, the application of such methods to cellulose would lead to the same conclusions, since chemical changes are reflected in IR spectra at much higher doses where the number of new chemical bonds is comparable to that present in the material. In fact, the pattern and intensity of IR absorption spectra of cellulose is retained during its irradiation up to an absorbed dose of 1000 kGy, but the conclusion as to its high radiation stability cannot be made on this basis.²³

The difficulties of studying the degradation of chitin are associated primarily with the selection of an appropriate solvent for this compound and determination of the viscosimetric properties as a function of the absorbed dose. The molecular mass of chitin was determined from the characteristic viscosity in a solution in *N,N*-dimethylacetamide containing 5% lithium chloride¹²⁸ according to the procedure suggested by Terboevich *et al.*¹²⁹ Chitin samples from various sources were studied. During the irradiation, the molecular masses of chitins decreased, and the content of the amino and carboxy groups increased (Table 7). The dependence of $1/P_v$ on the absorbed dose predicted by Eqn (6) for random degradation was obeyed well (Fig. 10). The radiation-chemical yields of degradation of chitins obtained from crab and krill shells were almost the same (1.8 ± 0.2), while the yield for

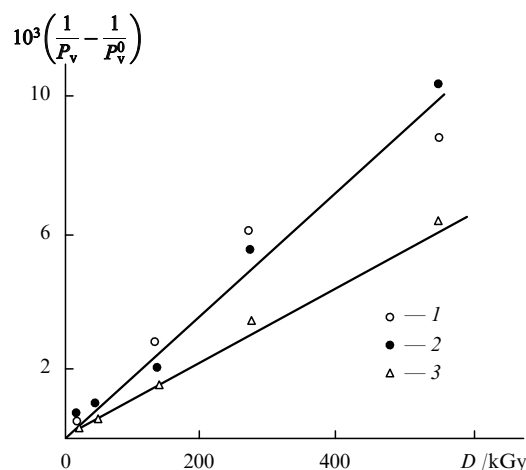


Figure 10. Dependence of the $1/P_v - 1/P_v^0$ difference in chitin on the absorbed dose;¹²⁸ chitin source: (1) crab shells; (2) krill shells; (3) shrimp shells.

chitin from shrimp shells was 1.1 ± 0.1 . It is seen that the yields of degradation decrease markedly on going from cellulose to chitin. Up to high absorbed doses, degradation occurred without changes in the crystalline structure and without violation of the intermolecular packing, as was shown by X-ray diffraction analysis.¹²⁸ Similar dependences were reported for irradiated cellulose.^{29, 130, 131}

The irradiation of chitin leads to its deacetylation, which results in free primary amino groups and acetic acid; the degradation of the polymer produces compounds with carboxy groups. Table 7 presents the concentrations of the amino groups and the total concentrations of the carboxy groups. The radiation-chemical yields of these groups in chitins from various sources are 9 ± 2 . The yield of chitin degradation is rather low (1.1–1.8); this fact allows one to assume that the major part of carboxy groups determined by chemical analysis is due to acetic acid. This may be regarded as an indication that the free amino groups and the carboxy groups (acetic acid) are mainly formed as a result of deacetylation upon γ -irradiation. At high absorbed doses, the chitin shows the tendency to undergo deamination and decarboxylation. Hydrogen and carbon dioxide are the major gaseous products of chitin radiolysis. Their yields for chitin from crab shells at an absorbed dose of 150 kGy are $\sim 1.1 \pm 0.3$ and $\sim 1.4 \pm 0.4$, respectively (which are considerably smaller than those found for cellulose radiolysis, *viz.*, 3.2 and 6.0, respectively).

The radiation-chemical transformations of deacetylated chitin (chitosan), which is now widely used in various fields of industry, agriculture, and medicine, are perhaps of particular interest.¹³² Chitosan undergoes degradation under irradiation, both in aqueous solutions and in the dry state.^{133, 134} However, the quantitative estimation of the degradation efficiency has not been made. This problem has been studied for chitosan with degree of deacetylation 85%.¹³⁵ Viscosimetric analysis was carried out in aqueous 2% acetic acid containing 0.2 M AcONa according to the published procedure.¹³⁶ The radiation-chemical yield of chitosan degradation was found to be 4.2 ± 0.3 , which is markedly higher than that for chitin and lower than that for cellulose. The yields of hydrogen and carbon dioxide were 1.3 and 1.5, respectively. The irradiation of chitosan results in its partial deamination. For example, at an absorbed dose 600 kGy, the content of amino groups decreases by $\sim 4\%$, which corresponds to a radiation-chemical yield of deamination of ~ 3 .

The nature of radical products of low-temperature radiolysis of chitin and chitosan is the same as in the case of cellulose. Both in chitin¹²⁸ and in chitosan,¹³⁵ terminal radicals appear with localisation of the unpaired electron at C(1) and C(4). These radicals appear in the ESR spectra as a doublet with a ~ 3.0 mT splitting

Table 7. Changes in molecular mass and functional composition of chitin from various sources exposed to γ -irradiation.¹²⁸

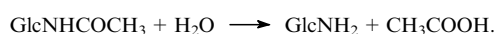
Dose /kGy	Amino groups / 10^{-6} mol g ⁻¹	Carboxy groups / 10^{-6} mol g ⁻¹	P_v
Chitin from crab shells			
0	2.2	3.6	806
25	23.8	—	600
50	35.3	—	567
137	29.8	26.7	247
181	—	—	152
275	25.7	24.3	140
550	—	—	100
Chitin from shrimp shells			
0	3.8	4.0	1356
25	10.4	14.7	977
50	63.3	11.4	937
137	39.1	40.0	455
275	33.4	38.0	247
550	—	—	144
Chitin from krill shells			
0	4.7	—	720
25	22.8	13.4	470
50	21.7	43.6	442
137	—	35.6	288
275	18.4	—	144
550	—	—	84

and a triplet with 2.6 mT splitting. The ESR spectra of chitin have some specific features, namely, the doublet components have a slight additional splitting. This splitting can be caused by an anisotropy of the hyperfine structure due to the amino group adjacent to the C(1) position or by overlapping with another doublet signal with a higher HFS coupling constant (~ 2.9 mT). The latter may be due to the different positions of pyranose rings in the crystal structure of chitin (two nonequivalent positions) resulting in a slight nonequivalence of the two radical centres. The radiation-chemical yields of radicals in the γ -irradiation of chitin and chitosan at the liquid nitrogen temperature are 2.3 (see Ref. 128) and 3.0 (see Ref. 135), respectively.

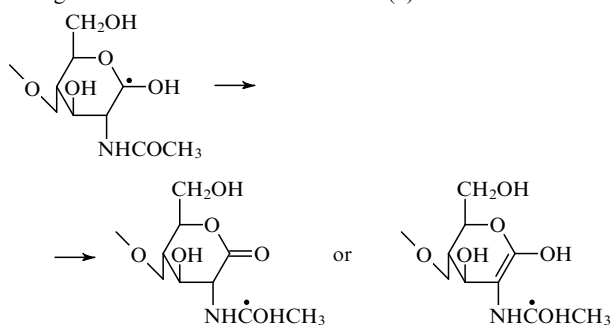
Of interest are specific features of thermal transformations of radicals in chitin. It was found¹²⁸ that a decrease in their concentration starts from ~ 200 K. The radical at C(1) is more stable than that at C(4). Furthermore, as the primary radicals disappear (even at room temperature), an ESR signal appears as a quartet with a 1:3:3:1 intensity ratio of the components and a ~ 1.4 mT splitting between them. This signal can be assigned rather definitely to the $\text{GlcNHC}(\text{OH})\text{CH}_3$ radical, where Glc is the glucose residue. The quartet structure of the signal of this radical is due to splitting of the unpaired electron with three protons of the CH_3 group. The parameters of the ESR signal of the $\text{NH}_2\dot{\text{C}}(\text{OH})\text{CH}_3$ radical formed upon γ -irradiation of acetamide¹³⁷ are similar to those of the radical indicated above.

Calculations show that the presence of the amino group at C(2) in chitin and chitosan instead of the hydroxy group in cellulose scarcely affects the coupling constant of the doublet signal. For cellulose, the triplet ESR signal might be due to the localisation of the radical centre not only at C(4) but also at C(2), which is not the case for chitin and chitosan. If the radical were localised at C(2), the HFS of the signal would be different due to coupling of the unpaired electron with the nitrogen nucleus (nuclear spin 1). Thus, the conclusion that terminal radicals are preferentially formed at the C(1) and C(4) atoms in the irradiation of polysaccharides appears to be well substantiated.

The similarity of the nature of radicals formed upon γ -irradiation of chitin, chitosan, and cellulose indicates that the initial processes of their radiation-chemical transformations are similar. However, the yields of scission of the polymeric chain in chitin (1.1–1.8) and chitosan (4.2) are much lower than those in cellulose (~ 6.0). The yields of gaseous products are also much lower. The predominating process is the deacetylation of chitin leading to the formation of free primary amino groups and acetic acid, as well as the deamination in the case of chitosan. In a general form, the formation of acetic acid under γ -irradiation of chitin can be represented as hydrolytic deacetylation

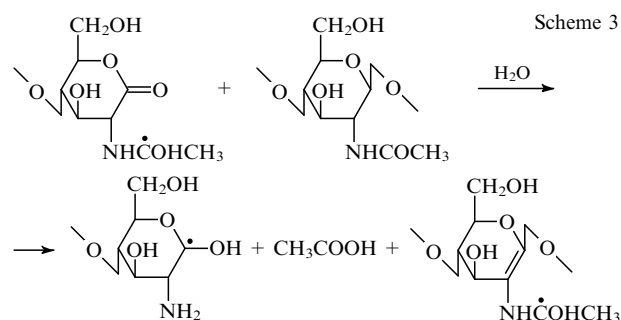


In fact, agreement between the yields of the formation of amino and carboxy groups has been found.¹²⁸ In addition, ESR studies indicate that the deacetylation mechanism involves the following transformations of radicals at C(1):



These transformations may involve both intra- and inter-molecular hydrogen shift. Subsequent reactions of the $\text{GlcNHC}(\text{OH})\text{CH}_3$ radicals result in chitin deacetylation. The considerably higher yield of deacetylation products in comparison

with the yield of radicals and degradation yield can be explained by the chain character of the process (Scheme 3).



The reason why the origin of chitin affects the nature of the radicals formed and the degradation efficiency remains unclear. This may be due to the different structures of the materials themselves.

Thus, the replacement of the OH groups in cellulose with the NH_2 (chitosan) or $\text{NHC}(\text{O})\text{CH}_3$ groups (chitin) increases markedly the radiation stability of materials against degradation. Along with degradation, deamination (in the case of chitosan) and deacetylation (in the case of chitin) occur in these polysaccharides.

3. Radiation-chemical transformations of starch and dextran

Like cellulose, starch consists of d-glucose residues linked by 1,4- α - rather than β -glucosidic bonds. Cellulose is a cellobiose-type and starch is a maltose-type polysaccharide. The interest in the study of radiation-chemical transformations of starch is partially caused by the wide use of irradiation for sterilisation of food. It was found^{138–144} that the action of γ -irradiation on starch from different sources (from waxy and amilose corn, potatoes, manioc, rice, beans, wheat, and other plant products) results in the accumulation of carbonyl groups,¹³⁸ organic acids,¹³⁹ and hydrogen peroxide¹⁴⁰ and is accompanied by degradation.^{141–144} The accumulation of new functional groups depends on the source of the starch; this is explained by differences in its structure. The acidity increased during storage of the samples, whereas the content of hydrogen peroxide decreased. The content of water-soluble dextrans increased linearly with the absorbed dose. The moisture present in starch inhibited the formation of dextrans and reducing groups. Unfortunately, the authors of the works cited did not report quantitative data on the efficiency of radiation-chemical degradation of starch (*i.e.*, the yields).

According to the degradation mechanism common for polysaccharides, it may be believed that a degradation act is accompanied by the cleavage of a pyranose ring to produce one carbon dioxide molecule and a carbonyl-containing compound. Therefore, the yields of these products can also, to some degree, serve as an indication of the efficiency of the polysaccharide degradation. In fact, this rule was valid for all of the polysaccharides considered. It was found for potato starch¹⁴⁵ that, in addition to hydrogen, whose yield is 4.5 molecules per 100 eV of the energy adsorbed, CO_2 and CO are formed in 5.5 and 1.5 yields, respectively, while the yield of carbonyl groups is 6.5.¹⁴⁶ It is also worthy of note that the yields of reducing compounds upon the radiolysis of various starches also do not exceed 6–10.^{147,148} Therefore, taking into account the possible errors in the chemical analysis of products of the radiation-chemical transformations of starch, it can be assumed that the yield of its degradation is within 5–7. The yields of gaseous products that formed upon γ -irradiation of potato starch were also measured.¹⁴⁶ The resulting $G(\text{H}_2)/[G(\text{CO}_2) + G(\text{CO})]$ ratio was approximately the same as that found by Ershov and Isakova.¹⁴⁵ However, the absolute yields were by about an order of magnitude lower (0.5 for H_2 , 0.5 for CO_2 , and 0.2 for CO). They did not correlate with the yields of carbonyl and carboxy groups (6.5 and 5.0, respectively) measured in the same study, which also characterise the efficiency of the

radiation-chemical degradation of starch. It should be noted that this low yield of hydrogen is generally untypical for irradiation of saturated compounds.¹⁴⁹ An unusual (oscillating) dependence of the formation of products of radiolysis of potato starch and dextran on the absorbed dose was observed.¹⁴⁶ It was also found that the presence of moisture in starch resulted in an almost 30-fold increase in the hydrogen yield, while the yields of other gases remained the same. It is unlikely that this fact can be reduced only to the specific radiolytic behaviour of water structured by polysaccharides.

The radicals formed upon the action of radiation on starch at the liquid nitrogen temperature have the same nature as those in other polysaccharides: they are terminal with localisation of the unpaired electron at positions C(1) and C(4) of the pyranose ring.^{144, 145} Therefore, there is reason to assume that the nature of the linkage between the glucose residues (α -linkage in the case of starch and β -linkage in the case of cellulose) does not affect markedly the mechanism or the efficiency of bond cleavage.

A systematic analysis of the products of radiation-chemical degradation of corn starch in the presence of oxygen was carried out.¹⁵⁰ It was shown that the main products include oxo compounds and water; carboxy and aldehyde groups are also accumulated in about an order of magnitude smaller yields. The efficient radiation-chemical oxidation of starch is explained by the involvement of peroxide radicals in the reaction. The latter are formed due to trapping of oxygen molecules by radicals formed in the irradiation. Low-molecular-weight dicarboxylic acids are found among the products of starch radiolysis at high absorbed doses (up to 1000 kGy): tartaric (42.4%), citric (33.5%), malic (16.4%), succinic (4.6%), lactic (1.8%), and fumaric acids (1.3%). The formation of a dicarboxylic acid molecule implies the insertion of two additional oxygen atoms into a monomeric unit, which presumes the formation and subsequent transformation of two peroxide radicals. The possibility of a chain mechanism of the reaction is not ruled out.¹⁵⁰ The suggested schemes of the formation of dicarboxylic acids take into account that the isomerisation and dehydration of a polysaccharide occur at high rates and that the reaction of radicals with an oxygen molecule is by an order of magnitude faster than recombination.

The dextran chain comprises mainly α -1,6-glucosidic units. It also contains branches, [mainly at C(3)] built of mono- and disaccharides. Early studies^{151–157} of radiation-chemical transformations of dextrans were carried out for aqueous solutions. The possibility of decreasing the molecular mass of this polysaccharide was studied with the aim of using it as plasma extender.¹⁵¹ A stronger decrease in characteristic viscosity was noted for solutions than for the solid polymer. This indicated the degradation of dextran in which radical products of water radiolysis played the decisive role. Thus, irradiation turns out to be an efficient tool for directed decreasing the molecular masses, making it possible to lower them by a factor of tens and hundreds.

It was found that in the radiolysis of dry dextran^{152–155} the molecular mass and viscosity decrease, the rate of cleavage of molecular chains depending on the molecular mass. The degradation was accompanied by narrowing of MMD,^{156, 157} and radiation-chemical modification.

Different polysaccharides differ in the degree of crystallinity and in the content of bound water. These factors can affect markedly the direction and efficiency of their radiation-chemical degradation. These factors can be revealed with sufficient reliability only in rare cases. However, their important role is obvious. In this respect, a study by Petrov *et al.*¹⁵³ that dealt with the radiolysis of potato starch deserves special attention. Starch granules contain linear amylose molecules along with branched amylopectin. The crystallinity index of potato starch is only $\sim 20\%$. The adsorbed water in it is distributed nonuniformly among the units and is mainly located in structural channels and cavities of amorphous regions of amylopectin. A study of fractions of irradiated potato starch by gel-permeation chromatography showed that amylopectin is the component which is

destroyed preferentially. At a dose of 200 kGy, the content of amylopectin is 15% (as compared to 75% for the native starch), while that at a dose of 600 kGy is only 2%. The considerable increase in the reducing power of fractions along with the decrease in their molecular masses¹⁵⁷ confirm the formation of low-molecular-weight aldehydes and acids in the radiation-chemical transformations of amylopectin.

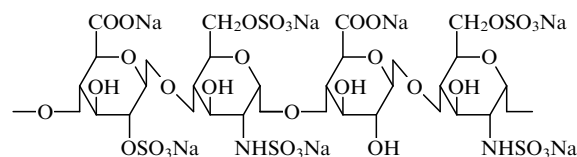
The effect of the structural factor on the radiation-chemical degradation and chemical transformations of native polysaccharides, which differed considerably in their degree of crystallinity and in the content of bound water, was studied under normal conditions and in a wide range of absorbed doses.¹⁵⁸ Cellulose, potato starch, amylopectin, and dextran were studied. Dextran macromolecules do not form a crystalline phase but exist as disordered coils with high density in the centre and low density at the periphery. The yields of reducing compounds and carboxy groups reach ~ 32 and ~ 14 , respectively, for dextran, as compared to 4–7 and 3–5 for other polysaccharides. The yields are determined by the density and type of distribution of amorphous regions, which provide free access of water and oxygen to the macroradicals and access of the H $\cdot$ and $\cdot$ OH radicals formed due to water decomposition to one or another carbon atom of the glucopyranose ring. The considerable yields of radiolysis products in dextran may indicate a chain mechanism of its radiation-oxidative decomposition.

The paper cited¹⁵⁸ also reports very low degradation yields of starch and dextran, namely, 0.3 and 1.0, respectively. These values disagree with the much higher yields of CO₂ and CO formation and the yields of reducing compounds and carboxy groups. Therefore, the conclusion is made about the possibility that these compounds are formed without the decomposition of the pyranose ring. However, this seeming contradiction is explained by the inapplicability of the approach used to describe degradation, which is valid only for linear polymers with the most probable MMD and random chain scission. This circumstance was noted even in early studies of the degradation of these polysaccharides in aqueous solutions. Native starch and dextran have very wide and nonuniform MMD, and the different nature of bonds in these branched polysaccharides does not presume *a priori* their equal proneness to radiation-induced degradation.

Numerous studies dealt with the action of radiation on aqueous solutions of such polysaccharides as agar-agar, alginic acids, pectins, glycogen, and some others. The results of these studies and the mechanism of the radiation-chemical transformations have been considered in sufficient detail by Bovey² and Kochetkov *et al.*¹⁵⁹ It was shown that degradation accompanied by a decrease in the molecular mass of the polymer is the dominating process.

4. Radiation-chemical transformations of heparin

Heparin is a natural acidic polysaccharide. It is a nonbranched heteropolysaccharide built mainly of two types of sulfated disaccharide residues linked through 1,4- α -glucosidic bonds. The structural formula of the repeating tetrameric unit of heparin can be written in the form:



Several studies were devoted to the radiolysis of heparin solutions.^{160–165} The degradation of macromolecular chains is the main radiolysis process. Specific features of the degradation of a dry polymer were studied by Kudryavtsev *et al.*¹⁶⁶ for the sodium salt of heparin in the form of a powder with a starting viscosity-average molecular weight (M_v) of 10,325 as an example. The reciprocal of M_v varied linearly with an increase in the absorbed dose according to Eqn (6); the calculated degradation

yield was 3.1 ± 0.4 . This is about half the degradation yields for cellulose, dextran, and starch. It can be concluded that the presence of sulfamino and sulfo groups in heparin, like the presence of acetamido groups in chitin, increases the resistance of the polysaccharide against radiation-induced degradation. Irradiation resulted in partial desulfation of heparin. Analysis of ESR spectra^{166–169} showed that radicals of the same types as those commonly observed in polysaccharides were present in irradiated heparin. These radicals appeared upon cleavage of glycosidic bonds, and their unpaired electrons are localised at positions C(1) and C(4). Chromatography of gaseous products did not detect carbon dioxide. It was concluded¹⁶⁶ that the radiolysis of heparin does not involve the degradation of the pyranose ring. However, it is hardly possible to agree with this conclusion. The observed formation of terminal radicals could not occur without rupture of the pyranose ring. Most likely, the sensitivity of the chromatographic method was insufficient to measure the concentration of CO_2 when using a small amount of the starting material. The yield of molecular hydrogen (~ 0.6 for dried heparin and 0.9 for non-dried heparin) was also low, which is difficult to explain.

It should be noted that the radiation-induced degradation of heparin is a convenient method for controlled variation of its molecular mass and for directed change of its properties.

XI. Radiation-chemical degradation of ethers and esters of cellulose and other polysaccharides

It is known²² that the presence of aromatic groups (benzyl, benzoyl, naphthoyl, *etc.*) in cotton cellulose increases considerably the tensile strength of fibres exposed to ionising radiation. Taking into consideration the decrease in the strength of cellulose materials upon degradation, it may be assumed that aromatic groups in cellulose favour a decrease in the degradation yield. It is also known^{106,107} that aromatic molecules are efficient energy acceptors.

Deactivation of excited states occurs with high probability without cleavage of chemical bonds.

The results of studies of the effect of irradiation on cellulose ethers and esters show that they also undergo degradation, although to a smaller extent.^{170–183} The efficiency of polymeric chain scission is determined by the nature of the substituent and the degree of substitution. The following cellulose derivatives have been studied:^{175,181} hydroxyethylcellulose (HEC), sodium salt of carboxymethylcellulose (Na-CMC), allyloxyethylcellulose (AOEC), allyloxycarbonylmethylcellulose (ACMC), and (methacryloyl)carboxymethylcellulose (MCMC). Samples with various degrees of substitution by allyl (j_a) and methacryloyl (j_m) groups (the number of groups per 100 anhydroglucose units) were used in the experiments. It was found that the solubilities of the ethers (ether-esters) before and after γ -irradiation differ greatly. For

Table 8. Change in the viscosity-average degree of polymerisation (P_v) of cellulose ethers (esters) as a function of the absorbed dose.¹⁷⁵

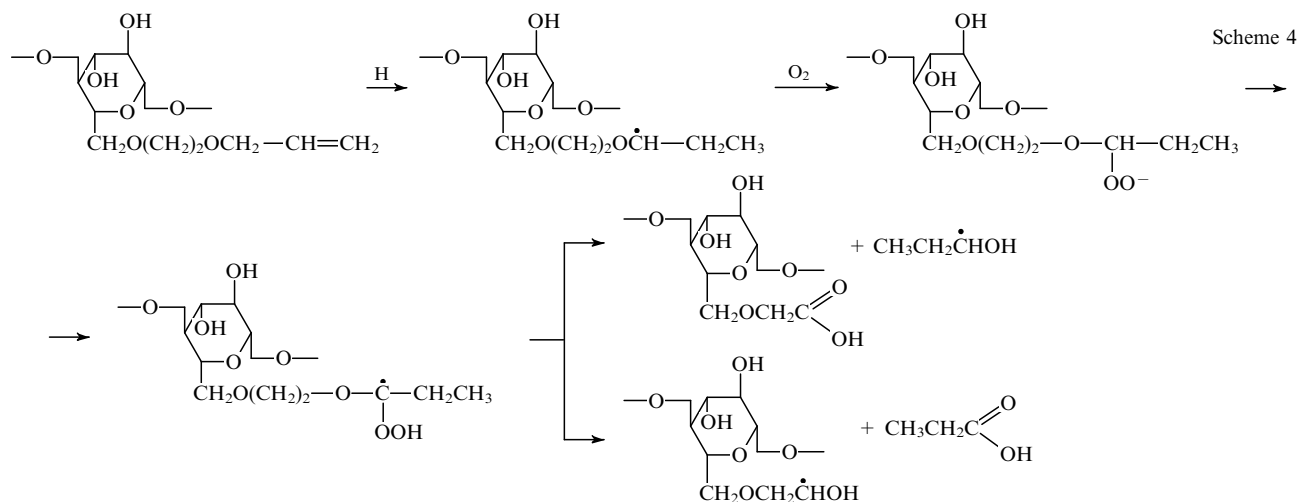
Cellulose derivative	Degree of polymerisation for absorbed dose /kGy						
	0	10	20	40	60	80	100
HEC	1995	—	1485	1187	908	617	565
Na-CMC	460	—	220	206	164	169	147
ACMC	359	213	185	196	—	157	140
($j_a = 5$)							
MCMC	348	219	224	219	—	160	—
($j_m = 4$)							

example, HEC, Na-CMC, ACMC ($j_a = 5$) and MCMC ($j_m = 4$) remain water-soluble at any absorbed dose (up to 120 kGy). However, AOEC ($j_a = 4$), AOEC ($j_a = 30$), and ACMC ($j_a = 40$) lose solubility even at a dose 10 kGy. This shows unambiguously that degradation processes dominate in derivatives of the first group, while cross-linking of polymeric chains resulting in the formation of a three-dimensional structure dominate in the second group. Table 8 demonstrates the dependence of the degree of polymerisation of various cellulose ethers and esters on the absorbed dose. It was found¹⁷⁵ that the dependence for Na-CMC is described well by Eqn (6). The degradation yield is almost the same within the experimental error and equals 2.5 ± 0.5 . This is consistent with the value of 2.8 calculated by us on the basis of other data.¹⁸² The yield for HEC is 1.5 ± 0.2 . Thus, the presence of functional groups in ethers determines their much lower degradation yield in comparison with cellulose.

Analysis for carboxy and peroxide groups and double bonds showed¹⁷⁵ that their content is primarily determined by the nature of substituent in the ether. For instance, no formation of double bonds or peroxide and carboxy groups is observed in HEC, unlike in the other ethers. According to IR spectroscopic data, only accumulation of carbonyl groups occurs with an increase in the absorbed dose. On the other hand, in AOEC with $j_a = 4$ and especially with $j_a = 30$, the number of double bonds decreases, while peroxide and carboxy groups are accumulated. These changes are probably caused by the addition of hydrogen atoms (formed due to radiation-induced cleavage of C—H bonds) to the allyl group followed by chemical transformations (Scheme 4).

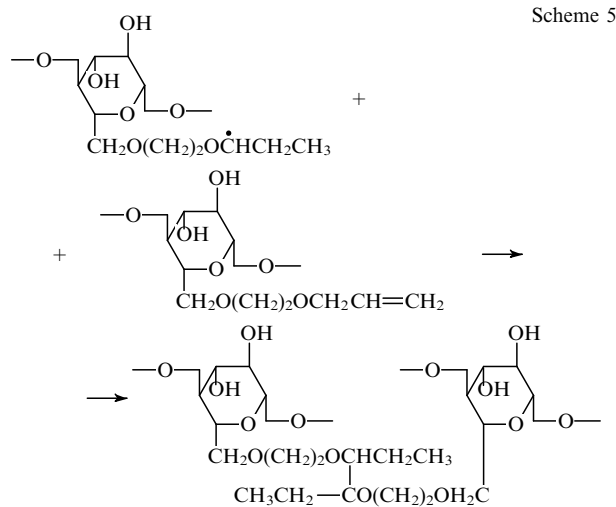
The suggested scheme of radiation-chemical transformations makes it possible to explain the inverse character of changes in the concentrations of double bonds and peroxide groups observed for allylic derivatives of cellulose.

In Na-CMC, as well as in ACMC with $j_a = 5$ and 40, the number of carboxy groups decreases. In addition, a decrease in the number of double bonds and accumulation of peroxide groups is observed in the latter two samples. The process in MCMC with $j_m = 4$ occurs similarly, the differences being that peroxide groups



are detected only at a dose of 120 kGy and that the change in the number of double bonds is less distinct.

Cross-linking of allyl ethers and methacryloyl esters occurs through double bonds (Scheme 5).

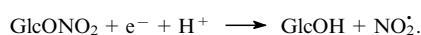


This process depends on the concentration of double bonds in the macromolecule and on the mobility of groups containing these bonds, *i.e.* on various steric factors. The probability of cross-linking of macromolecules increases with an increase in concentration of double bonds in the starting ether and with an increase in the length of the substituent, which is characteristic of AOEC where the reactive double bond is located at the end of a grafted chain of ethylene oxide units. Therefore, AOEC forms a three-dimensional insoluble structure at a lower content of allyl groups than APMC.

The ESR spectra of γ -irradiated HEC and AOEC exhibit mainly superpositions of the spectra of cellulose-type radicals. The predominant signal in the spectra of Na-CMC, APMC, and MPMC is a triplet with 2.1 mT splitting, which overlaps with additional signals of cellulose radicals. The presence of a triplet signal indicates most likely that the radicals are localised on the carboxymethyl group, which protects cellulose from degradation.

Thus, the introduction of allyl groups in HEC and CMC affects substantially the chemical transformations that occur, on the one hand, and does not affect the nature of the radicals formed, on the other hand. This apparent contradiction may be explained by that the formation of radicals due to the addition of hydrogen atoms or other radicals to the allyl group is the reason for the chain cross-linking of polymers. However, the concentration of allyl radicals is either much lower than that of radicals formed in hydroxyethyl and carboxymethyl derivatives of cellulose (and allyl radicals are therefore not detected by ESR), or these radicals are transformed into more stable ones, which are observed in the ESR spectra.

In the case of cellulose nitrate, a decrease in molecular non-uniformity upon γ -irradiation is observed.^{176, 178} At a dose of 20 kGy, the polydispersity index (M_w/M_n) is 2.8 (*cf.* 8.3 for the original sample).¹⁷⁷ The polydispersity index approaches the value of 2, which corresponds to the most probable MMD, at high degrees of degradation. The calculated radiation-chemical degradation yield is 2.5, which is close to 1.8 found in another study.¹⁷¹ The decrease in molecular mass with simultaneous narrowing of the MMD of cellulose nitrate leads to the conclusion that no efficient cross-linking of macromolecules under γ -radiolysis occurs. An interesting feature of the radiolysis of cellulose nitrate is that a signal of the $\text{NO}_2^\bullet$ radical predominates in the ESR spectrum obtained after radiolysis at 77 K. It can be concluded on this basis that mobile electrons formed in the initial ionisation step are mostly trapped by electrophilic nitro groups in the reaction



Annealing of cellulose nitrate results in the appearance in the ESR spectrum of a triplet anisotropic signal stable up to 370 K when the $\text{NO}_2^\bullet$ radicals disappear completely. This signal was assigned¹⁷¹ to the terminal radical at C(1) of the pyranose ring. It was assumed that the unpaired electron interacted with one α - and one β -proton. The formation of a macroradical was explained by the polymeric chain scission. However, as was shown later,¹⁸⁴ this radical is formed due to the thermal degradation of cellulose nitrate even without preliminary irradiation due to $\text{RNO}_2^\bullet$ or $\text{RNO}_2\text{H}^\bullet$ radicals. These radicals are formed in the reaction



The role of oxygen in the radiation-induced degradation of cellulose nitrate macromolecules was found to be insignificant. It is manifested in a post-effect, which is observed as a reaction of macroradicals with an oxygen molecule to give peroxide radicals.

Cellulose acetate also undergoes degradation under γ -irradiation.^{172–174, 180, 183} The yield for diacetate¹⁷¹ was found to be unexpectedly low (0.8), which indicates the high protective effect of the acetyl groups against the polymeric chain scission. Benzyl groups also possess high protective ability.

Unfortunately, there are only scant data on the radiation-induced degradation of the ethers of other polysaccharides. Only studies on the radiation-chemical transformations of allylchitosan can be mentioned.^{181, 185} As in the case of analogous cellulose derivatives, the tendency of allylchitosan to cross-linking increases with an increase in the degree of substitution. However, this is also accompanied by polymeric chain degradation, which is evident from the increase in the content of carboxy groups as the absorbed dose increases.

Thus, cellulose ethers and esters, like cellulose itself, undergo degradation. However, this process is less distinct due to the protective action of substituents, which can serve as centres for localisation of the excitation energy or primary radical-ion radiolysis products.

XII. Conclusion

Analysis of data on radiation-chemical transformations of cellulose and some other polysaccharides shows a similarity of the mechanisms of the formation of the final radiolysis products. Radiation-induced degradation is the process which determines changes in the physicochemical properties of these compounds. By itself, this is not a new fact, which was already known in the 1950s. The achievements of recent years include accurate quantitative estimation of degradation yields, the finding that this mechanism is common for many other polysaccharides, and the elucidation of the nature of the primary radicals and of the mechanism of polymeric chain scission and formation of the main final products. Both in cellulose and in other polysaccharides, ionising radiation causes preferential abstraction of hydrogen atoms from the C(1) and C(4) atoms of the pyranose ring, rupture of the latter, and scission of the polymeric chain to produce a carbon dioxide molecule and a carbonyl compound.

This mechanism implies approximately equal yields of the main products ($G_d \approx G_{\text{CO}_2} \approx G_{\text{RCHO}}$), which is obeyed well for almost all linear polysaccharides. The unusual degradation mechanism involving pyranose ring opening is due to the fact that cellulose and other polysaccharides are polymers with chains rigidly fixed by a system of hydrogen bonds. Under these conditions, abstraction of hydrogen atoms from the C(1) and C(4) atoms leads to the formation of metastable radical states in which the stable conformation with sp^2 -hybridisation can be formed only through cleavage of a glycosidic bond and rupture of the adjacent pyranose ring. Thus, radiation-induced cleavage of one C—H bond initiates subsequent explosion of a pyranose ring and a cascade of splittings of other chemical bonds. This unusual degradation mechanism is probably characteristic of not only polysaccharides but also other polymers and compounds with

rigidly fixed conformations in which the formation of metastable radicals is initiated by some factor.

The degradation yields for cellulose, xylan, and starch are in the range from 5 to 7 bonds per 100 eV of absorbed energy of the ionising radiation. Taking the possible errors into account, it may be believed that the degradation yields for these polysaccharides are approximately equal. Starch, like cellulose, consists of D-glucose residues. However, they are linked by 1,4- α -glycosidic bonds in starch and by 1,4- β -glycosidic bonds in cellulose. This does not affect noticeably the efficiency of the radiation-induced degradation. On going to chitin, which, unlike cellulose, contains the CH₃CONH group at position C(2) instead of the OH group, the degradation yield decreases 4–5-fold, and deacetylation rather than degradation becomes the dominating process. The same effect is observed on replacing the OH group with an NH₂ group in the case of chitosan. However, this conclusion is not indisputable. It cannot be ruled out that the enhanced radiation stability of chitosan is also due to the presence of residual acetyl groups. The problem is that it is practically impossible to deacetylate chitin completely to prepare chitosan. The degree of deacetylation in chitosan used by Ershov *et al.*¹³⁵ for the study of its radiation-induced degradation was 85%. Probably, the presence of chitin admixture in chitosan increases the radiation resistance of the latter. The degradation efficiency of cellulose and chitosan ethers decreases the more strongly the higher the degree of substitution. In the case of unsaturated mixed ethers-esters, two competing processes occur, namely, cross-linking at unsaturated bonds and degradation; their ratio depends on the number of unsaturated groups in the ether and on their structure.

One has to admit that the mechanism of radiation-chemical transformations of cellulose and other polysaccharides has not yet been studied sufficiently. This is hindered by difficulties in chemical determination of the composition of the products (compounds with carbonyl and carboxy groups, sugar isomers, *etc.*) localised in the polymeric chain. Probably, studies of the transformations occurring in them may involve the data obtained in studies of the radiation-chemical transformations of simple saccharides that are the fragments of complex polysaccharides.

Radiolysis of monosaccharides has been studied much more thoroughly.¹⁵⁹ In particular, a number of interesting regularities found for these compounds, which can also hold for polysaccharides, deserve steady attention. For example, it has been shown that irradiation of frozen aqueous solutions of monosaccharides results in their epimerisation the nature of which is determined by the structure of the original saccharide. The formation of isomeric saccharides is attributed to reactions of electrons with radicals localised in the matrix. Undoubtedly, this process can also play an important role in the irradiation of polysaccharides in which the mobility of carbohydrate radicals is limited and they themselves act as acceptors of the electrons formed upon irradiation. It was also found that simple aminosaccharides have low stability against radiation.¹⁵⁹ For example, the radiation-chemical yield of decomposition of glucosamine (a fragment of chitosan) is certainly an evidence that chain processes occur. Acetylation of the amino group decreases considerably the degradation yield. On the other hand, methyl glycosides of both aminosaccharides, which do not have an open glycosidic centre, have degradation yields typical of usual monosaccharides without amino groups. Therefore, one can agree with the authors of the monograph cited¹⁵⁹ that on going to biopolymers much higher radiation stability of these compounds should be expected in comparison with the monosaccharide constituents. The results of studies of radiation-chemical transformations of chitin, chitosan, and heparin discussed in the present review confirm this important conclusion.

The ability of ionising radiation to cause cellulose degradation is extensively used for the development of original techniques for the isolation of cellulose from raw plant materials and for its preliminary treatment for subsequent manufacture of various products. It was shown^{186–190} that irradiation of wood chips in air to relatively small doses absorbed (5–20 kGy) increases their

stability in storage and increases the yield of cellulose in the sulfite pulping of wood. It is promising to use irradiation for the preparation of powdered cellulose and fillers from cotton linter.^{191,192} The possibility of producing microcrystalline cellulose by irradiating usual cellulose is being considered.¹⁹³

Radiation pretreatment of high-molecular-weight, highly viscous sulfite cellulose with very low reactivity to an absorbed dose of 5–10 kGy changes its physicochemical properties and enhances the reactivity to such an extent that it becomes possible to use this cellulose in the production of viscose fibres.¹⁹⁴ Irradiation makes it possible to decrease the amount of CS₂ required for xanthation from 30%–40% to 10%–15% and to elaborate a process for molding films from cellulose hydrate.¹⁹⁵ It was found that irradiation affects strongly the rate of cellulose nitration and the degree of substitution.^{36,196,197} The content of bound nitrogen increases from 12.9% to 13.5% as the absorbed dose increases from 0 to 40 kGy. Nitration of pre-irradiated cotton cellulose (10–40 kGy) results in esters with practically uniform MMD. This improves considerably their physicochemical parameters. Optimum conditions for the radiation pretreatment of cellulose from various sources using modern electron accelerators were developed for the manufacture of nitrates.

Irradiation of plant raw materials decreases the content of difficultly hydrolysable polysaccharides and increases the content of readily hydrolysable ones.^{90–100} The enhancement of hydrolysability occurs due to the radiation-induced degradation of polysaccharides. The rate constants for polysaccharide hydrolysis increase markedly with the dose. The adoption of radiation technology can simplify the existing manufacture of valuable technical compounds (ethanol, furfural, xylitol, and others) from plant raw materials. Radiation pre-treatment of cellulose-containing wood materials and agricultural waste (straw) facilitates their subsequent high-temperature acid or enzymic hydrolysis to give glucose.^{198–205}

A promising field of the use of radiation technology is the production of high-quality food additives from waste of plant origin (primarily, the waste of agricultural production, *i.e.* straw, corn cobs, *etc.*).²⁰⁶ It was found^{206–209} that an increase in the absorbed dose in these plant materials decreases the content of indigestible cellulose and increases the fraction of polysaccharides assimilable by ruminant animals. As a result of such a treatment, a plant material acquires the properties of a high-quality food additive (foraging sugar). Unfortunately, the radiation treatment is still rather expensive.^{210,211}

The radiation technology for the production of composite materials from polymers and wood or compressed waste of cellulose industry (see, *e.g.*, Refs 212 and 213), which is rather widespread, remains of current interest. The method involves impregnation of these materials with a monomer or oligomers (most commonly, methyl methacrylate is used) followed by ionising radiation-induced polymerisation. The resulting materials are used for the manufacture of high-quality parquet and other items.

The value of plant biomass, whose main components include cellulose and other polysaccharides, as a reproducible source of bound carbon for the industrial production of valuable technical, forage and food products will increase with time. It can also be believed that the role of radiation methods for the processing of plant biomass aimed at extraction of cellulose and other polysaccharides from it and for imparting to them the required properties will also increase.

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

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

Biomimetic alkane oxidation involving metal complexes

E I Karasevich, V S Kulikova, A E Shilov, A A Shteinman

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Abstract. The state-of-the-art of investigations in the field of catalysis of biological oxidation of saturated hydrocarbons by molecular oxygen and simulation of this process based on metal complexes is reviewed. The bibliography includes 296 references.

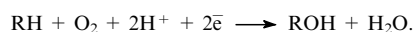
I. Introduction

Functionalisation of alkanes is of both theoretical and practical interest. Progress in homogeneous catalysis brought forth the problem of activation of C–H bonds as long as several decades ago. However, despite the considerable achievements in this area¹ practical requirements have stimulated the search for novel reactions and elaboration on their basis of more efficient procedures for alkane conversions. Currently, this is particularly urgent when the scantiness of natural resources of this valuable chemical raw material has become obvious. Petroleum and natural gas, the main sources of alkanes, are now mostly used as a fuel. Of nearly a billion tons of the petroleum extracted in the world, only 5% is chemically processed and direct functionalisation of alkanes is as low as fractions of a per cent. The inertness of alkanes is the main obstacle to the development of methods for their functionalisation; reactions with these compounds occur under drastic conditions and with low selectivity.

The main pathway of alkane functionalisation is their oxidation. In the living nature, this problem has been successfully solved in two ways: through aerobic oxidation, which involves molecular oxygen, and an anaerobic one. The corresponding natural enzymic systems still remain unsurpassed as regards the rate and the selectivity of alkane oxidation. Therefore, the biomimetic approach, *i.e.*, creation of chemical analogues of enzymes, seems to be especially promising in this respect. The current views about the aerobic biological oxidation of alkanes involving monooxygenases and its chemical simulation are discussed in this review.

II. Monooxygenases

The term ‘monooxygenases’ is generally applied to the enzymes that catalyse the oxidation of a substrate by molecular oxygen in the presence of a reducing agent according to the stoichiometric equation:



Thus, one atom of the oxygen molecule is incorporated into the substrate, whereas the other one forms water. Many monooxygenases contain metals as constituents, in the first place, iron and copper. Two equivalents of a reducing agent, which is needed for the monooxygenase cycle to be accomplished, come from an organic component that must be always present in the system. The role of this compound is to transfer electrons to the metal atom of the enzyme, which passes into the reduced state and thereby acquires the ability to react with molecular oxygen and activate it for further interactions with alkanes.

Hence, according to the current concepts,² activation of molecular oxygen resulting in the formation of metal peroxo- and oxo-complexes is the basic mechanism of the catalytic effect of monooxygenases. The chemistry of these complexes and their reactions with alkanes have attracted keen attention of investigators in the past decade.

1. Heme monooxygenases

a. Cytochrome P-450

Among monooxygenases, the suprafamily of cytochrome P-450 has been known for the longest time.^{3–5} Its active centre, like hemoglobin or myoglobin, contains heme, an iron-protoporphyrin complex. These enzymic systems can oxidise hundreds of thousands of low-molecular-weight compounds of both endogenous and exogenous origin.^{6–8} Cytochrome P-450 catalyses hydroxylation of alkanes, epoxidation of alkenes, *O*- and *N*-dealkylation, and other oxidation reactions. About 500 representatives of the cytochrome P-450 suprafamily are currently known.^{7,9} They differ from one another in the structure of their globular protein in the region of the active centre, but have identical prosthetic groups.

Cytochrome P-450 is the component of a multienzyme system, which also contains electron transfer enzymes. In mitochondria and most bacteria, electrons are transferred from NADH and NADPH to the enzyme by FAD-dependent reductase *via* iron–sulfur ferredoxin. In systems of the microsomal endoplasmic reticulum devoid of Fe₂S₂-ferredoxin, the electrons are transferred

E I Karasevich N M Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117977 Moscow, Russian Federation. Fax (7-095) 137 41 01. Tel. (7-095) 939 72 43

V S Kulikova, A E Shilov, A A Shteinman Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-096) 515 35 88. Tel. (7-095) 542 50 35 (V S Kulikova), (7-095) 524 50 35 (A E Shilov)

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from NADPH by cytochrome P-450 oxidoreductase, a flavoprotein that contains FAD and FMN.

The catalytic cycle of cytochrome P-450 varies depending on the electron source and the type of substrate being metabolised; however, its main stages are common for the whole cytochrome P-450 suprafamily (Fig. 1). The further the stage from the original state Fe^{III} in the catalytic cycle the less studied the structure of the intermediates and the mechanism of their formation. The reason is that the time of conversion of the corresponding intermediate may be too small for the latter to be registered by the modern technique.

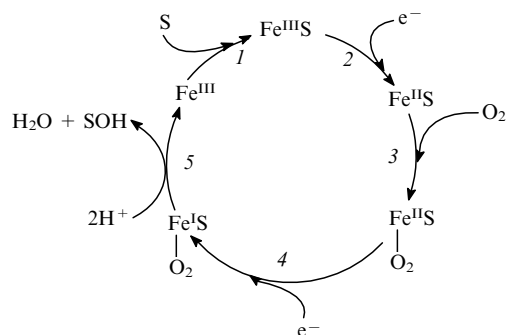


Figure 1. The catalytic cycle of cytochrome P-450.

The kinetics of individual stages of the catalytic cycle has been studied for both bacterial¹⁰ and microsomal⁷ cytochrome P-450. The system of camphor monooxygenation from *Pseudomonas putida*, cytochrome P-450_{cam} (CYP101),¹¹ is being studied in more detail in comparison with microsomal cytochrome P-450 membrane-bound proteins the analysis of which in the isolated state faces certain difficulties. Interaction with the phospholipid bilayer can influence the generation of a catalytically active conformation of membrane-bound enzymes. However, kinetic regularities of these systems have much in common¹² (Table 1), which makes it possible to propose a unified mechanism for oxygen activation in liver and bacterial cytochrome P-450.

Table 1. The rate constants for various stages of the catalytic cycle of cytochrome P-450 in bacterial and microsomal systems.^{7, 12}

Stage ^a	Cytochrome P-450 _{cam} ^b		Microsomal cytochrome P-450 ^c
	<i>T</i> /°C	<i>k</i>	<i>k</i>
1	4	47 s ⁻¹	50 s ⁻¹
2	25	30–33 s ⁻¹	18 min ⁻¹ 11.5 min ⁻¹ (see ^d)
3	20	1.7 × 10 ⁶ M ⁻¹ s ⁻¹	> 10 ⁶ M ⁻¹ s ⁻¹ (see ^e)
4		1–4 s ⁻¹	2–7 s ⁻¹

^a See Fig. 1; ^b turnover number is 1900 min⁻¹; ^c turnover number is 24 min⁻¹ (benzphetamine, cytochrome P-450_{LM2}); ^d without substrate; ^e 25 °C.

Numerous spectral studies^{7, 12, 13} have established, with a sufficient degree of reliability, the nature of the intermediate complexes formed in the catalytic cycle of cytochrome P-450, starting from the original Fe^{III} to the $\text{Fe}^{\text{II}}\text{O}_2$ -complex. An equilibrium between the low-spin and the high-spin states of Fe^{III} in the original enzyme is shifted towards the former owing to the presence of a water molecule in a *trans*-position relative to the thiolate.¹⁴ Hydrophobic binding of a substrate results in the dissociation of the ligand from the 6th position and a shift of the equilibrium towards the high-spin state ($S = 5/2$). This is accom-

panied by a simultaneous increase in the redox potential of the iron complex, which facilitates electron transfer from the reductase to yield a high-spin Fe^{II} -heme ($S = 2$). Interaction of the latter with O_2 gives an oxygen complex similar to that of hemoglobin. At lower temperatures, this complex is relatively stable and can be identified by spectral methods for various isoforms of cytochrome P-450.^{15, 16}

Transfer of the second electron to oxycytochrome P-450 results in the formation of $\text{Fe}^{2+}\text{O}_2^{2-}$ or $\text{Fe}^{3+}\text{O}_2^{2-}$ species. In the absence of the substrate,¹² decomposition of these species yields a superoxide, the rate constant being 29 min⁻¹. Binding of a substrate with the enzyme inhibits this process; the rate constant for the formation of oxidation products is about 30 min⁻¹ and it changes slightly depending on the nature of the substrate and the enzyme.

The intermediate stages following the oxycytochrome reduction occur too fast for the intermediates to be detected by spectral methods. The mechanism of transformation of the substrate–reduced oxycytochrome complex is the least understood in the catalytic cycle of cytochrome P-450. It is usually assumed⁷ that the known oxidation products are formed through heterolytic or homolytic cleavage of the O–O bond in the iron peroxo-complex. Different versions of this mechanism agree only with certain parts of the experimental data available. Presumably, the operation of a particular mechanism depends on the nature of the substrate and the enzyme.

Most of investigators postulate the pentavalent iron oxene complex ($\text{P-450-Fe}^{\text{V}}=\text{O}$) as the direct oxidant of a substrate by analogy with the reactive intermediates of the catalytic cycle of peroxidase, which have the oxoferryl group ($\text{Fe}^{\text{IV}}=\text{O}$) in their active centre. However, the Mössbauer and Raman spectra of cytochrome P-450 recorded under catalytic conditions¹² suggest the presence of iron-superoxide structures similar to oxyhemoglobin HbO_2 , but different from the ferryl species of peroxidase. Probably, the superoxide complexes are formed as intermediate products in the activation of oxygen on cytochrome P-450. Unfortunately, the iron oxene species postulated for the catalytic cycle of cytochrome P-450 have not been identified yet by any of the existing physical methods. At the same time, the oxene species in peroxidase systems are relatively stable, well-characterised intermediates.^{17–19} The formation of reactive species in the conversion of hydrogen peroxide by peroxidase occurs under conditions of acid-alkaline catalysis in the imidazole fragment of histidine localised in the distal region of the enzyme heme.^{18, 20} In contrast to peroxidase, thiolate is the proximal ligand of the cytochrome P-450 heme.^{14, 21, 22} Presumably, the effect of the thiolate ligand and the presence of a substrate in close proximity to the reactive oxygen of cytochrome P-450 decrease the lifetime of the active species and prevent their registration.

Not only the lack of direct proofs of the existence of iron–oxene complexes of cytochrome P-450, but some other data raise doubt about the nature of the reactive species in the catalytic cycle of this enzyme. According to calculations, the $\text{P-450-Fe}=\text{O}$ complexes must be electrophilic.⁷ In practice, the reactions catalysed by this enzymic system suggest either the electrophilic or the nucleophilic character of the reactive species. The role of the nucleophile in the catalytic cycle of cytochrome P-450 can be played by iron peroxide, whereas iron oxene and iron hydroperoxide (or hydroxide) are the possible candidates for the electrophilic reactive intermediates. Electron density calculations demonstrate that the oxygen atom that is directly bound to the heme in peroxo-ferryl complexes with thiolate ligands, bears a partial positive charge, whereas the external oxygen atom bears a partial negative charge. It may thus be assumed that peroxo-complexes function as monooxygenating species. The catalytic activity of ferrocycytochrome P-450_{cam} with superoxide anion is additional evidence in favour of this hypothesis.^{7, 23} The peroxo intermediate is regarded as a direct oxidant in the oxidation of lauric acid²⁴ and in the oxidative deformylation of aldehydes by aromatase,^{25, 26} it is involved in reactions catalysed by NO-syn-

thase²⁷ and heme-oxygenase.²⁸ However, the formation of epoxides and *N*-oxides in these reactions is inconsistent with reactive peroxide or superoxide intermediates and attests to the involvement of oxene species.

Cytochrome P-450 catalyses substrate oxidation in the absence of molecular oxygen with iodosobenzene, peroxides, peroxy acids, and other oxygen donors as oxidants.⁷ In these so-called by-pass systems, cytochrome P-450 transfers the oxygen that is already activated from the oxidant to the substrate. In other words, it functions either as an oxene transferase or it oxidises substrates by detaching electrons as does peroxidase. A by-pass system with iodosobenzene is considered to be the best, because the composition of its monooxygenation products is the closest to that in the complete enzyme system. It should be noted, however, that the identity of the oxidation products does not always imply the identity of the reactive species in these systems.

There is evidence⁷ that the structure of reactive intermediates generated in the interaction of PhIO with cytochrome P-450 is closer to that of peroxo-species (Fe—O—O) than to that of the iron oxene (Fe=O). The oxygen atom of iodosobenzene in these intermediates is analogous to the external oxygen atom of iron peroxide. Moreover, the use of radiolabelled water has shown that the products of oxidation in this by-pass system contain an oxygen atom from the solvent. Therefore, some investigators suggest that iron peroxide or iron hydroperoxide are the most probable reactive intermediates of the by-pass systems.

Adrenal cortex cytochromes P-450 involved in the biosynthesis of steroid hormones are highly regioselective, apparently due to the rigid fixation of the substrate in a hydrophobic pocket near the active centre. Bacterial cytochrome P-450 involved in the hydroxylation of lauric acid catalyses alkane oxidation exclusively at the methyl group,^{29,30} thereby manifesting an ω -hydroxylase activity. This points definitely to very strong steric hindrances during the approximation of the alkane molecule to the active centre. However, in the case of liver cytochromes P-450 involved in detoxication of xenobiotics and capable of oxidising a wide variety of substrates, the observed regioselectivity is apparently determined mainly by the intrinsic reactivity of the active intermediate.³¹ In the ω -hydroxylation of racemic, (*R*)-, and (*S*)-1,1,1-trideuterio-2-phenylpropane by rat liver microsomes, the stereoselectivity depends on the type of cytochrome P-450 and the structure of the active centre. This suggests that in this case, too, regioselectivity is determined by the structure of the apoprotein rather than by the nature of the reactive intermediate.³² It thus follows that, depending on the apoprotein structure, identical reactive intermediates can have different selectivity in the formation of oxidation products, while different active intermediates can have similar selectivity.

Thus the nature of monooxygenating reactive species in the catalytic cycle of cytochrome P-450 is still open to discussion. In our opinion, oxoferryl complexes in cytochrome P-450-containing monooxygenases are the reactive species that oxidise the C—H bonds of alkanes.

Studies with targeted mutations³³ have shown that polar amino acid residues in the distal part of the cytochrome P-450 heme can be involved in proton transfer to the oxygen of the peroxo-complex, thus enabling the formation of an intermediate that hydroxylates the substrate. This is confirmed by the increase in the amount of peroxide and the decrease in the rate of substrate hydroxylation when the normal course of protonation is inhibited by targeted mutagenesis of threonine.³⁴ Simultaneous mutagenesis of aspartic acid (Asp251) and threonine (Thr252) in cytochrome P-450_{cam} has demonstrated³⁵ a cooperative effect of these amino acid residues that results in the cleavage of the O—O bond. Very probably, this reaction is the key stage of the mechanism of formation of the oxidation products (Fig. 2).

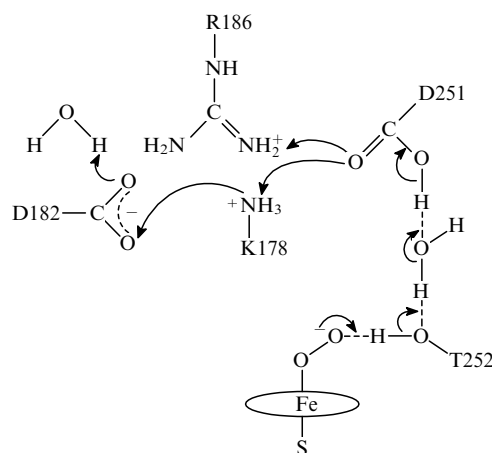


Figure 2. A schematic mechanism of the cleavage of the O—O bond in cytochrome P-450_{cam}.³⁵

b. *N*-Methylamine monooxygenase

It is necessary to mention another heme-containing monooxygenase from *Pseudomonas asinovorans*, which catalyses *N*-demethylation of secondary amines. Like peroxidase and unlike cytochrome P-450, it contains the imidazole moiety of histidine in the 5th axial (proximal) position of the heme; however, similarly to cytochrome P-450, it oxygenates the C—H bonds of methylamines. The intramolecular kinetic isotope effect (KIE) observed³⁶ for the methyl group of 1,1,1',1'-tetradeuterio-dimethylamine ($k_H/k_D = 1.76$) is close to the KIE for the analogous reactions of cytochrome P-450 and chloroperoxidase.

2. Non-heme monooxygenases

It has been established^{37–39} that non-heme iron-containing monooxygenases, such as methane monooxygenase and ω -hydroxylase, analogously to cytochrome P-450, can transfer the oxygen atom from a relatively weak oxidant, *viz.*, molecular oxygen (using two reducing equivalents) or from atomic oxygen donors, such as PhIO, ClO^- , H_2O_2 , RCOOOH , *etc.*, to the C—H bonds of alkanes.

a. ω -Hydroxylases

ω -Hydroxylases, which contain one iron atom in their active centre, are of considerable interest as the representatives of the family of non-heme monooxygenases. They mediate targeted hydroxylation of the methyl group of *n*-alkyl chains of various compounds including alkanes.

The non-heme monooxygenase system of *Pseudomonas oleovorans* comprises three components that are typical of any monooxygenase system: an iron-containing monooxygenase, a reducing agent, and a carrier. In this particular case, these are ω -hydroxylase, flavoprotein reductase, and rubredoxin.⁴⁰ Together with terminal hydroxylation of the methyl group in alkanes and fatty acids, this enzymic system can epoxidise terminal alkenes, convert sulfides into sulfoxides, and demethylate ethers.⁴¹ All these reactions are stereospecific⁴² with high KIE ($k_H/k_D = 6–8$).⁴³ The Fe=O species can serve as an active intermediate in the oxidation reactions catalysed by ω -hydroxylase.⁴⁴ The use of a 'radical clock' method with *trans*-1-methyl-2-phenyl-cyclopropane as the substrate has shown⁴³ that 1-phenyl-but-3-en-1-ol is the only oxidation product. The conclusion on the radical attack at the C—H bond can hardly be considered as unambiguous.

Non-heme ω -hydroxylase from *Pseudomonas aeruginosa*⁴⁵ oxidises *n*-alkanes ($\text{C}_5–\text{C}_{10}$) into the corresponding acids *via* the primary alcohols. The efficiency of oxidation is lower for branched alkanes. The methyl group in 1,4-dimethylcyclohexane

is oxidised only when it occupies the equatorial position, *i.e.*, the enzyme can oxidise compounds with a relatively planar conformation. Smooth oxidation was observed for alkylbenzenes. It was thus concluded that a hydrophobic cavity (5.8 Å) exists in the vicinity of the enzyme active centre. The presence of such a cavity in this particular enzymic system as well as in other monooxygenases may account for the unusual substrate specificity and regioselectivity observed in the oxidation of hydrocarbons.

b. Methane monooxygenase

Methane is the most widespread and the least reactive representative of the family of saturated hydrocarbons. Therefore, its catalytic oxidation under mild conditions is of the greatest interest. The examples of selective low-temperature oxidation of methane are rather scarce.^{37, 38, 46, 47} At the same time, the enzymic systems of various microorganisms, *viz.*, methane monooxygenases (MMO), catalyse efficient conversion of methane into methanol.^{48–51} Unlike heme monooxygenases and non-heme ω -hydroxylases, the iron at the active centre of MMO is a component of a binuclear centre, as in hemerythrin (HR), the protein, which is an oxygen carrier, like hemoglobin,^{52–54} and in ribonucleotide reductase (RR) where the binuclear iron complex performs one-electron oxidation of tyrosine. The latter is further involved in a complex oxidation–reduction cycle.^{55–58}

Several MMO from various bacterial sources, such as *Methylococcus capsulatus*,^{59, 60} *Methylosinus trichosporium*,⁶¹ and *Methylobacterium*⁶² have been studied. Depending on growth conditions, the enzyme can exist both in the membrane-bound and the cytoplasmic (soluble) form.⁶³

Water-soluble MMO from *M. capsulatus* has been studied in the most detail. This enzymic system oxidises the methyl group and the adjacent methylene group of *n*-alkanes [ω - and (ω -1)-hydroxylation]. In branched alkanes, it is the most remote from the branching part of the molecule that undergoes oxidation, which points to substantial steric hindrances in the vicinity of the active centre. Nevertheless, in the case of small molecules, *e.g.*, isobutane or *cis*-1,4-dimethylcyclohexane,⁶⁴ the oxidation affects predominantly the tertiary C–H bonds. These data suggest that the steric demands are determined not by the active centre itself, but rather by the protein environment, which forms a hydrophobic cavity of a definite size.

The MMO consist of three closely interrelated proteins, *viz.*, **A**, the monooxygenase (or hydroxylase) itself, which is a dimer and contains two to four iron atoms; **B**, a regulatory protein, and **C**, a reductase.^{65, 66} Protein **B** strongly affects the redox properties of the hydroxylase component of MMO.^{67, 68} In the case of *M. capsulatus*, the redox potentials of hydroxylase for the transfer of the first and the second electrons are equal to +48 and –135 mV (relative to the NHE) and are slightly shifted towards more negative potentials after the addition of a substrate. In the absence of the substrate, the hydroxylase cannot be reduced even at –200 mV. The transfer of the second electron occurs more easily than that of the first one, which makes it possible to avoid the formation of the unfavourable $\text{Fe}^{\text{III}}\text{Fe}^{\text{II}}$ state of the cluster. Similarly to cytochrome P-450, binding of a substrate facilitates the reduction of iron and initiates the catalytic cycle of MMO. Binding of protein **B** results in changes in the EPR spectrum of the $\text{Fe}^{\text{III}}\text{Fe}^{\text{III}}$ form of hydroxylase and strongly influences the rate and regioselectivity of alkane oxidation. Presumably, when protein **B** binds to hydroxylase, it induces conformational changes in the region of the active centre. This in turn changes the coordination environment of the iron and, as a consequence, the spectroscopic, redox, and catalytic properties.

It was reported^{69–72} that the active centre of MMO contains two iron atoms, which are linked by μ -oxo- μ -carboxylate bridges as in hemerythrin and ribonucleotide reductase.^{38, 54, 57, 58} As for the terminal ligands, some indirect data show that each iron atom in the active centre of MMO is coordinated to one imidazole moiety of histidine.^{73, 74}

An interesting comparison of MMO and RR can be made on the basis of X-ray data. The hydrophobic cavity in MMO is much larger than that in RR. This is consistent with the fact that MMO binds a hydrophobic substrate, *viz.*, methane. The position occupied by tyrosine in RR is occupied by cysteine in MMO. This allowed one to suggest an original hypothesis⁷⁵ about the catalytic mechanism of MMO with the involvement of the SH-group. Apart from cysteine, threonine (Thr213), which is apparently necessary for proton transport in the catalytic cycle, is the only amino acid containing a protonated group vicinal to the hydrophobic cavity; its effect is similar to that of Thr252 in cytochrome P-450.^{34, 35}

Thus, the spectral and X-ray data suggest that the iron in the active centre of MMO is the component of a binuclear μ -hydroxo-complex, which has much in common with the Fe–O–Fe centres of HR and RR for which X-ray data are also available (Fig. 3).⁷⁵

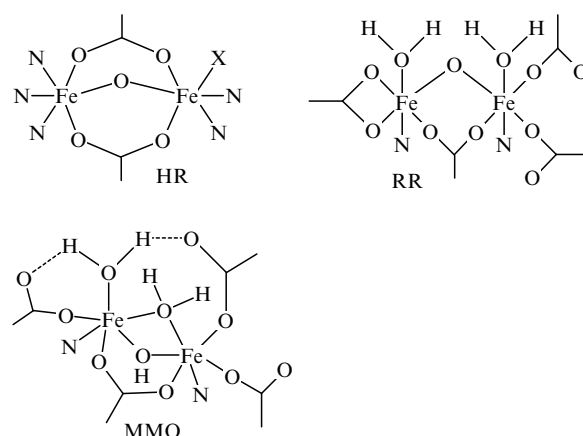
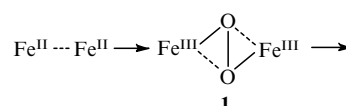


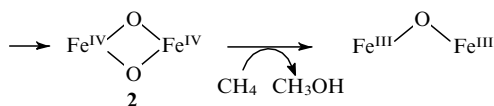
Figure 3. A schematic representation of binuclear active centres of hemerythrin, ribonucleotide reductase, and methane monooxygenase.

The catalytic cycle of MMO is very similar to that of cytochrome P-450. Alkane binding is followed by fast two-electron reduction of the μ -hydroxo- Fe_2^{III} to the μ -hydroxo- Fe_2^{II} state, which can rapidly react with O_2 .⁷⁶ One-electron reduction gives the μ -hydroxo- $\text{Fe}^{\text{III}}\text{Fe}^{\text{II}}$ intermediate, which slowly reacts with oxygen.^{48, 71}

The stepwise formation of three intermediates, *viz.*, **P**, **Q**, and **T**, from μ -hydroxo- Fe_2^{II} , has been established.⁵⁰ The intermediate **P** is formed immediately after mixing of O_2 with MMO subjected to two-electron reduction; it is then slowly converted into the intermediate **Q**. The rate of conversion of the intermediate **Q** depends on the nature and the concentration of the substrate, which suggests that the intermediate **Q** is the key oxidising agent. And finally, the intermediate **T** generated upon reaction of the intermediate **Q** with the substrate dissociates to give the oxygenated product. The dissociation of the intermediate **T** is the rate-limiting step of this reaction. According to Mössbauer spectroscopic data,^{49–51} the structure of the intermediate **Q** can be represented as a diferryl or a bis- μ -oxo-complex.

The binuclear structure of the active centre of MMO, the unusual substrate specificity and selectivity of alkane oxidation as well as the spectral characteristics of the reactive intermediates made it possible^{77–79} to develop new concepts of the catalytic mechanism of MMO:

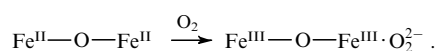




According to these concepts, activation of O_2 occurs with the formation of $\mu\text{-}\eta^2\text{-}\eta^2$ -peroxide **1** as a result of lateral binding of the O_2 molecule. This intermediate is further converted into the bis- μ -oxo- Fe_2^{IV} intermediate **2**, which reacts with methane and is an alternative to ferryl. Unlike ferryl, the O atom in this intermediate occupies the bridging position between two iron atoms and thus ensures its more efficient stabilisation.

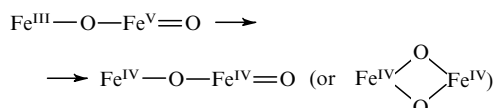
The interaction of the O atom of the intermediate **2** with the C—H bond of methane, which has the smallest length, allows an additional nucleophilic assistance of the second O-bridge, *e.g.*, due to the formation of a hydrogen bond with the H atom of methane. This speculation might rationalise the tunnelling effect of the proton in methane oxidation. Electronic and steric factors that control the interaction of the bis- μ -oxo- Fe_2^{IV} intermediate **2** with the C—H bond may account for the preferential oxidation of methane and lower alkanes and almost complete lack of selectivity in the oxidation of the bonds. Unexpectedly, the KIE for the interaction of the intermediate **Q** with CH_4 and CD_4 appeared to be very high (50–100).^{80, 81}

As has been noted above, mononuclear iron complexes at the active centres of various monooxygenases catalyse efficient oxidation of C—H bonds. The question of why Nature selected the binuclear iron complex as the active centre of MMO may be answered as follows: first, this allows simultaneous transfer of two electrons to the O_2 molecule thereby avoiding a thermodynamically and kinetically unfavourable stage of the formation of the oxygen radical anion en route to peroxide:



Second, both Fe^{III} ions can accept $\text{O}_2^{\cdot -}$ after heterolytic cleavage of the O—O bond without any preliminary protonation, which is extremely unfavourable in the strongly hydrophobic environment near the active centre.

Third, electron transfer from the neighbouring iron atom allows one to circumvent the superoxidised state of iron, which is unstable under the conditions of the non-heme environment.



In other words, the second iron atom plays the same role as the porphyrin ligand in compound **I** of peroxidase or in the active ferryl species of cytochrome P-450.

And finally, magnetic interaction between the iron ions of the complex enables coordination of the electron-orbital effects of both atoms in the attack at the C—H bond.

b. Toluene monooxygenases

Toluene monooxygenases T2MO, T3MO, and T4MO catalyse the formation of *o*-, *m*-, and *p*-cresols; they can also oxidise other hydrocarbons. The active centre of toluene monooxygenase comprises two iron atoms linked together by a hydroxyl bridge; its spectral characteristics are similar to those of MMO. Toluene monooxygenase catalyses the oxidation of substrates by either molecular oxygen in the presence of a reducing agent or hydrogen peroxide.^{82, 83}

Analysis of the data available on heme and non-heme monooxygenases demonstrates that the nature of the reactive intermediate formed in the monooxygenase-catalysed reactions is still controversial. Earlier, it was thought that the active complex of all iron-containing monooxygenases comprises the ferryl fragment —Fe=O with iron in the formal oxidation states IV and V. This concept could not be used to rationalise the experimental results

obtained for the non-heme enzyme, methane monooxygenase. This problem could be surmounted when it was assumed that oxygen can bind with two iron atoms to give $\text{Fe}^{\text{IV}}(\mu\text{-O})_2\text{Fe}^{\text{IV}}$, which can be regarded as a ferryl dimer. As far as heme systems are concerned, some investigators propose iron peroxide (or iron hydroperoxide) as the most probable reactive intermediate. Hence, a detailed structure of reactive intermediates of heme and non-heme monooxygenases has not been elucidated in full detail.

Another question of fundamental importance is the way whereby oxygen is transferred from the reactive oxidant to the hydrocarbon.

3. The mechanism of alkane monooxygenation

The nature of interactions of mono- and bi-nuclear ferryl intermediates in heme and non-heme monooxygenase systems with the C—H bonds of alkanes is still a widely debated topic.

The electronic structure of atomic oxygen is similar to that of the bivalent carbon compounds (carbenes) and by analogy it is termed oxene. Like carbenes, oxene in the triplet state reacts with alkanes as a free radical and detaches hydrogen. In the singlet state, it can also be inserted into the C—H bond to yield an alcohol.^{84, 85} Studies of the gas-phase reactions of singlet oxene with alkanes resulting in the generation of the OH radical showed⁸⁶ that this reaction can occur by two different routes, which are interpreted as the insertion of the O atom into the C—H bond and the detachment of the H atom. It should be noted that the insertion mechanism predominates if small molecules (CH_4 , C_2H_6) with strong C—H bonds are subject to attack, whereas hydrogen detachment takes place predominantly in the reaction with higher hydrocarbons [C_3H_8 , $\text{C}(\text{CH}_3)_4$] that are either sterically hindered and/or contain weaker C—H bonds. Thus the fraction of the route involving the detachment of H varies from 0.05 for CH_4 to 0.9 for $\text{C}(\text{CH}_3)_4$. It is concluded from these data⁸⁶ that the detachment can result from the intersection of two potential energy surfaces at the beginning of a single route that corresponds to insertion. The lifetime of the complex is 0.35×10^{-12} s for H_2 , 0.8×10^{-12} s for CH_4 , and 4.2×10^{-9} s for $\text{C}(\text{CH}_3)_4$.

The oxygen atom in the active centre of monooxygenase may be bound with the metal complex and its capacity to be inserted into the C—H bond or to detach the H atom is maintained. Such compounds (oxenoids) are related to the oxo-salts of transition metals. These compounds are also thought to be the intermediates possessing the superoxidative properties, *e.g.*, in the transfer of the oxygen atom from N_2O to metal ions.⁸⁷

Two possible mechanisms are usually considered: (a) synchronous insertion of the O atom detached from the metal ion into the C—H bond (the concerted, oxenoid mechanism)^{88–90} and (b) crypto-radical (the so-called oxygen rebound mechanism), which implies detachment of the hydrogen atom from the substrate molecule at the first stage with subsequent recombination of the alkyl radical formed with FeOH at the active centre of the enzyme.

The following data are in favour of the synchronous insertion mechanism. In the monooxygenase reaction, alkanes yield alcohols and retention of the original configuration of the asymmetric carbon atom where the oxidation involves the C—H bond is a characteristic feature in many cases.^{91, 92} It may therefore be assumed that this reaction proceeds without the intermediate formation of free radicals, which might lead to racemisation. Alkenes yield epoxides,⁹³ which retain the configuration of the original alkene.⁹⁴ Benzene and other aromatic hydrocarbons are converted into phenols and dihydrodiols.⁹⁵ Both types of compounds are formed *via* arene-1,2-oxides.⁹⁶ Migration of a group bound to the aromatic ring, which is characteristic of enzymic oxidation, from the position subject to hydroxylation to the neighbouring position (the NIH shift) is consistent with this conclusion.^{97, 98} Quantum-chemical grounds for the oxenoid mechanism have been published.⁹⁹

However, the oxygen rebound mechanism for heme and non-heme monooxygenases has recently received the most ample

recognition. This mechanism is usually supported by the following facts.

1. The large primary kinetic isotope effect in the cytochrome P-450-catalysed hydroxylation is attributed to the linear structure of the transition state ($\text{Fe}-\text{O}\cdots\text{H}-\text{R}$). It is assumed that the insertion of the O atom into the C—H bond must be characterised by a small isotope effect.¹⁰⁰

2. In some cases, partial or complete skeletal isomerisation of the original compound occurs en route to the reaction products. Presumably, this takes place in the intermediate alkyl radical.

3. The effect of radical traps. In the case of methane oxidation by methane monooxygenase, the use of radical traps allowed identification of the methyl radical.¹⁰¹

Evidence for a stepwise mechanism, which involves initial detachment of the hydrogen atom by a reactive oxidising species,^{102,103} follows from the high KIE (10–12) observed in hydroxylation by cytochrome P-450-containing monooxygenases^{104–107} and soluble MMO from *M. trichosporium*¹⁰⁸ as well as from the incomplete retention of the original configuration of the asymmetric carbon atom.

There are other facts in favour of the oxygen rebound mechanism. Thus allylic oxidation in a system with cytochrome P-450 resulted in the formation of isomeric allylic alcohols, which can be accounted for by the generation of the intermediate radical, $[\text{C}=\text{C}-\text{CH}^* \longleftrightarrow \text{C}^*-\text{C}=\text{CH}]$.¹⁰⁹ The rate constant for the recombination of the methylcyclopropyl and OH radicals was determined, $k_{\text{ox}} \approx 2 \times 10^{10} \text{ s}^{-1}$.¹¹⁰

Apparently, the ‘radical clock’ method¹¹⁰ not only confirms the intermediate formation of a radical, but also permits the quantitation of its kinetic behaviour. However, further applications of this method have shown that the increase in the isomerisation rate constant (due to the incorporation of the corresponding substituent into the cyclopropane ring) does not result in a parallel increase in the yield of the isomerised product. The ‘radical clock’ method yielded different k_{ox} values for different molecules [from $1.4 \times 10^{10} \text{ s}^{-1}$ to $(2-7) \times 10^{12} \text{ s}^{-1}$]^{111–113} with no obvious relation to the structure.^{111–113} Moreover, the use of a supersensitive probe¹¹⁴ gives an extremely high k_{ox} value of $1.4 \times 10^{13} \text{ s}^{-1}$ (based on the yield of the isomerisation product). The lifetime of a radical with such a great value of the recombination rate constant, which also includes diffusion, must correspond to the period of one vibration.

In the case of MMO from *M. capsulatus*,¹¹⁵ the rate constant for the recombination of the active oxo-species with a radical intermediate also exceeds 10^{13} s^{-1} . In this case, the reaction occurred with 100% retention of configuration,¹¹⁶ which obviously excludes the generation of an alkyl radical. The application of analogous tests to *M. trichosporium* has shown the formation of a small amount of rearranged products, which might attest to the presence of a radical intermediate. It was concluded from these data that the mechanism of this reaction can be different for different forms of MMO.

There are other data which are in conflict with the oxygen rebound mechanism. It was found¹¹⁷ that hydroxylation of the stereoisomers of deuterium-substituted camphor by cytochrome P-450_{cam} is accompanied by partial isomerisation and transfer of deuterium atoms from the *exo*- to the *endo*-position and *vice versa*. This phenomenon is considered as a proof of the radical mechanism. However, the camphor molecule at the active centre of the enzyme is fixed by a hydrogen bond and thus cannot rotate, which follows from the selectivity of this reaction: only 5-*exo*-hydroxycamphor is formed. This means that isomerisation owing to the rotation of the molecule is impossible. It was suggested¹¹⁷ that a certain radical exists, which can migrate freely and attack the camphor molecule at both the *exo*- and the *endo*-positions of the ring. It must be noted that the presence of this radical in the enzymic reaction is hardly probable.

Thus, neither of the two mechanisms mentioned above can explain the body of the experimental data for heme and non-heme monooxygenases altogether. Therefore, the hypothesis of the

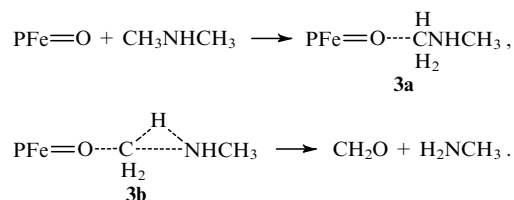
mechanism of synchronous insertion of the oxygen atom into the C—H bond has been recently supplemented with one important detail, namely: the insertion of oxygen is preceded by the formation of an intermediate complex of the active oxygen with the hydrocarbon molecule. Thus, the oxygen atom plays the crucial role in the complex formation, whereas the metal acts as a ligand at the oxygen atom rather than the centre of complex formation. The complex with active oxygen comprises a strongly distorted substrate structure with pentacoordinated carbon. It is assumed that two hydrogen atoms or one hydrogen and one deuterium atom of this complex can interchange very easily.^{118,119}

If the lifetime of this intermediate is small, *e.g.*, if the O atom is rapidly inserted into the C—H bond, the isomerisation does not take place; if the rate of isomerisation is comparable to that of oxygen insertion, the isomerisation products are formed in appreciable amounts. Thus, the mechanism of this reaction is similar for various enzymes but the ratio of the rate constants for the intermediate isomerisation and the O atom insertion into the C—H bond changes, which results in different selectivities of this reaction. Within the framework of the pentacoordinated carbon mechanism, the unusual stereoselectivity of the hydroxylation of the isotopically substituted camphor in a system with cytochrome P-450_{cam} has received natural interpretation without any recourse to improbable speculations.¹²⁰

The existence of an intermediate with pentacoordinated carbon has also been postulated in Ref. 116. If this hypothesis is true, the dynamics of hydroxylation of alkanes is qualitatively analogous to the dynamics of hydroxylation of aromatic compounds and epoxidation of alkenes. The same mechanism can also explain the drastic differences in the isotope effects for closely related substrates, such as methane and ethane in the case of MMO. If the hydroxylation occurs in two steps, its rate can be limited by both the first (binding of the O atom to the C—H bond) and the second stage (insertion of the O atom leading to an alcohol) depending on the substrate. Presumably, the maximum isotope effect must be manifested at the second stage. It is believed that it is in the case of methane, the C—H bonds of which are among the strongest, that the rate is determined by the second stage and the isotope effect is a maximum.

A paradoxical situation has been observed earlier for *N*-dealkylation:³⁶ the isotope effect (8–10) was high for peroxidases the mechanism of which involved an electron transfer, but it was small (1–3) for various forms of cytochrome P-450, chloroperoxidase, and *N*-methylaminomonooxygenase, where the activated O atom directly reacts with the C—H bond.

This paradox can also be overcome by assuming a two-step mechanism involving intermediates with pentacoordinated carbon (**3a** and **3b**), for cytochrome P-450 and its analogues:



The first stage results in the formation of the intermediate **3a**, which is further converted into the intermediate **3b**. This is followed by the second stage, *viz.*, splitting of formaldehyde.

If the rate of this reaction is limited by the first stage, the isotope effect will be small.

The formation of an intermediate complex of the metal-bound oxygen atom with the carbon atom of an unsaturated molecule is beyond doubt for epoxidation of alkenes and hydroxylation of aromatic compounds. At the same time, the absence of saturation in the case of alkane hydroxylation apparently rules out the possibility of formation of an analogous intermediate complex. This new hypothesis is attractive in that it unifies the mechanisms

of atomic oxygen transfer to the C–H bonds of saturated compounds as well as to alkene and aromatic C=C bonds.

III. Models of heme monooxygenases

In addition to monooxygenases, the iron porphyrin complex (FeP) is present in the O₂ carriers (hemoglobin, myoglobin) and enzymes (catalase, peroxidase). One of the reasons for such wide occurrence of the porphyrin system in living nature is its stability. In addition, the porphyrin ring can play the role of an electron donor owing to its ability to generate the radical cation and thus to become an active participant of the catalytic process. Therefore, it was natural to employ metal porphyrins (MP) as catalysts in the simulation of heme monooxygenases. The first model system that involved iron porphyrin (hemin) was proposed in 1972 by Belova (Kulikova) *et al.*¹²¹ Over the past 25 years, studies in this area have continued at a fast pace. This illustrates the fruitfulness of a biomimetic approach in both the analysis of fundamental problems of enzymic catalysis and the design of novel catalysts.^{7, 122–124}

1. Models with active oxygen donors

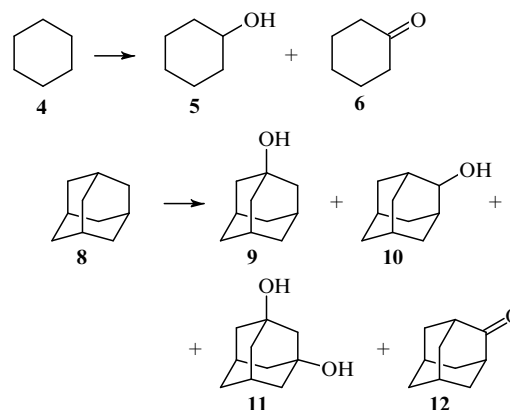
The simulation of enzymic oxidation with the use of metal porphyrin complexes and active oxygen donors, such as iodosobenzene and its fluorinated analogues, sodium hypochlorite, hydrogen peroxide and alkylhydroperoxides, peroxy acids, potassium persulfate, amine *N*-oxides, and nitrous oxide, has turned out to be very successful.

Iodosobenzene as the active oxygen donor was used for the first time in a biological system.¹²⁵ Later, it was employed in a simple system based on iron tetraphenylporphyrinate (FeTPP)¹²⁶ responsible for the oxidation of a series of substrates, including alkanes, with a selectivity which is close to that of the enzymic one. A great number of systems initiating alkane oxidation in organic solvents or water–organic solvent mixtures in the presence of phase-transfer catalysts have been described. The most interesting of them are presented in Table 2.

In these systems, cycloalkanes are oxidised under mild conditions to give the corresponding alcohols and ketones (sometimes, alkyl halides) in yields up to 60% with respect to the oxidant consumed and up to 90% with respect to the substrate. The yield of the products, selectivity, and the rate of oxidation depend on the nature of the metalloporphyrin, the axial ligand, the oxygen source, and the substrate. Depending on the system, oxidation of cyclohexane (**4**) gives variable proportions of cyclohexanol (**5**) and cyclohexanone (**6**); the use of NaOCl as the oxidant also yields chlorocyclohexane (**7**). Oxidation of adamantane (**8**) gives adamantan-1-ol (**9**), adamantan-2-ol (**10**), adamantane-1,3-diol (**11**), and adamantanone (**12**) (Scheme 1). The efficiency of the catalyst

increases substantially upon introduction of substituents into the *ortho*-position of the phenyl rings of tetraphenylporphyrin. The greatest turnover number (14 600) was observed for halogenated ruthenium tetraphenylporphyrinate,¹³⁵ which catalysed alkane oxidation by 2,6-dichloropyridine *N*-oxide (DCPO) at a rate of 800 cycles per min. The virtually complete retention of configuration of the chiral carbon atom and high efficiency open up new opportunities for the application of this system in the stereoselective synthesis of tertiary alcohols.

Scheme 1



Thus, the systems with active oxygen donors are good functional models of heme monooxygenases owing to their ability to oxidise hydrocarbons under mild conditions with the selectivity and at rates which are close to those in enzymic reactions. Another problem of fundamental importance is the nature of the active species that interact with the substrate. As has been mentioned above, a ferryl ($P^{+}Fe^{IV}=O$) or a perferryl ($PFe^{V}=O$) complex has been usually assumed as an active intermediate in heme monooxygenase systems.

In the case of chemical models, the formation of the ($P^{+}Fe^{IV}=O$) intermediates was recorded by low-temperature spectroscopy in polar solvents (CH_2Cl_2 , CH_3CN), *viz.*, for the interaction of iron tetramesitylporphyrinate (FeTMP) with *m*-chloroperbenzoic acid¹⁰³ and for a $PFe^{III}-O_2^{-}-Ac_2O$ system.^{136, 137} The only stable $PMn^{V}=O$ complex known so far contains a macrocyclic tetraamide as the ligand.¹³⁸

The intermediates $TF_5PPRu^{II}CO(DCPO)$ and $TF_5PP^{+}Ru^{II}CO(DCPO)$ were identified in a $Ru^{II}TF_5PPCO$ [ruthenium tetrakis(pentafluorophenyl)porphyrinate]–DCPO system at low temperature.¹³⁵ The compound $TF_5PPRu^{III}(DCPO)_2$ was identified in the fast phase of alkane oxidation at 65 °C.

High-valent oxo-complexes of iron porphyrinates were detected in systems with NaOCl, PhIO, and $KHSO_5$; however,

Table 2. Alkane oxidation according to Scheme 1 in the presence of metalloporphyrins with active oxygen donors.

Substrate	Catalyst	Oxidant	Products (ratio)	Yield (%)	Ref.
Cyclohexane (4)	MnTFPPCl ^a	NaOCl	5 + 6 + 7 (1 : 1.3 : 3.8)	24 ^b	127
	MnTDCPPCl ^c + Im ^d	H ₂ O ₂	5 + 6 (3 : 1)	40 ^b	128
	Ru ^{II} TF ₅ PP(CO)	DCPO ⁱ	5 + 6 (8 : 1)	95 ^g	135
	MnTDCPPCl + 4-Bu ^t Py	KHSO ₅	5 + 6 (8 : 1)	90 ^b	130
	FeTPPCl ^f	PhIO	5 + 6 (10 : 1)	26 ^g	131
	FeTF ₅ PPCl ^h	PhIO	5	67 ^g	133
	FeTPPCl	PhCMe ₂ OOH	5 + 6 (2 : 1)	60 ^b	131
	MnCl ₂ TMPCl ^e	KHSO ₅	9 + 10 + 12 (12 : 5 : 1)	60 ^b	129
Adamantane (8)	FeTTPCl	PhIO	9 + 10 + 12 (39 : 5 : 1)	45 ^g	132
	RuTMP(O) ₂ , HCl	DCPO ⁱ	9 + 11 + 12	94	134
	Ru ^{II} TF ₅ PP(CO)	DCPO ⁱ	9 + 11 (10 : 1)	97 ^g	135

^a TFPP is tetra(*o*-fluorophenyl)porphyrin; ^b calculated with respect to the substrate; ^c TDCPP is tetrakis(2,6-dichlorophenyl)porphyrin; ^d Im is imidazole; ^e TMP is tetramesitylporphyrin; ^f TPP is tetraphenylporphyrin; ^g calculated with respect to the oxidant consumed; ^h TF₅PP is tetrakis(pentafluorophenyl)porphyrin; ⁱ DCPO is 2,6-dichloropyridine *N*-oxide.

their structures differed from that of $P^+Fe^{IV}=O$ in all cases. According to their absorption spectra, these compounds were characterised either as $PFe^{IV}=O$ ^{103, 139–141} or $(PFe^{IV}-O)L$ ^{142–145} although the presence of the ligand L in the coordination sphere of the metal has not been established. Similarly, for manganese porphyrinates–NaOCl systems, the length of the Mn–O bond in the active species determined by the EXAFS method is more consistent with an Mn–O–Cl structure.¹⁴⁵ As the $PMn^{IV}=O$ and $PFe^{IV}=O$ complexes can oxidise alkenes but are inactive towards alkanes,^{146, 147} their monooxygenase function is usually associated with their ability to generate more reactive intermediates (formally, pentavalent metal oxo-complexes) at room temperature. The latter cannot be detected by physicochemical methods because of their extremely short lifetime under these conditions.

Other active oxygen donors are less suitable for the preparation of high-valent oxo-complexes of metalloporphyrins: anhydrous hydrogen peroxide destroys iron complexes even at $-30\text{ }^{\circ}\text{C}$;¹⁴⁸ *tert*-butyl hydroperoxide generates cationic isoporphyrins with the ROO-group linked at one of the *meso*-positions.¹⁴⁹

Systems with H_2O_2 and ROOH can generate several reactive species, such as hydroxyl or alkoxy radicals and metal oxo-complexes. Homolytic cleavage of the O–O bond in hydrogen peroxide or alkyl hydroperoxide coordinated with metalloporphyrin yields $PM^{IV}=O$ and free radicals ($HO^{\bullet}$ or $RO^{\bullet}$). Heterolytic cleavage generates $P^+Fe^{IV}=O$ and water (or the corresponding alcohol).

In systems based on cumyl and *tert*-butyl hydroperoxides with iron or manganese porphyrins, the kinetic characteristics and the selectivity of the reaction are independent of the nature of the metalloporphyrin; hence it was concluded^{131, 150, 151} that free radicals $RO^{\bullet}$ and $ROO^{\bullet}$ are reactive species in this process.

Introduction of imidazole (Im) into a manganese tetrakis(dichlorophenyl)porphyrinate (TDCPPMn)– H_2O_2 system changes the kinetic features and the composition of the oxidation products. The high activity of this system was explained¹⁵² by the fact that imidazole used as a nucleophilic axial ligand favoured heterolysis of the O–O bond with the formation of PMn^{VO} complexes and facilitated this cleavage as an electrophilic acid catalyst. The effect of axial ligands on the catalytic function of metalloporphyrins (up to complete suppression of epoxide formation) has also been observed in biomimetic systems of alkene oxidation by monopersulfate.^{153, 154} Cleavage of the O–O and one of the O–H bonds in hydrogen peroxide coordinated with metalloporphyrin is the rate-determining step in the reaction of metalloporphyrins with H_2O_2 .^{147, 155} Traylor *et al.*¹⁵⁶ have suggested that the O–O bond in a hydroperoxide coordinated with metalloporphyrin (as in the case of protic solvents) is always cleaved heterolytically to yield $PFe^V=O$, which further reacts with alkenes or hydrogen peroxide. The interaction with peroxides (H_2O_2 , ROOH) gives rise to the radical intermediates ($HO^{\bullet}$, $HO_2^{\bullet}$, $RO^{\bullet}$, $RO_2^{\bullet}$). By increasing the electronegativity of iron porphyrinate (by introducing substituents into the porphyrin ring), Traylor *et al.*¹⁵⁶ succeeded in performing the reaction of $PFe^V=O$ preferentially with alkenes and thus increased the epoxide yield up to 60%–100% with respect to H_2O_2 .

2. Models with molecular oxygen

The use of bound oxygen as the oxidant allows one, as a rule, to carry out the reactions with high selectivity and simplifies the analysis of reactive intermediates. However, the use of halogen-containing oxidants leads to the contamination of the reaction products with organohalogen compounds and other impurities. In this context, molecular oxygen is the oxidant of choice both from the ecological and the economic points of view.

It was found that Mn, Fe, and Cr tetramethylporphyrinates with azide as the axial ligand catalyse isobutane autooxidation to give *tert*-butyl alcohol at $80\text{ }^{\circ}\text{C}$ with a selectivity of 88%–92%.^{157–159} The activity of the catalyst increases abruptly

with a substitution of the hydrogen atoms in the porphyrin ring by halogen atoms.^{160, 161} When iron *meso*-tetrakis(penta-fluorophenyl)- β -octabromoporphyrinate ($FeTPPF_{20}-\beta-Br_8$) was used as the catalyst, isobutane oxidation proceeded with a selectivity of 92% at room temperature; the catalyst turnover number exceeded 13 000 over 70 h and the catalytic activity was retained for 74 h. However, such efficiency was observed only for the alkanes with tertiary C–H bonds. The system is far less efficient for secondary C–H bonds and is completely inactive with respect to primary C–H bonds.

High selectivity and the fact that no co-catalysts are needed have raised great interest in these systems. Analysis of the absorption spectra recorded at room temperature has revealed that $Fe^{II}TF_5PPCl$ and a Fe- μ -oxodimer ($FeTF_5PP$)₂O, which can be isolated from the solution, are formed in a $FeTF_5PPCl-O_2-C_6H_6$ –iso- C_4H_{10} system.^{160, 161} Non-halogenated FeTPP produce inactive μ -oxo complexes that do not catalyse oxidation of saturated hydrocarbons. Ellis and Lyons¹⁶¹ have postulated the generation of $PFe^{IV}=O$ as the reactive species in this system. However, further studies have demonstrated that the reaction of hydroperoxides with Fe^{II} yields free radicals, which further initiate the chain process.¹⁶²

3. Models with molecular oxygen and a reducing agent

Simulation of the key reaction of monooxygenase catalysis, *viz.*, the activation of molecular oxygen by a metal complex in the presence of an electron donor (reducing agent), is undoubtedly of theoretical and practical interest.

Superoxo- and peroxo-ferryl complexes synthesised from O_2 and iron porphyrinate (PFe) in the presence of a reducing agent are relatively stable compounds, which are inert with respect to alkanes. It was only the introduction of an additional component (acetic anhydride) into the system that has resulted in the first complete chemical model of cytochrome P-450 on the basis of PFe that was active towards saturated hydrocarbons.¹⁶³ The role of the effector in this system was played by acetic acid that was present in admixture with acetic anhydride purified using conventional procedures.^{164, 165}

Examples of these model systems are given in Table 3. Hydrogen in combination with colloidal platinum, sodium ascorbate, dihydropyridine, zinc (powder or amalgam), and electrolysis were used for reduction and a mineral or a carboxylic acid or water as the proton donor.^{163–168}

Alkane oxidation in the presence of O_2 and an electron (and proton) source occurs at normal temperature and pressure. The selectivity and the rate of the reaction depend on the nature of the metalloporphyrin as well as on the electron and proton donors. The product yield with respect to the reducing agent is usually low. The best yield (37%) was obtained in the oxidation of hydrocarbons having weak C–H bonds (indane and tetralin) with Zn as the reducing agent.¹⁶⁸ In non-enzymic systems, it is difficult to obtain high yields of the reaction products with respect to the reducing agent, since the reactive oxidant formed in this process reacts with the substrate and the reducing agent with equal ease. Model systems based on molecular oxygen and the reducing agent are usually less selective than the systems in which active oxygen donors play the role of the oxidants.

Nevertheless, the obvious advantage of such systems is a high oxidation rate, which sometimes exceeds that of enzymic reactions by more than one order of magnitude.

As in the catalytic cycle of cytochrome P-450, the generation of reactive intermediates in biomimetic systems based on molecular oxygen and the electron donor occurs in several consecutive steps. The first step, which is usually rate-limiting, is the reduction of metalloporphyrin. The reduced metalloporphyrins add oxygen to yield a dioxygen complex with a rate constant of the order $10^7\text{ M}^{-1}\text{ s}^{-1}$ (see Ref. 169). This reaction is reversible but the $TpivPPFe^{II}(O_2)(Im)$ complex could be isolated if sterically hindered iron tetrakis(*o*-pivaloylaminophenyl)porphyrinate

Table 3. Cycloalkane oxidation in systems with O₂ and a reducing agent.

Substrate	Catalyst	System	Solvent	Products (ratio)	Number of catalytic cycles /min ⁻¹	Ref.
Adamantane (8)	MnTPPCL ^a + MeIm ^b	H ₂ /Pt–HCl–(PhCO) ₂ O	MePh–EtOH	9 + 10 + 12 (15:1.7:1)	0.004	166
		Zn dust–AcOH	MeCN–CH ₂ Cl ₂	9 + 10 + 12 (20:2:1)	0.5	168
		Zn dust–AcOH	MeCN–CH ₂ Cl ₂	cyclooctanol + + cyclooctanone (1.8:1)	0.5	168
Cyclohexane (4)	MnTPPCL	sodium ascorbate	C ₆ H ₆	5 + 6 (1:7.5)	0.006	167
	hemin ^c + NaOH	thiosalicic acid	(Me) ₂ CO–H ₂ O	5 + 6 (1.8:1)	0.4	121
	FeTpivPPCL ^d	Zn dust–AcOH	MeCN	5 + 6 (1.7:1)	2	164
	FeTpivPPCL	Zn dust–AcOH–MV ^e	MeCN	5 + 6 (3.3:1)	50	164
	FeTPPCL	Zn dust–AcOH–MV	MeCN	5 + 6 (2:1)	340	164
	FeTPPCL	Zn dust–PhCOOH–MV	MeCN	5 + 6 (1.5:1)	340	164

^a TPP is tetraphenylporphyrin; ^b MeIm is *N*-methylimidazole; ^c hemin is a natural iron-containing protoporphyrin IX; ^d TpivPP is tetrakis(*o*-pi-valoylaminophenyl)porphyrin; ^e MV is methyl viologen.

(FeTpivPP) and *N*-methylimidazole (MeIm) or 1-tritylimidazole (TrIm) were used.^{170,171}

In the presence of a reducing agent, the addition of oxygen to the reduced metalloporphyrin is followed by the reduction of the oxygen complex. The rate constant for the reduction of TpivPPFe^{II}(O₂)(TrIm) by methylviologen (MV) radical cation is equal to $2.2 \pm 0.4 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ (Ref. 172).

Protonation of the oxygen atom of the peroxo group results in the homolytic or heterolytic cleavage of the O–O bond depending on the pH of the medium and the polarity of the solvent (similarly to the systems based on hydrogen peroxide).¹⁷³ However, no direct correlation between solvent polarity and the homolysis or heterolysis of the O–O bond in metalloporphyrin intermediates has been found.

The kinetics and the mechanism of generation of reactive species that interact with alkanes have been extensively studied for metalloporphyrin–O₂–carboxylic acid–Zn systems.^{165,174} The configuration of the chiral carbon atom of *cis*- or *trans*-1,2-dimethylcyclohexane is not retained in the catalysis by iron porphyrins. The competitive oxidation of C₆H₁₂ and C₆D₁₂ in this system has a relatively low KIE (2–3). These data permit one to postulate, with an equal probability, both a radical and a molecular mechanism. Analysis of substrate selectivity in the competitive oxidation of cyclopentane and cyclohexane (the so-called 5/6 parameter) was more informative. The dependence of this parameter on the nature of substituents in the phenyl rings of iron porphyrinate, and its magnitude (0.38–0.50), which is characteristic of an electrophilic attack by a positively charged reagent,¹⁷⁵ suggest that the ferryl (P⁺Fe^{IV}=O) or perferryl (PFe^V=O) complexes are the reactive species.

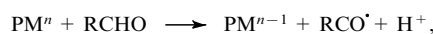
The ratio of the rate constants for the attack at the C–H bond of cyclopentane and cyclohexane (the 5/6 parameter) is being employed more and more often for the study of mechanisms of various reactions of cycloalkanes and alkanes. It is reasoned¹⁷⁵ that this parameter is a measure of the partial charge on the carbon that is attacked in the transition state. The 5/6 ratio is close to unity and does not depend on the reagent charge in reactions where H is detached by a radical or a radical ion. In the case of an electrophilic attack by a positively charged reagent, this parameter is equal to, or less than, 0.5 depending on the reagent charge.¹⁷⁵

In the catalysis by MnTPPCL in an O₂–carboxylic acid–Zn system, the value of the parameter 5/6 (0.7) is close to that observed in the absence of the metalloporphyrin. However, partial retention of configuration (25%) in the oxidation of *cis*- or *trans*-dimethylcyclohexanes shows that the reaction catalysed by MnTPPCL is not, at least partly, a free-radical process. Oxidation of alkenes and the regioselectivity of *n*-heptane oxidation in MnTPPCL–AcOH–Zn–MeIm and PhIO–MnTPPCL–MeIm systems follow the same regularities.¹⁶⁸

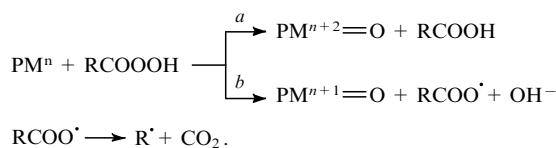
The experimental results altogether lead to a conclusion about a single mechanism of the generation of reactive species in the systems based on iron and manganese porphyrins with molecular oxygen and proton and electron donors. The candidates for the reactive intermediates in these systems are high-valent oxo-complexes of metalloporphyrins formed by reductive activation of molecular oxygen in the presence of a proton donor *via* a catalytic cycle that is similar to that of cytochrome P-450. The reactive species in these systems, as well as in the systems with different active oxygen donors may differ from each other depending on the starting reagents. This follows from the differences in the stereoselectivity and KIE in different systems that generate reactive metalloporphyrin complexes.¹²²

4. Models with molecular oxygen and an aldehyde

It was found¹⁷⁶ that cyclohexane can be efficiently oxidised to give cyclohexanol and cyclohexanone by molecular oxygen in the presence of halogenated metalloporphyrins and propionaldehyde at 30 °C. The relative yields of the oxidation products depends on the nature of the central ion and the porphyrin ligand of the catalyst. The maximum turnover number for the catalyst (**24**) and the maximum yield with respect to the substrate (5%) were obtained for manganese *meso*-tetrakis(2,6-dichlorophenyl)-β-octachloroporphyrinate (MnTDCPP-β-Cl₈). The ketone/alcohol ratio varied from 0.8 for FeTDCPP to 4.3 for MnTDCPP-β-Cl₈ depending on the conditions. After completion of the reaction, an appreciable amount of the surviving catalyst was found only in the case of halogenated manganese porphyrinate. This system involves two oxidants, *viz.*, molecular oxygen and a peroxy acid,^{176–178} which is formed according to the scheme:



The aldehyde acts simultaneously as the reducing agent for the metalloporphyrin and the source of an effective oxidant. The peroxy acid reacts with the metalloporphyrin either to form high-valent oxo-complexes [pathway (a)] or to decompose *via* a radical mechanism [pathway (b)].



Thus, according to this scheme,^{176–178} both high-valent oxo-complexes of metalloporphyrin and free radicals are the reactive species in this system. In addition, a possibility of direct inter-

action of a hydrocarbon with metalloporphyrins having a high oxidation potential (*e.g.*, PCo^{111}) can also be considered:



It is noteworthy that this oxidation mechanism is mostly hypothetical and demands further investigation.

5. Photocatalytic models with O_2

Irradiation of cycloalkanes with light of wavelength ~ 350 – 450 nm initiates their oxidation by molecular oxygen (20°C , 200 Torr O_2) in the presence of iron complexes with halogenated tetraphenylporphyrins. In this system, cycloalkanes are oxidised to the corresponding alcohols and ketones. The turnover number of the catalyst does not exceed 230 due to its destruction.

The selectivity of cyclohexene oxidation is distinguished from enzymic processes: epoxides are not produced, while the corresponding alcohol and ketone are formed in high yields (5000 and 4500 reaction cycles for cyclohexenol and cyclohexenone, respectively). Based on these data, a free-radical oxidation mechanism has been proposed for this system. Presumably, hydroxyl radicals generated in the photoactivation of $\text{PFe}^{\text{III}}-\text{OH}$ and peroxy radicals $\text{ROO}^\bullet$ formed in the reaction of alkyl radicals with oxygen are the reactive species.¹⁷⁹

Thus, in models of heme monooxygenases with various oxidants, alkanes can react under mild conditions due to their interaction with active radicals or high-valent metal complexes. The KIE and the stereoselectivity of all biomimetic systems generating high-valent oxo-complexes of metalloporphyrins vary considerably depending on the nature of the metal and the substituents in the phenyl rings of the metalloporphyrins, the nature of the active oxygen donor, and even the properties of the reaction medium.¹²²

There are two viewpoints as to whether the observed variations reflect differences in the structures of reactive intermediates. Some authors^{141,148} believe that it is the $(\text{P}^+ \cdot \text{M}^{\text{IV}}\text{O})$ complex formed in all these systems (*e.g.*, by disproportionation of two ferryl complexes) that is the species that gets alkanes involved in the oxidation. According to Shteinman¹⁸⁰ and Hill¹⁸¹ the reactive complexes that react with alkanes may vary depending on the structure of the original reagents and the reaction conditions. The differences in the stereoselectivity and the magnitude of KIE in systems with different oxygen donors point to differences in the structures of reactive intermediates. Analysis of the experimental data altogether for various types of systems provides a simple explanation for the effects of different factors (polarity, acidity or basicity, the presence of axial ligands in metalloporphyrins, *etc.*) on the structure of the reactive intermediates and, correspondingly, their reactivity with respect to different substrates.

It should be noted that the reactive complexes, $\text{P}^+ \cdot \text{M}^{\text{IV}}\text{O}$, bear a positive charge. Depending on the medium and the nature of the ion, different species can exist in the solution, such as free ions $(\text{P}^+ \cdot \text{M}^{\text{IV}}\text{O})$ (in polar media) and ion pairs $(\text{P}^+ \cdot \text{M}^{\text{IV}}\text{O})^+ \text{L}^-$ (in less polar and non-polar media). Naturally, their activity towards alkanes will also be different. Nucleophilic and electrophilic properties of the complex and the environment are important for the formation of $(\text{P}^+ \cdot \text{M}^{\text{IV}}\text{O})^+$, which is more reactive than $\text{PM}^{\text{III}}\text{OL}$. Axial ligands, such as imidazole, will play the role of nucleophiles, while acids will favour the heterolytic cleavage of the $\text{O}-\text{L}$ bond.

Thus, the model systems based on metalloporphyrins catalyse the oxidation of hydrocarbons in organic solvents; the parameters of this process (temperature, reaction rate) are in many cases similar to those observed in enzymic reactions. In the absence of the stabilising effect of the protein, metalloporphyrins undergo decomposition under the oxidation conditions, which results in the loss of the catalytic activity during the reaction. Analysis of the experimental data accumulated to date demonstrates that halogenation of the porphyrin macrocycles increases the stability and the catalytic activity of metalloporphyrin complexes. Halogenated metalloporphyrins containing halogen atoms both in the

phenyl and the pyrrole rings are superior in this respect. Halogenation enhances the oxidation potential both of the metal centre and of the porphyrin ligand. This, in turn, increases the stability of the complex under the oxidation conditions and the electrophilicity of the metal centre, and, correspondingly, the catalytic activity of the metalloporphyrin complex.

One of the ways of increasing the selectivity of biomimetic systems is the use of porphyrin ligands with bulky groups that create steric hindrances around the active centre. The molecular design of porphyrins is becoming more perfect in this aspect. Recently, a method for the synthesis of a new family of functional models of hemes (the so-called *double picket fence*) with chiral surfaces on both sides of the plane of the porphyrin rings has been proposed.¹⁸² The use of spatially organised porphyrin complexes strongly increases the proportion of primary alcohols and aldehydes in the products of oxidation of linear alkanes, thus simulating ω -hydroxylation, which is a characteristic feature of enzymic catalysis.^{29,183–185}

Another way of increasing the selectivity and the stability of catalysts is the simulation of the microenvironment of the active centre of enzymes through the construction of organised molecular systems. This term refers to multicomponent catalytic systems with an optimum spatial arrangement and energetic and orbital compatibility between the components of the catalytic system and the substrates. Some general principles for the design of organised molecular species, *viz.*, the models of cytochrome P-450, have been formulated in order to achieve optimum rates and selectivity of the monooxygenase reaction.¹⁸⁶ Methods of molecular design are widely employed for enhancement of various characteristics of the chemical models.

6. Metalloporphyrins in microheterogeneous environments and immobilised on supports

a. Micelles

The selectivity of cyclohexane oxidation in an iron tetrakis(*p*-hexadecyloxyphenyl)porphyrinate ($\text{FeTH}-\text{DOPP}$)– PhIO microheterogeneous system is higher than that of the homogeneous analogue (cyclohexanol becomes the only product) but the rate of the reaction decreases.¹⁴²

Different reactive species have different regioselectivities. To estimate it, the parameter $1^\circ/2^\circ/3^\circ$, *i.e.*, the ratio of the products of the attack at the primary, secondary, and tertiary $\text{C}-\text{H}$ bonds with allowance made for the number of bonds of each type, has been proposed.¹⁸⁷ In the case of metal complexes, steric factors can play an important role. Therefore, metal complexes can attack

Table 4. The regioselectivity of *n*-hexane oxidation by metalloporphyrin chemical enzymic systems.

Catalyst	Oxidant	Medium	Selectivity index ^a	Ref.
FeTHDOPPCl^b	PhIO	C_6H_6	0.003	142
	PhIO	$\text{H}_2\text{O}-\text{Triton X-100}$	0.021	
	PhIO	$\text{H}_2\text{O}-\text{DMPC}^c$	0.050	
	PhIO	$\text{H}_2\text{O}-\text{CD}^d$	0.211	
	PhIO	$\text{H}_2\text{O}-\text{MeCD}^e$	0.234	
MnTPPOAc	PhIO	C_6H_6	0.027	150
MnTTMPPOAc^f	PhIO	C_6H_6	0.041	
MnTTPPPAc^g	PhIO	C_6H_6	0.310	188
Cytochrome P-450 (CYP2B4)	O_2	H_2O	0.160	

^a The regioselectivity index is equal to the ratio of the yields of oxidation products of primary and secondary $\text{C}-\text{H}$ bonds taking into account the ratio of these bonds in the hexane molecule; ^b THDOPP is tetrakis(*n*-hexadecyloxyphenyl)porphyrin; ^c DMPC is dimyristoyl phosphocholine; ^d CD is cyclodextrin; ^e MeCD is methylcyclodextrin; ^f TTMP , is tetrakis(2,4,6-trimethoxyphenyl)porphyrin; ^g TTPPP is tetrakis(2,4,6-triphenylphenyl)porphyrin.

a methyl group or an adjacent methylene group more easily than the less accessible methine group or a CH₂ group inside a polymethylene chain.

Table 4 presents data on regioselectivity of hexane oxidation by cyclodextrin (CD) microheterogeneous model systems and (for comparison) enzymes. The regioselectivity with respect to the terminal group increases with an increase in the degree of ordering of the system by nearly two orders of magnitude in comparison with the homogeneous analogue. It is seen that the selectivity of certain microheterogeneous systems is close to that of the most regioselective isoform of cytochrome P-450_{LM2} (CYP2B4). Apparently, the molecules of hydrophobic PFe and alkane in these organised molecular systems are specifically arranged relative to one another in such a way that the reaction at the terminal CH₃ group becomes preferential.

b. Metalloporphyrins in a phospholipid bilayer

Groves and Neumann¹⁸⁹ have developed a system with an optimum spatial arrangement based on membrane-bound Mn tetrakis[*o*-(cholenylamido)phenyl]porphyrin, Mn^{III}(ChP)Cl, which simulates the hydrophobic microenvironment of the active centres of enzymes. Being incorporated into phospholipid vesicles, the catalyst occupies the central position in the lipid bilayer in such a way that the plane of the porphyrin ring becomes parallel to the water surface. Both molecular oxygen in the presence of a reducing agent and sodium periodate can be used as alkane oxidants.

Selective hydroxylation of the C(25) carbon atom of cholesterol, which does not involve the more reactive C(5) = C(6) double bond of the molecule, is the most striking result of the application of molecular design principles to this particular system. Groves and Neumann¹⁸⁹ attribute this effect to the proximity of the tertiary carbon atom C(25) to the metal in the centre of the complex. The selectivity of the process depends on the oxidant. The reaction rate is very low, but the catalyst retains its stability over a long period of time.

c. Metalloporphyrins immobilised on supports

The number of a catalyst's reaction cycles is usually restricted due to the drop of its activity in the course of oxidation. This problem has been solved in Groves' molecular organised systems, but the system itself is extremely complex. Another approach to the

simulation of the catalyst's microenvironment is its immobilisation on a solid support, *i.e.*, the formation of heterogeneous oxygenase systems. Examples of such systems are given in Table 5.

Immobilisation of a metalloporphyrin on porous glass or polyvinylpyrrolidone (PVP) markedly increases the selectivity of alcohol formation. Immobilisation of an iron–porphyrin complex on zeolites¹⁸⁸ and especially on graphite, strongly increases the steric effects, which are observed in hexane oxidation in model systems with active oxygen species.¹⁹² The effect of the matrix is not confined to the increase in the steric hindrances around the active oxidant. It can also be accompanied by a sieve effect, which is well-known for zeolites and accounts for the differences in the substrate specificity.

Heterogeneous systems of alkane photooxidation by oxygen in the presence of iron and manganese porphyrins immobilised on TiO₂-modified montmorillonite have also been developed.¹⁹³

As expected, the heterogenisation of metalloporphyrin catalysts is accompanied by a decrease in the rate of hydrocarbon oxidation. At the same time, heterogeneous systems have significant advantages over their homogeneous analogues. Immobilisation of metalloporphyrins on various supports not only enhances the selectivity of the reactions catalysed by them but also increases their stability in the majority of cases. For example, immobilisation of iron porphyrinate on porous glass¹⁶⁴ increased the number of reaction cycles nearly 200-fold.

It is generally accepted that the reactive species in systems with metalloporphyrins immobilised on supports are similar to those in solution. Apparently, in most cases this conclusion reflects the real situation; however, it should be kept in mind that binding of the catalyst with the support can change its coordination properties and the ability to produce reactive intermediates.

7. The mechanism of alkane oxidation in systems based on metalloporphyrins

The transfer of the oxygen atom by porphyrin complexes to C—H bonds in natural and model systems is a matter for debate. Various types of molecular mechanisms and a crypto-radical oxygen rebound mechanism have been considered in the context of enzymic hydroxylation. In model systems where the yield of radicals into bulk solution is not excluded, an ordinary radical process can also occur *via* the intermediate formation of a hydro-

Table 5. Alkane oxidation catalysed by metalloporphyrins immobilised on supports.

Substrate	Oxidant	Catalyst	Medium or support	Product ratio alcohol : ketone	Number of catalytic cycles	Ref.
n-Octane	PhIO	MnCl ₁₂ TSMPPAc ^a	solution	1.8	42	190
			PVP ^b	2.4	24	
			[PVPMe][TsO] ^c	11.7	76	
Adamantane (8)	PhIO	MnCl ₁₂ TSMPPAc	PVP	21	238	190
			[PVPMe][TsO]	53	322	
			amberlite IRA-900	16	50	
	PhIO	Mn(T4MPyP)Cl ^d	solution	14	1.5	191
			SiO ₂	37	7.6	
Cyclooctane	PhIO	Mn(T4MPyP)Cl	clay (5%)	28	11.8	191
			solution	0.8	2.2	
			SiO ₂	5.2	8.1	
			clay (5%)	8.8	11.8	
Cyclohexane (4)	PhIO	Mn(T4MPyP)Cl	solution	2.0	1.2	191
			SiO ₂	6.5	6.0	
			clay (5%)	8.8	7.8	
			solution	2	10	
	O ₂ , Zn—AcOH—MV ^e	FeTHDOPPCl ^f	porous glass	5	1800	164
	O ₂ , aldehyde	CoTMeP ^g	SiO ₂	0.53	14.7	176

^a Cl₁₂TSMPP is tetrakis(3-chloro-5-sulfo-2,4,6-trimethylphenyl)-β-octachloroporphyrin; ^b PVP is polyvinylpyrrolidone; ^c [PVPMe][TsO] is polyvinyl-methylpyrrolidone tosylate; ^d T4MPyP is tetrakis(4-*N*-methylpyridino)porphyrin; ^e MV is methyl viologen; ^f THDOPP is tetrakis(*n*-hexadecyloxy-phenyl)porphyrin; ^g TMeP is tetramethylporphyrin.

peroxide; the final products of its conversions are an alcohol and a ketone.

High values of KIE and isomerisation of the molecules subject to oxidation are usually regarded as proofs of the oxygen rebound mechanism both in natural and model systems.¹³² However, despite the seemingly convincing character of these arguments, a careful scrutiny of the experimental data has demonstrated a discrepancy in this concept for biomimetic systems.

Isomerisation observed in the hydroxylation of aromatic compounds (the NIH shift) and in the epoxidation of alkenes (simultaneous formation of aldehydes and epoxides) in chemical and enzymic systems points to the existence of reactive intermediate complexes (rather than free radicals). The effect of radical traps on alkane oxidation may also indicate both the generation of free radicals in parallel and the formation of an intermediate complex in which the alkyl group may acquire sufficient mobility for its reaction with the traps. In addition, the thermodynamic feasibility of radical formation, especially in the case of a strong C–H bond, raises certain doubt. Calculations have shown¹⁹⁴ that if a purely radical mechanism is realised in the first stage, high rates of the reaction of high-valent metal complexes with alkanes can be reached only in the case of weaker tertiary C–H bonds.

The value of the KIE is widely used in the interpretation of mechanisms as the criterion of hydrogen transfer in the form of H^+ , H^- , or $H^\bullet$ in the limiting step as well as in the analysis of the transition state structure.^{100, 195} Small values of KIE ($\sim 1-2$) have been determined for oxidation reactions involving a very reactive (and therefore very non-selective) $^{\bullet}OH$ radical. Higher values of KIE point to the involvement of a more selective intermediate (e.g., metallooxene) as the active oxidant.

For many metalloporphyrins as well as for cytochrome P-450, hydroxylation of C–H bonds in the presence of atomic oxygen donors is characterised by a high isotope effect ($k_H/k_D > 9$). As in the case of natural monooxygenases, for their chemical models^{138, 186, 196} it was assumed that the formation of the ($PMOH + R^\bullet$) pair results from the transfer of the hydrogen atom from the substrate to the reactive intermediate, while the differences in the KIE values are accounted for by a different degree of linearity of transition states. High value of k_H/k_D must correspond to a symmetrical linear transition state for the transfer of the H atom. At the same time, theoretical calculations show that the transition state becomes practically linear after detachment of the hydrogen atom from the methane molecule by H and O atoms or by the $^{\bullet}OH$ radical, but the experimental values of the KIE are small in this case. Moreover, it was established that in some model systems based on metalloporphyrins and active oxygen donors, the experimental values of the KIE substantially exceed the maximum values calculated from the difference in zero point energy levels of the C–H and C–D bonds ($k_H/k_D \sim 7-8$ at 20 °C).¹⁹⁵ The high value of the KIE (> 9 at 25 °C) may indicate a contribution to the mechanism of proton tunnelling (rather than that of the deuteron, which is heavier than the proton and less prone to tunnelling).¹⁰⁰ Obviously, the tunnelling conditions develop gradually but not spasmodically. It is natural to speculate that in all the reactions that occur by this mechanism, the tunnelling effect is present to a greater or a lesser degree, this should be observed for high and narrow barriers.

Hence, a question arises as to why the KIE is so different in the hydroxylation reactions occurring *via* a similar mechanism. It should be noted that in reactions with a high KIE ($k_H/k_D > 6$) its increase is accompanied by an increase in stereoselectivity.¹⁷⁴ At the same time, for systems with a relatively low KIE (about 2), the stereoselectivity varies over a very wide range: from 0% for the $FeTPPCl-O_2-Zn-AcOH$ system to 90% for the $MnTDCPPCl-KHSO_5$ system.

The effect of the medium polarity on the KIE can be accounted for by the lowering of the potential barrier with an increase in ionisation and by the tunnelling effect. In more polar

media, the proton is somewhat 'heavier', being more strongly solvated by the solvent molecule, and the ratios of the masses of the solvated protons and deuterons are smaller than those of the free ones.

Apparently, direct interaction of a high-valent metalloporphyrin complex with the C–H bond of the substrate, which is accompanied by the insertion of the O atom into the C–H bond *via* an intermediate complex with a pentacoordinated carbon is the most probable mechanism for the systems that simulate biological hydroxylation. That the direct insertion is possible follows from the complete retention of the original configuration of the tetrahedral carbon atom observed in some cases, e.g., in the hydroxylation of 1,2-dimethylcyclohexane by an iron–porphyrin complex in a biphasic water–benzene system in the presence of $NaOCl$.^{142–145}

Isomerisation, which is sometimes observed in the oxidation and which is usually considered as evidence in favour of the intermediate formation of radicals, is often in contradiction with the radical mechanism on closer inspection. Thus the hydroxylation of *all-exo*-2,3,5,6-tetradeuterionorbornane using the *meso*-tetrakis(2,6-dichlorophenyl)- β -octabromoporphyrin complex ($Br_8TDCPPFe$) with pentafluoriodosobenzene¹⁹⁷ was accompanied by a partial transfer of deuterium to the *endo*-position. This was interpreted by intermediate formation of a norbornyl radical; however, analysis of the distribution patterns of the hydroxylation products has led to a conclusion that the probabilities of the rotation of the radicals generated by hydrogen detachment from the *exo*- and *endo*-positions of the ring differ drastically (by more than one order of magnitude). If it is assumed that the isomerisation occurred within the intermediate complex in which the carbon atom coordinates the oxygen atom linked with the Fe atom, then it follows from the same data that the rotation leading to the isomerisation is equally probable when the oxygen is added at both the *exo*- and the *endo*-positions. In our opinion, the second mechanism is preferable, especially if one takes into consideration the results obtained for the natural cytochrome P-450.

Hydroxylation of *R*- and *S*-enantiomers of monodeuterio-ethylbenzene with iodobenzene in the presence of a chiral iron–porphyrin complex, which yields all possible isomers of 1-phenylethanol and its deuterioisotopomers, has been studied.¹⁹⁸ It has been found that the main product is formed stereoselectively in both cases and is virtually pure monodeuteriophenylethanol, whereas the deuterium content in the minor product is only 50%. In order to explain these results within the framework of the oxygen rebound mechanism, Groves and Viski¹⁹⁸ had to assume that the intermediate radical formed rotates with a marked probability only in the detachment of H from the *pro-S*-position but does not rotate at all when the detachment occurs from the *pro-R*-position. If one admits the mechanism of oxygen insertion with intermediate formation of a pentacoordinated carbon, the observed results can be easily explained by the isotope effect observed in the insertion of the O atom into the C–H and C–D bonds. If the isotope effect is great, the rate of its insertion into the C–H bond can be much higher than the isomerisation rate, whereas for the C–D bond the rates of the insertion and isomerisation are comparable.

Quantitative estimation of the relative rates of insertion and isomerisation for this reaction¹²⁰ gave a correlation between the rate constants for addition, insertion, and isomerisation. The parameters obtained permit comparison of the experimental and the calculated relative yields of the hydroxylation products (see Table 6). Complete agreement of the experimental and calculated ratios of the reaction products provides evidence for the proposed mechanism. Indeed, the ratio of the reaction products, e.g., for (*S*)-deuterioethylbenzene, can be predicted from the parameters calculated for the *R*-isomer without any additional postulates, and the calculated and the experimental values coincide.

Table 6. The relative yields of the isomers and the deuterioisotopomer of 1-phenylethanol during the oxidation of (*R*)- and (*S*)-(1-deuterioethyl)benzene.¹²⁰

Substrate	Isomer ^a	Relative yield (%)	
		experimental ¹⁹⁸	calculated ¹²⁰
(<i>R</i>)-(1-Deuterioethyl)benzene	<i>R</i> _H	23	22.9
	<i>R</i> _D	19	19.1
	<i>S</i> _H	1	1.1
	<i>S</i> _D	57	56.9
(<i>S</i>)-(1-Deuterioethyl)benzene	<i>R</i> _H	2	1.7
	<i>R</i> _D	87	87.3
	<i>S</i> _H	6	6.0
	<i>S</i> _D	5	5.0

^a The H and D indices are related to the products of oxidation of the C—H and C—D bonds, respectively.

It can be noted that theoretical calculation¹⁹⁹ shows that triprotonated methane, CH₃³⁺ (*i.e.*, heptacoordinated carbon) can, in principle, exist; other authors^{200,201} have succeeded in obtaining complexes of penta- and hexa-coordinated carbons as stable crystalline salts, $\{[(C_6H_5)_3PAu]_5C\}^+$ and $\{[(C_6H_5)_3PAu]_6C\}^{2+}$.

Thus, the non-radical mechanism of oxidation, which involves the attachment of the oxygen atom at the C—H bond and its subsequent insertion into this bond, provides quantitative characteristics for the rationale of the unusual distribution of the reaction products and the isotope effects of hydroxylation of isotopically modified molecules in enzymic and biomimetic systems in which H and D atoms interchange in the course of hydroxylation. Analysis of the rates of the separate stages of this reaction calculated for the new mechanism has revealed interesting and unusual dynamics of the hydroxylation process. The kinetic parameters give a noncontradictory pattern of the reaction dynamics without any recourse to improbable statements, which distinguishes it favourably from the oxygen rebound mechanism employed so far.

Thus, the systems based on metalloporphyrins discussed above not only represent functional models of heme monooxygenases. Many of them simulate the natural process both as regards the reactive species and the oxidation mechanism. Recent data demonstrate significant advances in the design of novel systems based on metalloporphyrins and shed additional light on the mechanisms of reactions occurring in them, although the proposed oxidation schemes are often hypothetical. Further investigations are necessary in order to create more efficient systems and gain a deeper insight into their mechanisms.

IV. Models of non-heme monooxygenases

1. Mononuclear models of non-heme monooxygenases

The systems in which alkane hydroxylation is concomitant with the oxidation of low-valent metals by molecular oxygen can be regarded as the simplest functional models of non-heme monooxygenases. The concomitant oxidation of cyclohexane in systems with FeCl₂ and SnCl₂ in acetonitrile, which is a rather efficient process, can serve as an example.^{202–204} The yield of the alcohol (calculated with respect to the metal) can be increased by lowering the concentration of the complex. Under optimum conditions, it can reach 20% with SnCl₂ and 30% with FeCl₂. The system with SnCl₂ manifests high selectivity (under certain conditions the alcohol is formed as the only product). Thus with an excess of the substrate, the SnCl₂:O₂:ROH ratio is 1:1:1, *i.e.*, it is the same as for the monooxygenase reaction. However, a detailed kinetic analysis has shown that this reaction proceeds *via* a

branched radical-chain mechanism, which involves the [•]OH radical.¹

A great number of analogous systems including simple salts (FeCl₂, FeBr₂, FeI₂, MnCl₂, MnBr₂, VCl₂, CuCl₂, NiCl₂) in which cyclohexane is oxidised to give the alcohol and the ketone, have been described; the yields are nearly identical for different salts.²⁰⁵ The oxidation of cyclohexene does not yield the epoxide, cyclohex-2-enol being the main product. The regioselectivity of hydroxylation of 2-methylbutane (*i.e.*, the ratio of yields of the tertiary, secondary, and primary alcohols formed, is in accord with the regularity that is characteristic of the [•]OH radical: 3°/2°/1° = 13:5:1. Toluene is oxidised to both benzyl alcohol and isomeric cresols (predominantly the *ortho*- and *para*-isomers). These systems are usually characterised by a low value of KIE in the oxidation of C₆H₁₂ and C₆D₁₂,²⁰² which is also typical of the hydroxyl radical.

One of the few proofs of the participation of non-radical intermediates in such systems has been found in the study of alkane oxidation in the Ph₂Sn—O₂ system.²⁰⁶ Partial stereospecificity (20%) observed in the oxidation of *trans*-dimethylcyclohexane is suggestive of the oxenoid reaction that occurs as a background to the radical process. It has been assumed²⁰⁶ that the peroxo complex Ph₂SnO₂ is the reactive intermediate in this reaction.

The system discovered in 1954 by Udenfriend *et al.*²⁰⁷ was one of the first functional models of non-heme monooxygenases based on iron complexes. This system was made up of ascorbic acid and an Fe^{II} complex with ethylenediaminetetraacetate (EDTA) and could hydroxylate aromatic compounds by molecular oxygen. Later, Hamilton⁸⁸ found that this system could also hydroxylate cyclohexane (although in low yield) and epoxidise cyclohexene. In further studies, numerous systems containing non-heme complexes of bi- and tri-valent iron together with oxygen and a reducing agent or a source of active oxygen in various solvents have been proposed and analysed (Table 7).

As can be seen from Table 7, these systems simulate many reactions of atomic oxygen transfer catalysed by monooxygenases, such as aliphatic and aromatic hydroxylation, oxidation of heteroatoms, and epoxidation of alkenes. It is also evident that the characteristics of model systems (selectivity, isotope effect) strongly depend on the nature of the ligand, the source of active oxygen, and the presence of water.

Peroxides or molecular oxygen as oxidants together with various reducing agents are generally used in non-heme models. There is little or no data on the non-heme complexes (other than with cyclam²¹⁴ and cyclidene¹⁹⁷) that can hydroxylate alkanes by atomic oxygen donors, such as iodosobenzene. Peroxides as oxidants simulate more completely molecular oxygen activation by monooxygenases including the stages of peroxo complex formation and O—O bond cleavage. However, difficulties emerge because free radicals generated simultaneously with the ferryl species initiate radical-chain oxidation.²¹⁷ Most papers devoted to this problem are aimed at the search for new ways of estimating the non-radical contribution to the overall oxidation.

One first proof of the non-radical hydroxylation catalysed by iron salts was found in cyclohexanol oxidation by hydrogen peroxide in the presence of Fe^{II}(ClO₄)₂ in acetonitrile.²⁰⁸ It was found that the main oxidation product was *cis*-cyclohexane-1,3-diol obtained in a more than 70% yield. Such selectivity was attributed to the formation of a complex between the active oxidation intermediate, Fe^{IV}=O, and the OH group of the original alcohol. The nearest C—H bond, which is accessible for the attack, is that at the C(3) atom. Later, it was shown that this system can hydroxylate methane (*k*_H/*k*_D = 5) and ethane and oxidise dimethyl sulfoxide to dimethyl sulfone with a selectivity of about 96%.^{209,218} The data obtained have led to a conclusion about the involvement of oxoferryl in the hydroxylation of light alkanes at a low (below 1.5 M) concentration of H₂O₂ in solution.

It has been found that the selectivity of hydrocarbon oxidation concomitant with the activation of H₂O₂ on iron complexes in

Table 7. Effects of non-heme mononuclear models of monooxygenases.

Substrate	Catalyst	Oxidant	Products ^a	Ratio	KIE	Yield per oxidiser (%)	Ref.
Cyclohexanol (5)	Fe(ClO ₄) ₂	H ₂ O ₂	<i>cis</i> -cyclohexane-1,3-diol + other alcohols	7 : 3	1.18		208
Methane	Fe(ClO ₄) ₃	H ₂ O ₂	CH ₃ OH + CH ₂ O		5		209, 218
Dimethyl sulfoxide	Fe(ClO ₄) ₃	H ₂ O ₂	Me ₂ SO ₂			96 ^b	209, 218
Adamantane (8)	[Fe(MeCN) ₆](ClO ₄) ₃	NaIO ₄	10 , (12 + 9)	1 : 24			210
Cyclohexane (4)	FeCl ₃	H ₂ O ₂	5 , (6 + 7)	3 : 1	2.9 and 11	40 ^c	211
	Fe(bipy) ₂ ²⁺ (see ^d)	Bu ^t OOH	5 , 6 , Bu ^t OOC ₆ H ₁₁	1 : 15 : 4	see ^e	40 ^c	211
	Fe(cyclam)(OTf) ₂ ^f	H ₂ O ₂	C ₆ H ₁₁ OOH, 5 , 6	25 : 5 : 2	2.5 ^c	8–10 ^c	214
	Fe(cyclam)(OTf) ₂	PhIO	5 , 6	2.5 : 1	4.3 ^c	8–10 ^c	214
	[Fe(TPA)Br ₂](ClO ₄) ^g	Bu ^t OOH	5 , (C ₆ H ₁₁ Br + 6), Bu ^t OOC ₆ H ₁₁	9 : 13 : 9	5.4	36 ^c	216
	[Fe(TPA)Br ₂](ClO ₄)	MCPBA ^h	5 , (C ₆ H ₁₁ Br + 6)	20 : 9		26 ^c	216
Cyclohexene	FeCl ₃	H ₂ O ₂	epoxycyclohexane, (allyl alcohols + ketone)	1 : 2.5		41 ^c	212
	Fe(cyclam)(OTf) ₂	H ₂ O ₂	the same	13 : 1		30 and 3	214
	Fe(cyclam)(OTf) ₂	PhIO	"	14 : 1		30 and 3	215
n-Hexane	Fe(cyclam)(OTf) ₂	H ₂ O ₂	C(1)/C(2)/C(3) ⁱ	1 : 6 : 7			214
	Fe(cyclam)(OTf) ₂	PhIO	the same	1 : 14 : 18			214
PhOMe	FeCl ₃ –PC–Py ^j	O ₂ –Ascorbic acid	<i>o</i> -, <i>m</i> -, <i>p</i> -methoxy-phenols	66 : 1 : 33		96 ^k	213

^a See Scheme 1; ^b with respect to the DMSO; ^c overall product; ^d bipy is 2,2'-bipyridyl; ^e KIE 4.8, > 10.5, 5.4, respectively; ^f cyclam is 1,4,8,11-tetraazacyclotetradecane; ^g TPA is tris(2-pyridylmethyl)amine; ^h MCPBA is 3-ClC₆H₄COOOH; ⁱ C(1)/C(2)/C(3), relative yield of 1-, 2-, and 3-hexanols normalised per the C–H bond; ^j PC is Py·CrO₃; ^k with respect to Fe.

aprotic solvents ^{219, 220} differs markedly from the selectivity of the radical-chain oxidation initiated by ·OH radicals. ²⁰² This can be accounted for by the possibility of heterolytic cleavage of hydrogen peroxide with the formation of high-valent iron oxo-complexes, Fe^{IV}=O and Fe^V=O, as the active oxidation intermediates.

The system based on the Fe^{II} complex with 1,4,8,11-tetraazacyclotetradecane (cyclam) and H₂O₂ (Table 7) is specific in that it can effectively epoxidise alkenes and hydroxylate alkanes. ²¹⁴ It was suggested that this system contained an iron peroxo-complex stabilised by a hydrogen bond with the nitrogen of the ligand as the reactive epoxidising agent.

Various tripodal ligands have been used to control the coordination sphere of iron ²¹⁶ (Table 7). By applying Me₂S as the oxene trap, Leising *et al.* ²¹⁶ have demonstrated that the formation of the alcohol and the ketone in the cyclohexane oxidation by *tert*-butyl hydroperoxide occurs *via* a pathway which is different from that operating in the formation of dialkyl peroxide: the former two are apparently generated through an oxoferryl intermediate, while the latter is formed under the action of radicals. The results obtained earlier for heme models were also confirmed: electron-donor ligands at the Fe atom favour heterolytic dissociation of the peroxide and provide the stabilisation of the high-valent state of iron in the oxo-complex.

2. The Gif systems

The so-called Gif systems (named after the French town Gif-sur-Yvette) the first variant of which was proposed by Barton *et al.* ²²¹ can also be related to the above-described model systems. In the decade that followed, these systems were intensely investigated, ^{222–226} and several versions were proposed (Table 8).

In all these versions, the Gif systems had a similar composition analogous to that of the above-mentioned mononuclear models. A characteristic feature of these systems is that they employ a pyridine–carboxylic (usually, acetic) acid mixture in various proportions (as a rule, 10 : 1) as the solvent. The majority of Gif systems utilise iron complexes as the catalyst with various ligands that strongly influence the rate of the reaction. Thus, the addition of picolinic acid to FeCl₃·6H₂O increases the reaction rate by a

Table 8. Gif systems.

System ^a	Catalyst	Reducing agent	Oxidant	Ref.
Gif ^{III}	Fe(II)/Fe(III)	Fe ⁰ (powder)	O ₂	221
Gif ^{IV}	Fe(II)/Fe(III)	Zn ⁰ (powder)	O ₂	235, 236
GO	Fe(II)/Fe(III)	Hg (cathode)	O ₂	237, 238
GOAgg ^I	Fe(II)/Fe(III)		KO ₂ /Ar	239
GOAgg ^{II}	Fe(II)/Fe(III)		H ₂ O ₂ /Ar	240, 241
GOAgg ^{III}	Fe(II)/Fe(III)/picolinic acid		H ₂ O ₂ /Ar	242
GOChAgg ⁰	Cu(I)/Cu(II)	Cu ⁰ (powder)	O ₂	243
GOChAgg ^I	Cu(I)/Cu(II)		H ₂ O ₂ /Ar	227

^a The nomenclature of the Gif systems was proposed by Barton. ²²³

factor of tens, whereas pyridine-2-phosphoric acid fully inhibits this process. ²³⁹

The Gif systems have attracted the attention of investigators owing to their unusual selectivity in alkane oxidation. It was believed at first that secondary C–H bonds are oxidised more efficiently than tertiary ones (the 2°/3° ratio in the oxidation of adamantane reached 22, and for *trans*-decalin it was 36), the ketone being the main product. Later, it was found that in addition to the oxidation products, tertiary adamantyl radicals also yield coupling products with pyridine the content of which increases with a decrease in the oxygen concentration. At the same time, secondary adamantyl radicals do not form coupling products with pyridine irrespective of the oxygen concentration. ²²⁷ The regioselectivity of adamantane oxidation in these systems is 2°/3° = 1.0 : 1.1 taking into account coupling products. Although the tertiary C–H bond does react several times faster than the secondary one, the selectivity of this reaction still differs markedly from that observed in ordinary radical processes.

Gif reactions can be conducted in *tert*-butyl alcohol and even in water at the corresponding pH values. ^{228–230} The predominance of a ketone among the reaction products, which is characteristic of the Gif systems, is determined by the solvent

(pyridine–acetic acid), which plays the role of a buffer by maintaining the pH at 6.5 which favours the catalytic dehydration of alkyl hydroperoxide to ketone.

The oxidation of alkyl-aromatic compounds in Gif systems yields the corresponding aldehydes and the ketones. The oxidation involves predominantly the secondary C–H bonds, but not the aromatic ring.²³¹ In the case of terminal disubstituted alkenes, the cleavage of the C=C bond yields a ketone and formaldehyde.²³² The presence of readily oxidisable substrates, such as alcohols, thiols, PPh₃, *etc.*, does not produce any inhibitory effect on the alkane oxidation in these systems.^{228, 233, 243}

The detection of an alkyl hydroperoxide as an intermediate product of the cyclohexane oxidation was an important stage in the study of the mechanism of action of the Gif systems.²³⁴ In these systems, cyclohexyl hydroperoxide is nearly completely converted into cyclohexanone (the ketone/alcohol ratio reaches 10). Alkyl hydroperoxides are intermediate products in the alkane oxidation in all the versions of the Gif systems including copper-containing ones.²⁴³ Experiments with ¹⁸O₂ have shown that it was molecular oxygen (but not H₂O₂) that was the donor of the oxygen atoms in the alkyl hydroperoxide.²²⁸

It is natural to suppose that alkyl radicals are the precursor of hydroperoxides. This assumption has been confirmed by experiments with radical traps (Ph₂Se₂, Ph₂S₂, CCl₄, *etc.*), which generate the corresponding monosubstituted alkanes instead of the ketone.^{234, 244} At low pressure (down to 40–10 mm Hg), where the concentration of O₂ and the yields of the oxidation products are minimal, a paramagnetic trap, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO), yields the corresponding derivatives with secondary and tertiary adamantyl radicals, the yield and the selectivity index (2°/3°) being the same as those for the oxidation products at normal pressure.²²⁸

At the same time, some experimental data, particularly the absence of coupling products of secondary adamantyl radicals with pyridine even at low concentrations of O₂ is a serious argument against the generation of free secondary alkyl radicals. Some other data are also in contradiction with the formation of free-radical alkyl intermediates.^{245, 246}

Barton *et al.*²²⁹ have interpreted the data concerning the selectivity of Gif systems in a framework of a reaction mechanism that included the generation of a complex of highly oxidised iron with oxygen, Fe^V=O. Its reaction with the secondary C–H bonds of an alkane gives a metal-alkyl complex, HO–Fe–R, with an Fe–C bond. The insertion of molecular oxygen or other reagents into this bond yields an alkyl hydroperoxide or different alkane derivatives. However, it was understood that this hypothesis fails to explain the whole body of evidence obtained with the Gif systems, particularly the lack of an obvious dependence of the reaction parameters on the nature of the metal.

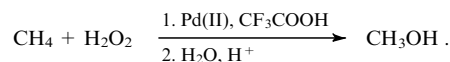
Sawyer *et al.*,^{220, 247} who paid much attention to the study of hydrogen peroxide activation on metal complexes suggested that such oxidative intermediates as LFe^{II}OOH and LFe^{IV}(OH)OOH (the latter is formed when the peroxide is in an excess over iron), which interact with alkanes to give intermediate complexes with Fe–C or FeOO–C bonds, can be generated in Gif and related systems. The simultaneous presence of radical and non-radical reactive intermediates in this reaction is also possible.

3. Functional models of methane monooxygenase

The selective oxidation of methane is a most serious problem because of the high strength of its C–H bond. Very few chemical systems known thus far can oxidise methane to methanol simulating enzymic oxidation under mild conditions.

The chlorides of some metals can promote hydroxylation of light alkanes concomitant with autooxidation in organic solvents.²⁴⁸

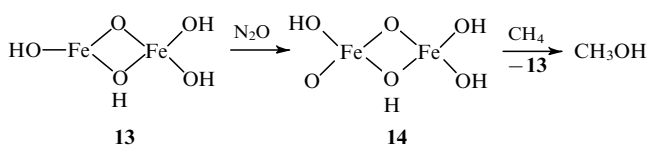
Recently, several systems for methane oxidation by hydrogen peroxide in trifluoroacetic acid under relatively mild conditions have been proposed. Methyl trifluoroacetate is formed in the presence of Pd(II) and can further be hydrolysed to methanol.²⁴⁹



Catalysis by Ru(II)²⁵⁰ gives methanol and formaldehyde in a 4:1 ratio. These systems can catalyse the transfer of the oxygen atom from H₂O₂ to the C–H bond of methane, although metal-complex activation of the methane itself should not be ruled out.

A system for methane and ethane oxidation by oxygen in aqueous media in the presence of a metal catalyst (Pd/C) and a reducing agent (CO)²⁵¹ for which 1000 catalytic cycles were obtained at 85–100 °C is an interesting example of a heterogeneous analogue of methane monooxygenase (MMO). In this system, ethane is oxidised to CH₃CO₂H, HCO₂H, and CH₃CH₂OH in the 221:50:15 ratio. It is assumed that the 'OH radical does not take part in a hydrocarbon oxidation despite the intermediate formation of hydrogen peroxide.

Apparently, one of the best functional models of MMO is the oxidation of methane, carbon monoxide, and benzene by nitrous oxide on the so-called α -centres of iron-containing zeolites, ZSM-5.²⁵¹ These centres result from iron release from the crystalline lattice of the zeolite upon thermal treatment. Their nature still remains obscure. It is believed^{252, 253} that they represent surface iron hydroxide clusters.¹³ The dissociation of N₂O on α -centres results in the addition of the oxygen atom to yield the active oxidant **14**, which oxidises methane stoichiometrically at room temperature:



The use of functional models has made it possible to carry out mild homogeneous oxidation of methane; however, structural factors, such as the binuclear nature of the active centre of MMO, have not been taken into consideration.

4. Binuclear model systems

Binuclear iron complexes with one μ -oxo- or μ -hydroxo-bridge of the (L_nFe)₂O(H) type are the simplest models of the active centre of MMO.²⁵⁴

One of the first attempts to use a binuclear μ -oxo complex, iron hydro(tris-1-pyrazolyl)borate, {Fe[HB(pz)₃]}₂O, in alkane hydroxylation by oxygen in the presence of a reducing agent (zinc) and an effector (acetic acid in CH₂Cl₂) was undertaken in 1988.²⁵⁵ This work did not raise the problem of the preservation of the binuclear structure during functioning of the complex. However, further studies have shown that most of the binuclear complexes with a single μ -oxo bridge were unstable in the presence of reducing agents.²⁵⁴ Later, Kitajima *et al.*²⁵⁶ improved this system by introducing an additional stabilising ligand (hexafluoroacetylacetonate) into the binuclear complex; the excess of the ligand simultaneously fulfilled the role of an effector instead of acetic acid.

The Fe₂O(DTBC)₂Cl₄ complex, where DTBC is di(*tert*-butyl)catechol, catalyses the oxidation of alkanes (including methane) by molecular oxygen in the presence of a reducing agent (hydrazobenzene).²⁵⁷ The binuclear complex proved to be stable under reaction conditions. The mononuclear complex is one order of magnitude less active than the binuclear one. The change in the regioselectivity of the hexane and adamantane oxidation as the binuclear complex is substituted for the mononuclear one shows that the iron complex is involved in the reaction with alkanes. It is concluded from these data that the binuclear oxoferryl intermediate plays the role of the active species. However, the structure of the hypothetical intermediate remains obscure.

The catalytic activity of a series of complexes of the [Fe₂OL₄X₂](ClO₄)₂ type, where L is 2,2'-dipyridyl (bipy), 4,4'-dimethyl-2,2'-dipyridyl or phenyl, and X is a labile ligand (H₂O,

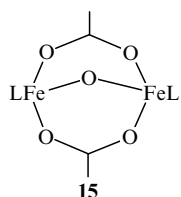
Cl^- , CH_3CO_2^- , CF_3CO_2^-), was studied in the reaction of alkane oxidation by peroxides.^{258,259} It was shown that the efficiency of these complexes depends on the lability of the ligand X. The rate of the reaction drops with an increase in the basicity of the ligand L. The best results in the cyclohexane oxidation by *tert*-butyl hydroperoxide (the yield of the oxidation products is > 50%, the reaction rate is 17 cycles per min) were obtained for the $\text{Fe}_2\text{O}(\text{bipy})_4(\text{H}_2\text{O})_2(\text{ClO}_4)_4$ complex in alkane oxidation (involving methane) by peroxides. The catalytic activity of the binuclear iron complex, $[\text{Fe}_2\text{OL}_4(\text{H}_2\text{O})](\text{ClO}_4)_4$, was found to depend on the nature of the substituent in the ligand.²⁶⁰ The dependence of the selectivity of hydroxylation of a series of alkanes and epoxidation of limonene on the nature of the ligand substituent and the effect of oxygen on the selectivity and the yield of the reaction products demonstrated that these processes occur not only by a radical mechanism, but also by a molecular mechanism, *i.e.*, with the transfer of the oxygen atom from the peroxide to the hydrocarbon mediated by the metal complex.²⁶¹

Cyclohexanol is the single product of cyclohexane oxidation by *tert*-butyl hydroperoxide catalysed by $[\text{Fe}_2\text{O}(\text{TPA})_2(\text{H}_2\text{O})_2]^{4+}$, where TPA is tris(2-pyridylmethyl)amine, under conditions where the concentration of the hydroperoxide exceeds that of the catalyst by more than one order of magnitude. The peroxo complex $\text{Fe}^{\text{III}}\text{OOR}$, which can oxidise alkanes and the excess of the hydroperoxide by initiating radical-chain oxidation, has been assumed to be the reactive intermediate. The relative contribution of each of these mechanisms is determined by the concentration of the peroxide.²⁶²

Cyclohexane is also oxidised in high yield but at a much lower rate in the presence of two-bridge complexes of the $(\text{L}_n\text{Fe})_2\text{O}(\text{OAc})$ type with μ -oxo- and carboxylate (OAc) bridges.^{258,263} The reactive intermediate in alkane oxidation by *tert*-butyl hydroperoxide in MeCN involving the binuclear complex, $[\text{Fe}_2(\text{TPA})_2\text{O}(\text{OAc})](\text{ClO}_4)_3$, was shown to be a metallocomplex compound. The substitution of TPA in the complex for analogous tetradentate ligands alters the KIE in the alcohol formation reaction, which provides direct evidence in favour of the involvement of the iron complex in the transfer of oxygen. Addition of Me_2S completely inhibits the formation of the alcohol and the ketone without any effect on diperoxide production. It is suggested²⁵⁸ that the alcohol and the ketone are formed by the oxenoid mechanism, whereas the diperoxide is formed by the radical-chain reaction. The KIE of the diperoxide formation ($k_{\text{H}}/k_{\text{D}} = 7.7$) does not depend on the nature of the complex used. This fact is an additional proof that the metal complex intermediate does not take part in the diperoxide formation.^{264,265}

Three-bridge binuclear complexes structurally closely resemble the active centre of MMO. The first models **15** containing the nucleus, $(\text{LFe})_2\text{O}(\text{OAc})_2$, were developed by Wieghardt *et al.*²⁶⁶ in Germany and by Lippard *et al.*²⁶⁷ in the USA who employed terminal tridentate ligands.

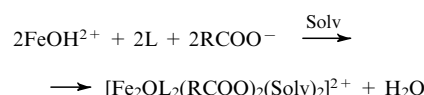
A number of analogous complexes with different terminal and bridge ligands have been obtained. All these complexes efficiently simulate the spectral and magnetic properties of hemerythrin and ribonucleotide reductase (but not MMO), but do not possess any functional activity due to the lack of vacant sites for O_2 binding in their coordination spheres.



L is $\text{C}_6\text{H}_{15}\text{N}_2$,²⁶⁶ 1,4,7-triazacyclononane;²⁶⁶ $\text{HB} \left(\text{N} \begin{array}{c} \diagup \diagdown \\ \text{---} \text{---} \end{array} \right)_3$.²⁶⁷

The methods for preparing iron binuclear complexes with labile coordination sites have been elaborated in the past decade;

some of these are based on the self-assembly from simple molecules:^{268–270}



Solv is the solvent molecule.

This reaction can yield binuclear or tetranuclear complexes depending on the conditions.

The catalytic activity of such three bridge binuclear complexes in alkane oxidation is usually low.²⁷¹ The oxidation of methane and other alkanes by hydrogen peroxide catalysed by $[\text{Fe}_2\text{O}(\text{bipy})_2(\text{OBz})_2\text{Solv}_2](\text{ClO}_4)_2$ (where OBz is benzoate and Solv is H_2O or MeOH) in acetonitrile has been studied.²⁷⁰ The solvent molecule in these complexes represents a labile ligand and can apparently be substituted by H_2O_2 . The KIE for the oxidation of C_6H_{12} and C_6D_{12} ($k_{\text{H}}/k_{\text{D}} = 3.0$), the selectivity of hexane oxidation, and the 5/6 parameter for cyclopentane and cyclohexane oxidation suggest the involvement of the $\text{Fe}=\text{O}$ formed by the splitting of the FeOOH intermediate. It has been shown that such complexes with a labile coordination sphere are more active in alkane oxidation than complexes with a closed coordination sphere.

In a recent study²⁷² it has been shown that the $[\text{LFe}_2\text{O}(\text{OAc})_2](\text{ClO}_4)_2$ complex, where L is the tetradentate hexapyridine ligand, efficiently catalyses alkane oxidation by *m*-chloroperbenzoic acid. If dichloromethane and dibromomethane were used as the solvents, the products of oxidation of cyclohexane (**4**) contained chlorocyclohexane (**7**) and bromocyclohexane, respectively. Radical traps completely inhibited the oxidation. These results together with the regioselectivity data and the KIE led the authors²⁷² to conclude that alkane oxidation in this system occurs *via* a radical mechanism with the formation of an alkyl radical.

As new information about reactive intermediates of the catalytic cycle of binuclear monooxygenases became available, attempts were undertaken to synthesise the corresponding model compounds.^{273–276}

Early studies on simulation of peroxo intermediates were based on the reactions of binuclear complexes of trivalent iron with hydrogen peroxide.^{274–276} Later, a series of Fe_2^{II} complexes with an open coordination sphere and the ability to bind O_2 have been synthesised.²⁷³ The ligands able to bind two metal centres that have been prepared on the basis of 1,3-diaminopropan-2-ol and the carboxylate bridge provide the appropriate ligand environment (N_3O_2) for each Fe^{II} atom. In addition, one molecule of water is sometimes coordinated to one of them. Reversible²⁷⁷ and irreversible^{278,279} binding of molecular oxygen to these and related complexes is observed at low temperatures. An increase in temperature results in the formation of oxidised Fe_2^{III} (see Refs 278 and 279). The oxygen adducts have been characterised as $(\mu\text{-}1,2\text{-peroxo})\text{Fe}_2^{\text{III}}$ complexes on the basis of their Raman and Mössbauer spectra.

The factors that enhance the stability of peroxo complexes have been established. They include the presence of bulky substituents in the tetradentate ligand that attenuate the electron-donor properties of nitrogen and form simultaneously a hydrophobic environment for the peroxo-centre.^{277,278} The peroxo-intermediate, $\text{Fe}^{3+} - \text{O}_2^{2-} - \text{Fe}^{3+}$ on the basis of the $[\text{Fe}_2(\text{Ph-bimp})(\text{C}_6\text{H}_5\text{COO})](\text{BF}_4)_2$ complex (where Ph-bimp is 2,6-bis-{bis[(1-methyl-4,5-diphenylimidazol-2-yl)methyl]aminomethyl}-4-methylphenoxide) is stable even at room temperature.²⁸⁰ The introduction of donor substituents into the bridge ligand accelerates the decomposition of the peroxo complexes. This is accounted for by an increase in the electron density at the metal, which facilitates the cleavage of the O—O bonds and simultaneously stabilises the highly oxidised state.²⁷³ The stabilising effect of polar solvents on peroxo intermediates has also been reported.^{277,279,280}

The parameters of the optical and the Raman spectra of model peroxo complexes are in good agreement with the corresponding parameters of the intermediate P formed in the catalytic cycle of MMO.^{76, 281}

The catalytic systems based on binuclear iron complexes are rather unstable. In the course of the reaction, such complexes either decompose into mononuclear complexes or are destroyed due to ligand oxidation. Moreover, reductive activation of O₂ can be accompanied by nonproductive reactions between the oxidised and reduced forms of the iron complexes, which decreases the activity of the homogeneous systems. Immobilisation of complexes on solid supports favours their stabilisation and decelerates nonproductive bimolecular reactions.

5. Immobilised binuclear complexes

The synthesis of an iron complex on the surface of silica gel modified by imidazole derivatives has been reported.^{282, 283} The structure of a binuclear complex has been proposed on the basis of UV, EPR, and Mössbauer spectroscopic data. This heterogeneous catalyst induces the oxidation of methane and other alkanes by molecular oxygen at room temperature in the presence of a reducing agent (zinc dust), an effector (acetic acid), and an electron carrier (methyl viologen) in acetonitrile. The regioselectivity of hexane oxidation suggests that the [•]OH radical is the reactive species in this system. A recent report²⁸⁴ deals with cyclohexane oxidation by an analogous heterogeneous complex which, in contrast to the former, has two μ -oxo bridges and a dimethylamino group instead of imidazole, but no carboxylate bridges. This complex effectively hydroxylates cyclohexane (57 cycles per catalyst), but does not oxidise methane at an appreciable rate.

6. The mechanism of alkane oxidation and reactive intermediates in non-heme model systems

Fish *et al.*^{285, 286} have concluded that alkane oxidation in all the systems having a composition $LFe^{II/III} + H_2O_2 - O_2$ yield an alkyl hydroperoxide or its complex with iron, FeOOR, as the intermediate product, which, in turn, points to the formation of the substrate-derived radical R[•] as the intermediate. This conclusion was confirmed by the detection of diperoxides in the systems based on mono- and bi-nuclear iron complexes with *tert*-butyl hydroperoxide as the oxidant.^{262, 287}

Evidence that alkane oxidation in the

$[Fe_2O(bipy)_4(H_2O)_2](ClO_4)_4 - H_2O_2$,²⁶¹ $[Fe_2O(tmima)(OAc)_2](ClO_4)_2 - H_2O_2$ ²⁸⁶

[tmima is tris(1-methylimidazol-2-yl)amine],

$[Fe_2O(TPA)_2(H_2O)_2]^{4+} - Bu^tOOH$, and

$[Fe(TPA)Cl_2]^+ - Bu^tOOH$ ²⁷²

systems involves alkyl radicals is provided by the dependence of the concentration and composition of oxidation products on the concentration of molecular oxygen in the reaction medium.

Presumably, radical oxidation is initiated by the oxygen radicals generated either by activation of peroxides on metal complexes^{288, 289} or in the oxidation of the excess of peroxide by oxenoid intermediates.^{156, 262} The possibility of generation of the alkyl radicals R[•] through detachment of hydrogen from the hydrocarbon by reactive peroxo- or oxo-iron complexes has also been considered.^{252, 272, 286} Redox potentials for the formation of radicals from hydrocarbons with the general formula $HCH_{3-n}(CH_3)_n$ varies from 1.60 to 2.25 eV;¹⁹⁴ therefore, the detachment of H by oxenoid intermediates occurs apparently only in the oxidation of the less stable (tertiary or activated) C—H bonds.

Although short-living oxenoid intermediates have been detected in systems with non-heme iron, they have not been adequately characterised. The intermediate $Fe^{IV}=O$ has been effectively generated by laser photolysis of a Fe^{II} salen complex (salen is 1,2-disalicylideneaminoethane) with molecular oxygen.²⁹⁰ It was shown that iron complexes with EDTA, like their

porphyrin analogues, can transfer an oxygen atom from peroxy acids and peroxides by splitting the latter *via* a heterolytic mechanism.²⁹¹ The formation of a non-heme ferryl complex has been observed in aqueous solutions by spectral methods.²⁹²

The ability of binuclear Fe^{II} complexes with 1,2-bis(2-hydroxybenzamido)benzene to transfer the oxygen atom from a peroxy acid and PhIO to cyclohexene *via* the intermediate formation of $Fe=O$ has been established.^{293, 294} In the absence of the substrate, the spectroscopically identified $Fe=O$ intermediate (its lifetime is 1.5 h at $-78^\circ C$) was converted into the μ -oxo complex.

A reactive oxidative intermediate generated in the reaction of a binuclear iron μ -oxo complex, $[Fe_2O(TPA)_2](ClO_4)_4$, with H_2O_2 , in a system that hydroxylates alkanes and epoxidises alkenes, has been characterised in the most detail.²⁹⁵ Analysis of the EPR, Mössbauer, and Raman spectra, together with the data from the elementary and mass-spectrometric analyses,²⁹⁶ suggest that the reactive intermediate has an $Fe_2(\mu-O)_2$ nucleus with a delocalised electron. In its characteristics it is similar to the reactive intermediate X in the catalytic cycle of ribonucleotide reductase.²⁹⁶

Obviously, these are only the first steps on the way to the simulation of non-heme monooxygenases. On the whole, this problem is still far from being finally solved. There are relatively few systems for which the involvement of well-characterised binuclear complexes in alkane oxidation has been confirmed experimentally. There are practically no reliable data on the nature of the reactive intermediates. At the same time, the experimental results altogether suggest that the construction of efficient analogues of MMO is a task of the nearest future. One important problem on the way is the stabilisation of binuclear complexes during the catalytic cycle. Preliminary data show that a major breakthrough can be expected from the application of complexes immobilised on solid supports. A strong impetus for the construction of adequate models of MMO is the X-ray determination of MMO structure. However, the design of efficient structural and functional analogues will also require great skills of synthetic chemists because the modelling of the protein environment of the active centre is fraught with considerable difficulties. Apparently, the design and synthesis of more complicated models that reproduce, with a great degree of accuracy, the structure of the iron complex and its environment in the protein globule will play a prominent role in both the simulation of cytochrome P-450 and the construction of analogues of non-heme monooxygenases.

V. Conclusion

The results presented in this review allow one to make a conclusion about the increasing interest in the enzymic oxidation of alkanes and the construction of chemical models of these reactions. Special interest of investigators has recently been focussed on the relatively poorly investigated enzyme, methane monooxygenase, as well as on the biomimetic systems based on non-heme binuclear iron complexes. Studies of cytochrome P-450 and its chemical models for which many fundamental problems still remain unsolved are also very important.

Undoubted progress in the field of natural and biomimetic monooxygenase systems should be mentioned. The use of modern physical methods permits the prediction, with an increasing degree of reliability, of the structure of reactive species involved in the transfer of the oxygen atom to the substrate. The formulation of a hypothesis about the intermediate formation of species with pentacoordinated carbon during the insertion of the oxygen atom into the C—H bond has been important for the understanding of the mechanism of monooxygenation. This hypothesis, which allows prediction of the quantitative distribution of the oxidation products in some cases has eliminated the contradictions evolved in the analysis of the two earlier proposed mechanisms, namely, the oxenoid mechanism, which entails direct

insertion of the O atom into the C—H bond, and the cryptoradical (oxygen rebound) mechanism.

The progress in the chemical simulation of monooxygenases demonstrates that novel efficient, highly selective catalytic systems for alkane oxidation will hopefully be created based on them in the nearest future.

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Intermetallic borocarbides: electronic structure, chemical bonding, and properties

A L Ivanovskii

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Abstract. In 1994, the superconductivity of intermetallic borocarbides (IBC) of composition $\text{LnM}_2\text{B}_2\text{C}$, where Ln is a rare-earth metal and M is Ni or Pd, was discovered. This discovery stimulated numerous works on the synthesis of new quaternary borocarbide phases and solid solutions based on them and studies of their crystal chemistry and magnetic, superconducting, and transport properties. Almost simultaneously, investigations of the fundamental electronic properties of IBC and specific chemical bonding in this new class of materials have been initiated. The results of theoretical and experimental investigations in these fields are summarised. The bibliography includes 179 references.

I. Introduction

The year 1994 was marked by a discovery in the physical chemistry of a poorly studied class of multicomponent intermetallic compounds, *viz.*, intermetallic borocarbides (IBC): the superconductivity effect was observed in the Y–Pd–B–C and Lu–Ni–B–C systems. Superconducting transitions at $T_c \approx 23$ K and $T_c \approx 16$ K for a heterophase specimen with the composition $\text{YPd}_3\text{B}_3\text{C}_{0.3}$ and a single-phase specimen of borocarbide $\text{LuNi}_2\text{B}_2\text{C}$, respectively, were reported.¹³

The attention of researchers was immediately drawn to IBC since they appeared to be the first superconducting quaternary intermetallic systems known which are devoid of copper and oxygen ions. The above phases had nickel and palladium as components. At the same time, it was well known that the presence of ferromagnetic nickel in compounds resulted in suppression of their superconducting properties, whereas very few superconductors studied contained appreciable quantities of palladium (for instance, PdH_x , metallic palladium saturated with boron and carbon ions, and several hydrogenated Pd alloys with *d*-metals (Cu, Ag, Au, Nb, Mo, and W)).⁴

The observation of superconductivity in nickel-containing IBC stimulated an active search for other multicomponent phases containing magnetic transition-metal ions. Currently, information on the synthesis of superconducting intermetallic silicides and carbides, namely, LaNiSi , LaNiC_2 , $\text{La}_{1-x}\text{Th}_x\text{NiC}_2$, and $\text{Tm}_2\text{Fe}_3\text{Si}_5$ is available.^{5–8}

The initial stage of experimental studies of IBC was characterised by a quest to extend the class of known quaternary phases of the $\text{LuNi}_2\text{B}_2\text{C}$ type by replacing Lu by magnetic rare-earth metal ions and to determine the critical temperature of superconducting transition (T_c) for compounds produced. This kind of study was carried out for IBC containing Tm ($T_c \approx 10.8$ K), Er ($T_c \approx 10.5$ K), Ho ($T_c \approx 8.5$ K), and Dy ($T_c \approx 6.2$ K).^{9–14} Similar attempts to 'chemically modify' the superconducting properties were made by changing the type of the transition metal. In particular, it has been established that for $\text{YNi}_2\text{B}_2\text{C}$ ($T_c \approx 15.6$ K)² such substitutions appreciably affect the T_c value, which is equal to 10.0, 23.0, and 0.0 K for Pt,¹⁵ Pd,^{16,17} and Co,¹⁸ respectively.

One more remarkable discovery was made at the same period. It has been established in studies of the properties of IBC containing magnetic rare-earth metal ions (Pr, Dy, Ho, Er, Tb, *etc.*)^{19–25} that these compounds form a unique class of superconducting materials with close-lying temperatures of magnetic ordering, namely, the Neel temperature (T_N) and the temperature of superconducting transition. In this regard, no other analogues of IBC are known so far.

The current stage of investigations of IBC is characterised by both a search for new quaternary phases, in which the metallic sublattice is composed of actinides [for instance, phases in the UMBC systems (M = Ni, Pd, and Pt)],^{26–29} and attempts to synthesise intermetallic boron nitrides^{30,31} as well as by a tendency to perform more flexible variation of the composition and properties of IBC by doping their sublattices with a finite (variable) concentration of dopants. Transition metals (M'), as a rule, play the role of dopants. The concentration dependences of physicochemical characteristics of solid solutions (SS) of the type $\text{Ln}(\text{M}_{1-x}\text{M}'_x)_2\text{B}_2\text{C}$ ^{32–35} or $\text{Ln}(\text{M}_{1-x}\text{M}'_x)\text{BC}$ ^{36,37} are being studied intensively. Thermobarochemistry techniques are also used to affect the crystal structure.³⁶ Attention is focused on the effect of possible processing conditions (for instance, annealing) on the properties of the specimens. On the whole, the majority of

A L Ivanovskii Institute of Solid State Chemistry, Ural Branch of the Russian Academy of Sciences, Pervomaiskaya ul. 91, 620219 Ekaterinburg, Russian Federation. Fax (7-343) 274 44 95. Tel. (7-343) 249 30 82

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experiments deal with the studies of the nature of superconducting, magnetic, and kinetic properties of IBC and the ways of their targeted control.

Each group of superconducting materials [high-temperature superconducting (HTSC) cuprates, fullerites, Chevrel's phases, A-15 compounds, *etc.*] is characterised by its individual crystal structure and the structure of the energy bands. Therefore, it is natural that a set of experiments on studying the specific character of the electron states in IBC were initiated almost simultaneously with the discovery of superconductivity in borocarbide phases.

The information on the electronic energy spectra (EES) and the nature of chemical bonding in IBC obtained to date using computational methods of solid state quantum chemistry and experimental spectroscopic techniques is analysed in the present review. Attempts aimed at interpreting the observed physico-chemical properties of IBC from the viewpoint of their electronic structure are considered.

II. Phase relationships in Ln–M–B–C systems

No detailed studies of phase equilibria in Ln–M–B–C systems have been reported to date; information on phase relationships in these systems and plausible structures of compounds that formed is scarce and is of tentative character so far.³⁸

In the first papers,¹³ the $\text{LuNi}_2\text{B}_2\text{C}$, $\text{YNi}_2\text{B}_2\text{C}$, and $\text{YPd}_2\text{B}_2\text{C}$ phases as well as the related LuNiBC phase were identified as superconducting ones. The efforts of chemists were focused on obtaining a series of isostructural compounds in analogous systems. To date, the $\text{LnNi}_2\text{B}_2\text{C}$ phases for most 4f-elements, Y, and Sc have been synthesised.^{1–3, 9–14, 39, 40} Substances obtained by complete substitution of Ni by Pd, Pt, Rh, or Ir appear to be thermodynamically stable only for early lanthanides.^{1, 15, 40} As to borocarbides with the composition LnMBC , the attempts to synthesise isostructural phases corresponding to various combinations of rare-earth and transition metals made it possible to establish reliably the existence of only borocarbides LuNiBC and YNiBC , whereas the attempts aimed at obtaining stable single-phase specimens with La, Ce, Ni, Co, and Cu failed.^{9, 36, 41, 42}

The crystal structure of the borocarbides $\text{LuNi}_2\text{B}_2\text{C}$ and LuNiBC was first studied by Schmidt *et al.*⁹ The fragments of these structures are shown in Fig. 1 and some of the crystallographic parameters are listed in Table 1. The structure of $\text{LuNi}_2\text{B}_2\text{C}$ can be considered as a modified 'filled' variant of the body-centred tetragonal (BCT) structure of the ThCr_2Si_2 type (see Ref. 38) with the space group $I4/mmm$ composed of alternating Ni_2B_2 layers (with tetrahedral coordination of Ni atoms) and plane LuC nets, where the atomic ordering is of the rock salt type.

The Ni_2B_2 layers in LuNiBC borocarbide are separated by two LuC nets; however, several interatomic distances appear to be very close for both phases (see Table 1).

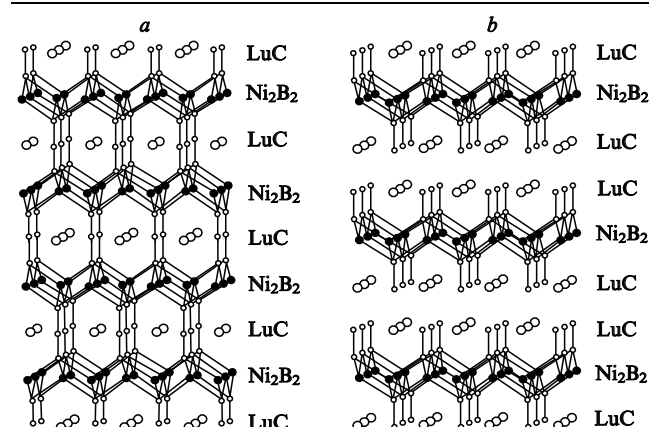


Figure 1. The crystal structures of borocarbides.⁹ (a) $\text{LuNi}_2\text{B}_2\text{C}$; (b) LuNiBC .

Table 1. Crystallographic parameters of $\text{LuNi}_2\text{B}_2\text{C}$ and LuNiBC .

Parameter	$\text{LuNi}_2\text{B}_2\text{C}$	LuNiBC
Symmetry group	$I4/mmm$	$P4/nmm$
Unit cell parameter /Å		
<i>a</i>	3.4639	3.4985
<i>c</i>	10.6313	7.7556
Unit cell volume /Å ³	127.56	94.93
The number of formula units per unit cell	2	2
Atomic <i>x</i> , <i>y</i> , <i>z</i> positions of the element		
Lu	0, 0, 0	1/4, 1/4, 0.1602
Ni	1/2, 0, 1/4	3/4, 1/4, 1/2
B	0, 0, 0.3621	3/4, 3/4, 0.1523
C	1/2, 1/2, 0	3/4, 3/4, 0.3489
Interatomic distance /Å		
Lu–C	2.449	2.475
Lu–B	2.855	2.867
Ni–B	2.10	2.11
Ni–Ni	2.449	2.474
B–C	1.47	1.52

In accordance with the classification suggested by Gangopadhyay *et al.*,³⁷ the $\text{LnM}_2\text{B}_2\text{C}$ phases have the simplest (for this series of compounds) structure with alternating M_2B_2 and LnC layers (the so-called 'one-layered' phases) and can be described by the general formula $(\text{LnC})_n(\text{MB})_m$, where $n = 1$, and $m = 2$. Compounds with the composition LnMBC belong to the 'two-layered' phases ($n = 2$, $m = 2$). Schmidt *et al.*⁹ and Gangopadhyay *et al.*³⁷ assumed that the systems in question may exist as extended homologous series with the compositions $(\text{LnC})_n(\text{MB})_2$ and $(\text{LnC})(\text{MB})_{m+2}$ with variable content of the nets of the LnC and M_2B_2 phases, respectively, and their combination, the $(\text{LnC})_n(\text{MB})_{m+2}$ phase. No experimental confirmations of the existence of such compounds are available to date.

Analysis of the structure of the $\text{LnNi}_2\text{B}_2\text{C}$ phases has shown⁹ that the constants *a* and *c* of the BCT lattice change almost linearly depending on the lanthanide radius $r(\text{Ln})$ ^{43, 44} (Fig. 2) in contrast to the expected effect of conventional lanthanide compression according to Vegard's rule. The only exception is $\text{CeNi}_2\text{B}_2\text{C}$, which is explained by variable (or mixed) valence of cerium ($\text{Ce} \sim 3.75$) due to hybridisation of its 4f shell with the states of the valence band of the crystal.^{45–47}

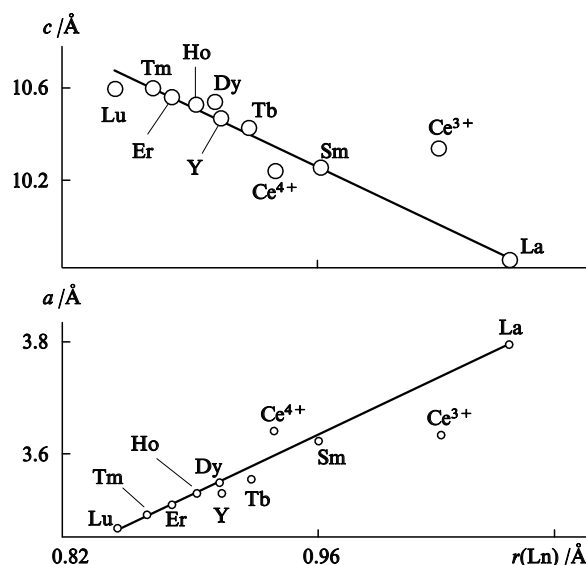


Figure 2. Dependence of the BCT lattice parameters of $\text{LnNi}_2\text{B}_2\text{C}$ phases on the ionic radius of the lanthanide.

Table 2. Structural parameters of the $\text{LnNi}_2\text{B}_2\text{C}$ phases.⁴⁷

Parameter	CeNi ₂ B ₂ C	PrNi ₂ B ₂ C	NdNi ₂ B ₂ C	TbNi ₂ B ₂ C	DyNi ₂ B ₂ C	HoNi ₂ B ₂ C	ErNi ₂ B ₂ C	TmNi ₂ B ₂ C	YbNi ₂ B ₂ C
$a/\text{\AA}$	3.638	3.707	3.678	3.554	3.534	3.513	3.502	3.487	3.478
$c/\text{\AA}$	10.227	9.999	10.081	10.435	10.488	10.528	10.558	10.586	10.607
$V/\text{\AA}^3$	135.346	137.383	136.370	131.778	130.999	130.271	129.48	128.682	128.323
Lu–B/ $\text{\AA}$	2.972	3.012	2.995	2.921	2.907	2.896	2.885	2.888	2.877
Lu–C/ $\text{\AA}$	2.572	2.621	2.601	2.512	2.499	2.487	2.476	2.469	2.459
Ni–B/ $\text{\AA}$	2.109	2.113	2.111	2.101	2.101	2.101	2.100	2.095	2.091
B–C/ $\text{\AA}$	1.489	1.489	1.485	1.489	1.485	1.483	1.481	1.485	1.483
B_i –Ni– B_{ii} /deg	104.85	103.33	103.93	106.53	107.02	107.41	107.74	107.92	107.92
B_i –Ni– B_j /deg	119.16	122.61	121.25	115.55	114.51	113.69	113.03	112.64	112.64

Note. Atomic positions in the unit cell: Ln (0, 0, 0), Ni (1/2, 0, 1/4), B (0, 0, z), C (1/2, 1/2, 0), B_i (x , y , z), B_{ii} (1/2 + x , 1/2 + y , 1/2 – z).

The most detailed study of crystallochemical properties of the $\text{LnNi}_2\text{B}_2\text{C}$ (Ln = Y, Ce, Pr, Nd, Tb, Dy, Ho, Er, Tm, and Yb) phases (Table 2) was carried out by the neutron diffraction technique.⁴⁷ The interatomic Ln–C and Ln–B distances increase appreciably with the lanthanide radius, which results in a decrease in the thickness of the Ni_2B_2 layer and distortion of NiB_4 tetrahedra it is composed of. Since the Ni–B distances are little changed, the most pronounced changes occur in the bond angles of the NiB_4 fragments (Table 2). The interatomic B–C distances appear to be the least ‘sensitive’ to the $r(\text{Ln})$ values, which is explained⁴⁷ by the strongest interspecies interactions in the C–B–C groups (see below).

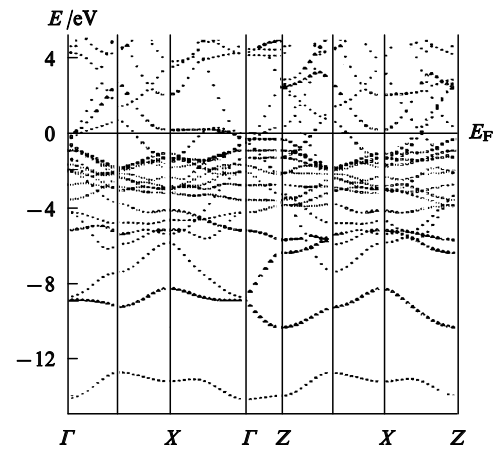
It should be noted that the strongly anisotropic quasi-two-dimensional (2D) structure of IBC can indicate at first glance the similarity in the nature and mechanism of superconductivity in these phases and in 2D high-temperature superconducting cuprates. Such a similarity seems to be real, in particular, taking into account the assumptions by Disalvo⁴⁸ and Geballe⁴⁹ that partial replacement of copper atoms in cuprates by atoms of other transition metals and that of oxygen atoms by more electro-positive ions (N, C, B) can be considered in several cases as the factor that prognostically favours superconductivity. However, it should be immediately noted that all information concerning the specificity of the electronic structure of IBC available to date rules out the possibility of the above analogy.

III. Electronic structure of nonmagnetic superconductors $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{YNi}_2\text{B}_2\text{C}$

The first numerical calculation of the electron states of $\text{LuNi}_2\text{B}_2\text{C}$ was carried out by Mattheiss⁵⁰ in the framework of the local electron density formalism (LEDf) by using the scalar relativistic linearised augmented plane waves (LAPW) method.^{51,52} The exchange-correlation effects were taken into account by the use of Wigner’s interpolation formula.⁵³

The dispersion dependences $E(\mathbf{k})$ are shown in Fig. 3. The lowest energy band is formed by the $\text{C}2s$ states. The allowed states in the interval from –10 eV to the Fermi level are composed of contributions of the $\text{B}2s$, $\text{B}2p$ – $\text{C}2p$, and $\text{Ni}3d$ states (in order of increasing energy). The Fermi level cuts the $\text{Ni}3d$ bands partially ‘seizing’ the bottom of the $\text{Lu}(d_{x^2-y^2})$ subband (at the point Γ). The major contribution to the maximum near the Fermi level [$N(E_F)$] comes from the $\text{Ni}3d$ states: 2.4 states per eV for a transition metal, which is approximately twice as large as the corresponding value for copper in the case of HTSC cuprate La_2CuO_4 (see Ref. 54) and is close to $N(E_F)$ for vanadium in the ‘conventional’ A-15 superconductor V_3Si .⁵⁵ Hence, Mattheiss⁵⁰ has come to the conclusion that $\text{LuNi}_2\text{B}_2\text{C}$ must be considered as a ‘conventional’ superconductor with the known T_c vs. $N(E_F)$ (or T_c vs. γ , where γ is the electronic heat capacity) dependence.⁵⁶

Experimental measurements of γ for $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{LaPt}_{1.7}\text{Au}_{0.3}\text{B}_2\text{C}$ have been performed⁵⁷ almost simultaneously with

**Figure 3.** The band structure of $\text{LuNi}_2\text{B}_2\text{C}$.⁵⁰

Mattheiss’ calculations,⁵⁰ with γ values being close to those of A-15 compounds.

Analysis of the distribution of the valence s , p , and d states of lutetium (Fig. 4) shows⁵⁰ that their contributions to the formation of $N(E_F)$ cannot be neglected, in contrast, for instance, to the case of HTSC lanthanum cuprate.⁵⁴ The near-Fermi region of the spectrum of $\text{LuNi}_2\text{B}_2\text{C}$ contains all five $\text{Ni}3d$ subbands.⁵⁰ The contributions of the d_{xy} and $d_{yz,zx}$ states to $N(E_F)$ exceed those of the $d_{x^2-y^2}$ and $d_{3z^2-r^2}$ states only by 16% and 6%, respectively. The inclusion of Lu $4f$ levels into the valence basis set has nearly no effect on the shape of the curve of the total density of states (TDOS). In this case, the shapes of TDOS for $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{YNi}_2\text{B}_2\text{C}$ appear to be similar (Fig. 4). The latter was calculated by Schmidt *et al.*⁹ using the values 3.53 and 10.57 Å for the lattice parameters a and c , respectively.

Judging from the results obtained, the energy-band spectra of Lu and Y borocarbides do not satisfy the criterion for that of promising HTSC phases,⁵⁸ which requires that the σ^* band formed as a result of interaction between the degenerate anionic and cationic levels be half-filled. Unlike cuprates, where the corresponding bands are in the immediate vicinity of E_F , the $\text{Ni}3d$ – $\text{B}2s$ or $\text{Ni}3d$ – $\text{C}2p$ bands of borocarbides have different energetics owing to a specific character of interatomic σ -bonds in the NiB_4 tetrahedra.

Data on the energy band structure of $\text{LuNi}_2\text{B}_2\text{C}$ obtained by the LAPW method⁵⁹ in the LEDf parametrisation^{60–63} using the lattice constants $a = 3.464$ Å and $c = 10.631$ Å, and $z/c = 0.1379$, where z characterises the position of the B atoms above the Lu–C plane, coincide in general with those obtained by Mattheiss *et al.*^{58,64} The shape of the Fermi surface determined by Pickett *et al.*⁵⁹ appeared to be rather complicated: the $\text{Lu}d$ and $\text{Ni}d$ – $\text{B}2p$ type spheroids that form the Fermi surface are centred at the centre of the Brillouin zone. The fact that the dispersion of the

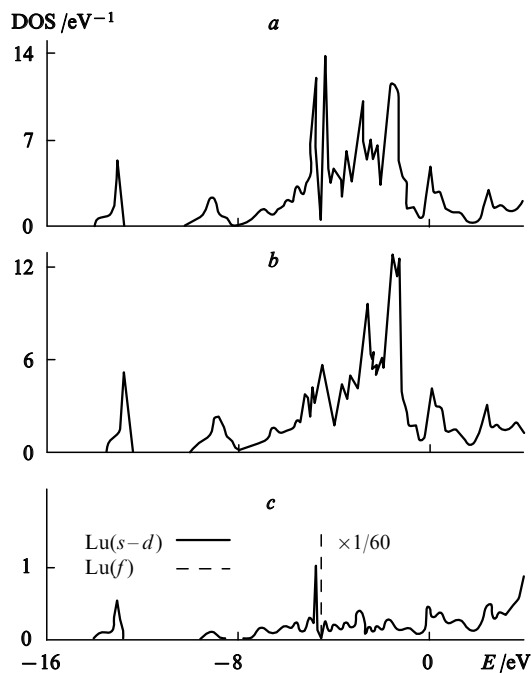


Figure 4. The energy distribution of the total densities of states for $\text{LuNi}_2\text{B}_2\text{C}$ (a), $\text{YNi}_2\text{B}_2\text{C}$ (b), and partial (s - f) Lu states in $\text{LuNi}_2\text{B}_2\text{C}$ (c); calculations by the LAPW method.⁵⁰

corresponding energy bands is comparable in the atomic planes and along the c axis, as is the case in Mattheiss' calculations,⁵⁰ is an unambiguous evidence for the three-dimensional (3D) nature of the electronic energy spectra of IBC.

Particular attention was given to the analysis of the structure of bands near the Fermi level responsible for the formation of the DOS maximum at the Fermi level. Its presence is associated with the formation of plane energy bands in the (110) direction (the Γ - X direction in Fig. 3), which include antibonding ($\text{Ni}d_{z^2}$ - $\text{Ni}d_{z^2}$), bonding (Bp - $\text{Ni}d$), and impurity ($\text{Lu}d_{xz,yz}$) states. Taking into account an appreciable contribution of the $\text{Ni}d$ states to $N(E_F)$, one can assume that (by analogy with the known ferromagnetic behaviour of metallic nickel or nickel films) this peak in IBC is unstable according to Stoner. However, no ferromagnetic instability of this type was shown in calculations⁵⁹ carried out with consideration of the spin moments.^{65,66}

Pickett *et al.*⁵⁹ emphasised that the appearance of the near-Fermi $3d$ -like band of Ni separated from all the other filled $\text{Ni}d$ bands is one of the most remarkable features of the $\text{LuNi}_2\text{B}_2\text{C}$ electronic spectrum and studied its genesis in detail. To this end, the sublattices of the 'empty' BCT phase were progressively 'filled' with the corresponding atoms. Calculations of isolated Ni and Ni_2B_2 monolayers that retained their atomic geometry in the bulk of $\text{LuNi}_2\text{B}_2\text{C}$ did not result in splitting of the $\text{Ni}d$ subband; only the addition of bridging carbon atoms made it possible to detect a resonance DOS peak of the $\text{Ni}3d$ type separated from the main d band of nickel. However, the energetics and structure of the near-Fermi maximum characteristic of a superconducting IBC is formed finally in the presence of the Lu atoms, *i.e.*, when Ni-C interactions are corrected taking account of the carbon-lutetium bonds.

Such analysis not only confirms the 3D nature of IBC,[†] but is of importance from the viewpoint of methodology. It shows that the local models that take into account only the closest environment of the transition-metal atom cannot be used for interpreting the superconductivity effects in IBC, which was the usual practice in the first stages of the description of electronic energy spectra of

HTSC cuprates (for a review, see Ref. 67). Therefore, one should be extremely careful when applying cluster quantum-chemical methods to the class of intermetallic borocarbides; in particular, the chosen fragments must be balanced with respect to the stoichiometric composition of real IBC materials. Analogous conclusion was drawn by Kim *et al.*⁶⁸ who have calculated the energy band structure of $\text{LuNi}_2\text{B}_2\text{C}$ by the *ab initio* pseudopotential method.⁶⁹

The energy band structure of the BCT borocarbide $\text{YNi}_2\text{B}_2\text{C}$ was studied by Mattheiss,⁵⁰ Coehoorn,⁷⁰ Lee *et al.*,⁷¹ Ravindran *et al.*,⁷² and Zeng *et al.*⁷³ The dispersion dependences $E(k)$ and DOS distributions for the $\text{YNi}_2\text{B}_2\text{C}$ phase found by these authors are in good agreement with each other despite certain deviations in numerical estimates of EES inevitable if different methods and approximations are used for the accepted models. For this reason, the results obtained by Lee *et al.*⁷¹ will be used in the subsequent description of characteristic features of the electronic structure of $\text{YNi}_2\text{B}_2\text{C}$. The calculations were performed by the self-consistent linearised muffin-tin orbital (LMTO) method with the lattice parameters $a = 3.527 \text{ \AA}$ and $c = 10.5427 \text{ \AA}$.⁷⁴

The structure of the energy bands of $\text{YNi}_2\text{B}_2\text{C}$ is shown in Fig. 5, several parameters of the electron states are listed in Table 3. Lee *et al.*⁷¹ draw attention to the composition of the bands near the Fermi level, which consist mainly of the $\text{Ni}3d$ contributions and appreciable admixtures of the $\text{Y}4d$, $\text{B}2p$, and $\text{C}2p$ states. The flat band crossed by the Fermi level at the point Γ results in the appearance of the van Hove-like singularity on the TDOS curve. Cross-section of the Fermi surface by the $k_z = 0$ plane of the Brillouin zone is shown in Fig. 6. Its topology (see Fig. 5) is formed with participation of the bands that determine the combination of the electron and hole states. An appreciable energy dispersion of the $\text{C}2p$ -like bands in the Γ - Z direction was noted.⁷¹ It was also emphasised that it is carbon that plays the crucial role in the formation of the 3D nature of the given phase, whereas a quasi-2D behaviour is expected for a hypothetical IBC with an 'empty' C sublattice.

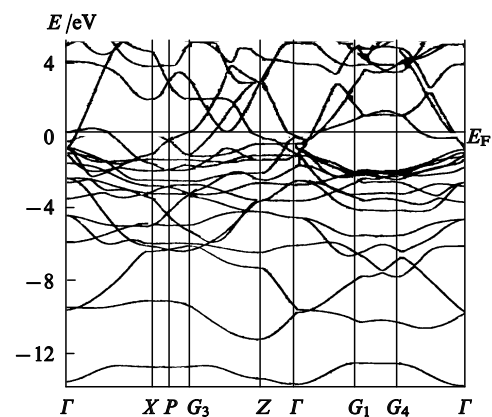


Figure 5. The band structure of $\text{YNi}_2\text{B}_2\text{C}$ calculations by the LMTO method.⁷¹

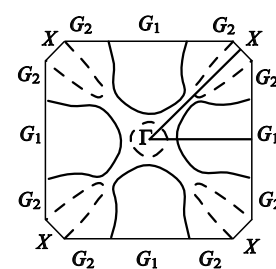


Figure 6. Cross-section of the Fermi surface of BCT $\text{YNi}_2\text{B}_2\text{C}$ by the $k_z = 0$ plane.⁷¹

[†] The states of all of the atoms that constitute the material are involved in the formation of subtle features of the near-Fermi interval of the energy band spectrum responsible for superconductivity of 3D IBC.

Table 3. Contributions of individual states ($N_{s,p,d}$) to the DOS at the Fermi level, charges ($Q_{s,p,d}$) of the ‘muffin-tin’ spheres for individual atoms in the $\text{YNi}_2\text{B}_2\text{C}$ phase, and radii of atomic spheres (R); calculations by the LMTO method.

Parameter	Y	Ni	B	C
N_s /state per 1 eV	0.02	0.03	0.04	0.03
N_p /state per 1 eV	0.07	0.22	0.18	0.14
N_d /state per 1 eV	0.64	1.09	—	—
N_{s+p+d} /state per 1 eV	0.73	1.34	0.22	0.17
Q_s /e	0.58	0.67	0.86	1.08
Q_p /e	1.18	0.87	1.58	2.48
Q_d /e	2.37	8.86	—	—
Q_{s+p+d} /e	4.13	10.22	2.44	3.56
R /a.u.	3.36	2.55	1.97	1.94

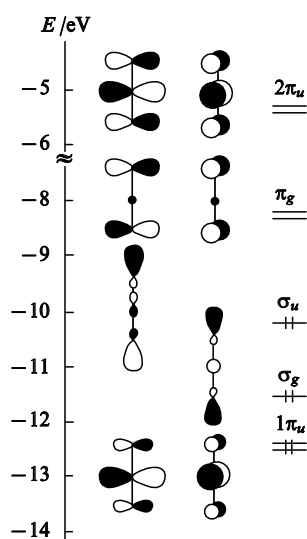
The nature of chemical bonding in IBC has not been analysed in detail.^{50, 59, 64, 68, 70–73} Certain qualitative conclusions on the dominance of one or another type of interaction were based on the energy distributions of the local densities of states (LDOS) considered in Refs 75 and 76.

IV. Chemical bonding in intermetallic borocarbides

The nature of the formation of chemical bonds in IBC and the role of particular atoms and atomic groups were considered by Zeng *et al.*⁷³ and Halet.⁷⁷ The main attention was given to calculations of the indices of local interatomic interactions such as the overlap integrals (OI) of effective atomic orbitals.

A semiquantitative analysis of chemical bonding for $\text{LuNi}_2\text{B}_2\text{C}$ was performed by Halet⁷⁷ in the framework of the tight-binding method,^{78, 79} which is the energy-band version of the extended Hückel method.

The molecular orbital (MO) diagram of the isolated B_2C^{2-} group (Fig. 7) illustrates the character of the interaction between the boron and carbon atoms, which form the corresponding sublattices in IBC. Hybridisation of $2s$ and $2p$ atomic orbitals (AOs) of the B and C atoms results in the formation of six σ -type MOs, two of which are bonding, two are nonbonding (σ_g and σ_u), and two are of pronounced antibonding nature. In addition, the MO system includes degenerate π -type orbitals corresponding to bonding ($1\pi_u$), nonbonding (π_g), and antibonding ($2\pi_u$) interactions of the p - p states.

**Figure 7.** The molecular orbital (MO) diagram of $(\text{B}_2\text{C})^{2-}$ group for an IBC with the BCT structure of the ThCr_2Si_2 type.

The energy interval (the ‘forbidden gap’) between the highest nonbonding (π_g) and the lowest antibonding ($2\pi_u$) MO depends⁷⁷ on the formal charge ascribed to the B_2C group and diminishes sharply on going from $(\text{B}_2\text{C})^{3-}$ to $(\text{B}_2\text{C})^{2-}$. The subsequent decrease in the ‘forbidden gap’, which is absent in a real IBC material, is associated with the formation of metal–nonmetal covalent interactions.

Numerical estimates of OI and effective atomic charges (q_{ef}) are listed in Table 4. Interactions of a complex, ionic-covalent type, which differ considerably for particular intervals of the energy spectrum, have been found in IBC. In particular, the hybridised σ -bonding $\text{Ni}-\text{B}_2\text{C}$ states and the nonbonding (π_g and σ_u) states of the B_2C group with admixture of the antibonding π states of $\text{Lu}-\text{C}$ participate in the formation of states near the Fermi level.

Table 4. Overlap integrals (OI) and effective charges (q_{ef}) of the atoms and groups in $\text{LuNi}_2\text{B}_2\text{C}$.

Atomic pair	OI /e	Atom, group	q_{ef} /e
Ni–Ni	0.138	Lu	+1.48
Ni–B	0.304	Ni	–0.50
B–C	1.023	B	+0.35
Lu–B	0.072	C	–1.18
Lu–C	0.157	B_2C	–0.48

Zeng *et al.*⁷³ discussed the nature of the formation of individual interatomic bonds in $\text{YNi}_2\text{B}_2\text{C}$ using the discrete variational^{80–82} embedded-cluster approach in the framework of the local electron density functional. According to this model, the interaction between the chosen 71-atomic fragment $[\text{Y}_{12}\text{Ni}_{15}\text{B}_{32}\text{C}_{12}]$ with D_{2d} symmetry and the crystalline environment was calculated using a scheme developed by Ellis and co-workers.^{83–85} The von Barth–Hedin exchange-correlation potential⁸⁶ was used, and the numerical basis set included the following AOs: $4s$, $4p$, $4d$, $5s$, and $5p$ of Y; $3s$, $3p$, $3d$, $4s$, and $4p$ of Ni; and $1s$, $2s$, and $2p$ of B and C.

The AO populations and OIs for this cluster in the $\text{YNi}_2\text{B}_2\text{C}$ structure are listed in Table 5. According to these data, the metal and nonmetal atoms in $\text{YNi}_2\text{B}_2\text{C}$ are in the cationic and anionic states, respectively, while the largest charge transfer is believed to occur in the plane nets from Y to C. As to the covalent component of the bond, the pair B–C bonds appear to be the most populated, as in $\text{LuNi}_2\text{B}_2\text{C}$. The Ni–B bonds are much less populated, whereas the Y–C interactions should be considered to be antibonding ones. It is clearly seen on the contour plots of the electron density distribution $\rho(r)$ ⁷³ that the electron density is concentrated along the lines of the Ni–Ni bonds (in the xy plane), that the bonding states are formed between the atomic Ni and Y layers, and that the interactions of the Ni– B_2C type arise in the yz plane.

Table 5. Orbital populations, effective atomic charges, and overlap integrals for the 71-atomic cluster in the structure of $\text{YNi}_2\text{B}_2\text{C}$ according to discrete variational calculations.

Atom	Orbital population			q_{ef}	Type of the bond	OI
	d	s	p			
Ni(1) ^a	9.06(3d)	0.38(4s)	0.52(4p)	+0.11	Ni(1)–B	0.64
Ni(2) ^b	9.11(3d)	0.41(4s)	0.39(4p)	+0.16	Ni(2)–B	0.66
Y	0.54(4d)	0.06(5s)	0.05(5p)	+2.49	Y–C	–0.18 ^c
B		0.82(2s)	2.53(2p)	–0.35	B–C	1.14
C		1.40(2s)	4.35(2p)	–1.75		

^a The central nickel atom in the cluster. ^b Peripheral nickel atoms in the cluster. ^c The ‘minus’ sign corresponds to antibonding.

V. The effect of the composition of metal and metalloid sublattices on the energy band structure of the $\text{LnM}_2\text{B}_2\text{C}$ phases and their solid solutions

The study of the effect of the composition of metal and metalloid sublattices on the electronic energy spectra of IBC became a natural continuation of investigations into determination of the energy band structure of $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{YNi}_2\text{B}_2\text{C}$, where either a complete replacement of one or several types of ions were by ions of another type was performed or a variable concentration of possible impurities was considered in the framework of the initial BCT structure.

1. Phases of composition $\text{LnM}_2\text{B}_2\text{C}$ ($\text{M} = \text{Co}, \text{Cu}, \text{Pd}$, and Pt)

Mattheiss and co-workers⁶⁴ performed LAPW calculations of the EES for a series of BCT intermetallic borocarbides of composition $\text{LnNi}_2\text{B}_2\text{C}$ ($\text{Ln} = \text{La}, \text{Pr}, \text{Pm}, \dots, \text{Tm}, \text{and Lu}$). The energy band structures of these IBC appeared to be similar to those of $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{YNi}_2\text{B}_2\text{C}$ discussed above. For all the phases under study, the valence band (of width ~ 14 eV) contains 18 filled energy bands, including 10 $\text{Ni}3d$ bands. The latter can be arbitrarily combined into two subbands located immediately near and below the Fermi level. Figure 8 presents the band structure of $\text{LaNi}_2\text{B}_2\text{C}$ as an example. For this phase, the free $4f$ states are localised $\sim 3\text{--}4$ eV higher than E_F .

Special emphasis was placed by Mattheiss and co-workers⁶⁴ on the dispersion of the sp band (Γ_{2-} , indicated by the solid line in Fig. 8) near the Fermi level depending on the specific features of the structure of the individual phases, in particular, on the geometry of the NiB_4 tetrahedra. Calculations (in accordance with the experimental data discussed above) show that the lattice constants a and c in the $\text{LnNi}_2\text{B}_2\text{C}$ series change in different manner. A progressive distortion of the NiB_4 tetrahedra occurs

with increase in radius of the lanthanide atom. Thus, the bond angles α change from 108.7° (Lu) to 102.1° (La), which results in the sharp (by ~ 2 eV at the Γ point, see Fig. 8) change in the energetics and dispersion of the sp band and in a decrease in its contribution to the Brillouin zone and the degree of its filling. In turn, this affects the energy and character of filling of the $\text{Ni}3d$ band (along the $\Gamma-X$ direction).

Mattheiss and co-workers⁶⁴ argue that these distinctions in subtle features of the energy distribution of the bands near the Fermi level are determined not by the type of the rearrangement of interatomic interactions resulting from the $\text{La} \rightarrow \text{Lu}$ substitution, but first and foremost by the structural factor, namely, by the degree of distortion of the NiB_4 tetrahedra, which increases with the lanthanide ionic radius. A trial calculation has been performed for a hypothetical 'ideal' compound $\text{LaNi}_2\text{B}_2\text{C}$ containing layers formed by regular NiB_4 tetrahedra ($\alpha = 109.5^\circ$, $d(\text{Ni}-\text{B}) = 2.33$ Å). Its band structure appeared to be close to that of $\text{LuNi}_2\text{B}_2\text{C}$ ($\alpha = 108.5^\circ$, $d(\text{Ni}-\text{B}) = 2.11$ Å). The $N(E_F)$ value for the 'ideal' $\text{LaNi}_2\text{B}_2\text{C}$ increases substantially (by $\sim 90\%$), thus approaching the $N(E_F)$ value for superconducting $\text{LuNi}_2\text{B}_2\text{C}$. It has been assumed⁶⁴ that the degree of distortion of the NiB_4 tetrahedra in the $\text{LnNi}_2\text{B}_2\text{C}$ phases as well as that of MB_4 tetrahedra ($\text{M} = \text{Pt}, \text{Pb}, \text{Ru}, \text{and Ir}$) in other known IBC can be deliberately controlled by using high-pressure techniques. In this case, the experiments on the hydrostatic or axial compression of IBC can result in revealing nontrivial T_c dependences on the lattice parameters for each particular material.

A comparative analysis of the energy band structure of $\text{LuNi}_2\text{B}_2\text{C}$ and $\text{LaPt}_2\text{B}_2\text{C}$ was carried out by Singh.⁸⁷ The energy spectra of these compounds calculated by the LAPW method were found to be similar. The distribution of the near-Fermi states has a pronounced 3D character and is close to an isotropic one, which means that the superconductivity of $\text{LaPt}_2\text{B}_2\text{C}$ ($T_c \simeq 11$ K)⁴⁰ can be considered in the framework of conventional Bardeen–Cooper–Schrieffer (BCS) mechanism by the analogy, for instance, with transition metal B1 carbides and nitrides.^{88,89} The main specific features of the energy spectrum of $\text{LaPt}_2\text{B}_2\text{C}$ are associated with the position of the flat $\Gamma(110)$ band about 0.4 eV above the Fermi level. We remember that the corresponding band in $\text{LuNi}_2\text{B}_2\text{C}$ is in the immediate vicinity of the Fermi level and crosses it. As a result, the DOS maximum of the near-Fermi bands for $\text{LaPt}_2\text{B}_2\text{C}$ appears to be shifted toward the region of unfilled states. This leads to an appreciable decrease in $N(E_F)$ for $\text{LaPt}_2\text{B}_2\text{C}$ as compared to that for $\text{LuNi}_2\text{B}_2\text{C}$ despite the fact that the contributions of the d states of Ni and Pt to $N(E_F)$ for both phases are comparable in magnitude. Singh⁸⁷ explained the distinctions indicated above by the increase in the width of the $\text{Pt}5d$ band (as compared to the $\text{Ni}3d$ band) due to enhanced hybridisation of the platinum d states with metalloids (increased splitting of d states), which, in turn, is determined by greater extension of the d orbitals of Pt and La compared to those of Ni and Lu, respectively. Using the concepts of a relationship between T_c and $N(E_F)$ and the rigid band model,^{4,88,89} Singh⁸⁷ assumed that an increase in the concentration of valence electrons (CVE), for instance, due to partial substitution of carbon atoms by those of more electronegative metalloids or the introduction of another 'electron donor' will have a favourable effect on the change of T_c of $\text{LaPt}_2\text{B}_2\text{C}$. For this phase, the optimum concentration of the 'excess' electrons, at which E_F coincides with the DOS maximum, is equal to ~ 1.2 electrons per cell.⁸⁷

Coehoorn⁷⁰ performed a detailed analysis of the composition of energy bands near the Fermi level for yet another representative of BCT borocarbides, *viz.*, $\text{YPd}_2\text{B}_2\text{C}$, using the scalar relativistic version⁶⁹ of the augmented spherical waves (ASW) method. It was found for this compound that E_F coincides with the local DOS peak $N(E_F) = 3.26$ eV⁻¹ and the maximum contributions to $N(E_F)$ come from $\text{Pd}4d$ and $\text{Y}4d$ states (Table 6), as in nickel-containing Y and Lu borocarbides. It can be seen from the data in Table 6 that an appreciable filling of $d_{xz,yz}$ and d_{xy} orbitals occurs for yttrium and palladium, respectively. In the bulk of the crystal,

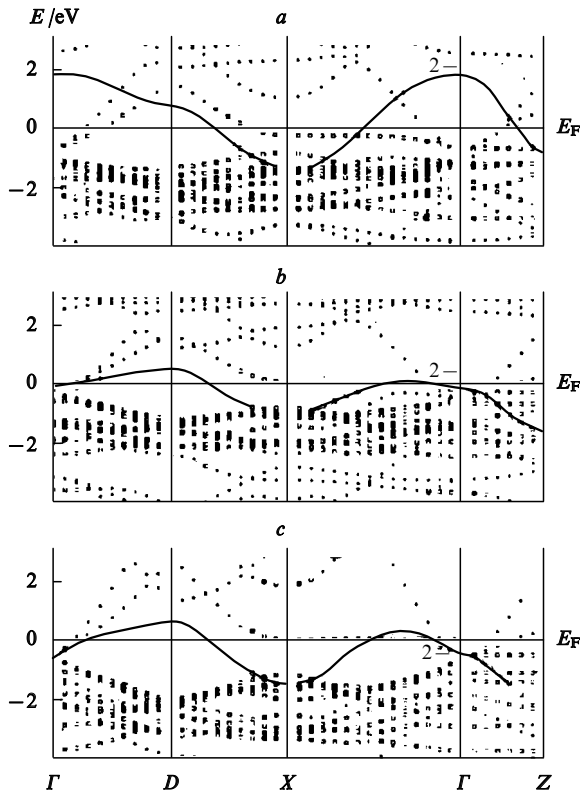


Figure 8. Dispersion of energy bands near the Fermi level for $\text{LaNi}_2\text{B}_2\text{C}$ (a), 'ideal' $\text{LaNi}_2\text{B}_2\text{C}$ (b), and $\text{LuNi}_2\text{B}_2\text{C}$ (c).

The band of nonmetal sp states near the Fermi level is indicated by solid line.

Table 6. Occupation numbers (state per 1 eV) of valence orbitals in the region $-0.2 \leq E_F \leq 0.2$ eV for $\text{YPd}_2\text{B}_2\text{C}$; calculations by the ASW method.

Atom	Occupation numbers							
	s	p_x, p_y	p_z	d_{xy}	$d_{xz, yz}$	$d_{3x^2-y^2}$	$d_{x^2-y^2}$	total value
Y	0.02	0.01	0.05	0.09	0.26	0.09	0.15	0.67
Pd	0.03	0.08	0.31	0.19	0.15	0.13	0.14	1.03
B	0.06	0.07	0.13	0.00	0.00	0.00	0.00	0.26
C	0.02	0.07	0.10	0.00	0.00	0.00	0.00	0.19

the Y atoms occupy the centre of the unit cell, the Pd atoms occupy positions $(0, 1/2, 1/4)$ and $(1/2, 0, 1/4)$; one of the ‘blades’ of the Y $d_{xz, yz}$ AOs is oriented along the Y–Pd bond, whereas the Pd $4d_{xy}$ AOs are directed towards neighbouring Pd atoms. Considerable concentration of these states near E_F is due to their splitting into bonding and antibonding ones as a result of interatomic (and interlayer) interactions. This splitting is an additional indication of the 3D nature of the electron distributions in BCT intermetallic borocarbides.

Coehoorn⁷⁰ was the first who attempted to take into account the role of the magnetic order in the formation of energy spectra of IBC in ASW calculations of ferromagnetic $\text{GdNi}_2\text{B}_2\text{C}$. The major effect was the splitting of the DOS peak near the Fermi level by ~ 0.2 eV due to the direct intraatomic $4f$ – $5d$ exchange interaction on Gd atoms. In the first approximation, the exchange splitting for all ferromagnetic compounds $\text{LnNi}_2\text{B}_2\text{C}$ is assumed to be proportional to the local magnetic moment. Then, the magnitude of this splitting for each Ln atom will be much larger than the width of the superconducting energy gap, which can be estimated as $\Delta E \approx 0.05$ eV for $\text{LnNi}_2\text{B}_2\text{C}$ in the framework of the BCS theory; this indicates that the superconductivity is only possible in the case of antiferromagnetic spin ordering.

With the aim of elucidating the tendencies in the filling of the near-Fermi states, Coehoorn⁷⁰ calculated hypothetical ideal BCT crystals $\text{LuCo}_2\text{B}_2\text{C}$, $\text{LuCu}_2\text{B}_2\text{C}$, and $\text{LuCo}_2\text{B}_2\text{B}$; the interatomic distances in the above compounds were assumed to be identical and equal to those for $\text{LuNi}_2\text{B}_2\text{C}$ ($a = 3.4639$ Å and $c = 10.6313$ Å). It was concluded on the basis of calculations that the rigid band model will give reasonable results for the description of $N(E_F)$ changes in the case of chemical modification of IBC composition.⁷⁰

2. Phases of composition $\text{YNi}_2\text{B}_2\text{X}$ ($\text{X} = \text{B}, \text{C}, \text{N}$, and O)

The effect of variable concentration of the valence electrons on the filling of the near-Fermi states and the position of the Fermi level for BCT intermetallic borocarbides due to substitution of carbon atoms by other atoms was considered using $\text{YNi}_2\text{B}_2\text{X}$ as an example. Calculations of hypothetical $\text{YNi}_2\text{B}_2\text{B}$, $\text{YNi}_2\text{B}_2\text{N}$, and $\text{YNi}_2\text{B}_2\text{O}$ phases were carried out by the LMTO method.

It was established⁷¹ that the structure of valence bands is strongly dependent on the composition of the X sublattice. The binding energies of quasi-core $\text{X}2s$ bands increase in the series $\text{B} < \text{C} < \text{N} < \text{O}$ and are equal to 10, 13, 17, and 21 eV, respectively. The $\text{X}2p$ -like subbands fall into a similar sequence on the energy scale. Lee *et al.*⁷¹ paid the major attention to the relative position of E_F and the DOS maximum near the Fermi level. It was shown that the position of the Fermi level for $\text{X} = \text{B}$ is lower, whereas that for ‘boron oxide’ and, especially, for ‘boronitride’ is higher than the maximum of the DOS peak. The obtained estimates of $N(E_F)$ for $\text{YNi}_2\text{B}_2\text{X}$ are 1.7, 4.40, 2.8, and 1.0 states per eV for $\text{X} = \text{B}, \text{C}, \text{N}$, and O , respectively. Lee *et al.*⁷¹ believe that this indicates the maximum superconductivity of the borocarbide.

Naturally, the assumptions accepted⁷¹ (first of all, the identity of the lattice parameters for all phases) make it possible to consider the results obtained as purely qualitative ones, especially with account of the data on the substantial role of B–C interactions in the formation of the crystal structure of IBC (see

above). Obviously, the formulation of the problem of simulation of the effect of doping the nonmetal IBC sublattice on their energy band structure and, all the more, on their properties requires performing correct calculations of the energy parameters for substitution processes of such kind, estimates of the stability of solid solutions formed, and direct calculations of the values of their lattice constants.

3. Substitution solid solutions of composition $\text{Y}(\text{Ni}_{1-x}\text{M}_x)_2\text{B}_2\text{C}$ ($\text{M} = \text{Fe}, \text{Co}, \text{Ru}$)

Specific features of the electronic structure of the ‘ideal’ quaternary BCT $\text{LnM}_2\text{B}_2\text{X}$ phases depending on the composition of their sublattices were considered above. Corresponding sites in such sublattices were occupied by atoms of rare-earth or transition metals, or by $2p$ atoms of the same sort.

A much more subtle effect on the properties of IBC can be exerted in the case of partial substitution of the atoms of a sublattice by ‘related’ atoms of another sort with the formation of quinary (and more complex) substitution solid solutions.

The first calculations of similar systems were carried out by Zeng *et al.*⁷³ in 1996 in the framework of the embedded-cluster approach. Before turning our attention to the results of these calculations, let us briefly consider experimental studies of the properties of the solid solutions mentioned above, in which the parameters of electronic spectra of multicomponent alloys are discussed.

It has been shown in the first numerical calculations of IBC that the d states of transition-metal atom play the determining role in the formation of the near-Fermi band, whereas the DOS of the conduction electrons genetically related to the rare-earth ions is rather low. Hence, the doping effects of a transition-metal sublattice will be the most ‘impressive’; for this reason, fairly well studied $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LuNi}_2\text{B}_2\text{C}$ phases were mainly used as matrices and $3d$ and $4d$ transition metals (Co, Cu, Fe, Rh, Pd, *etc.*) were used as dopants.

Schmidt and co-workers⁹⁰ have synthesised single-phase specimens of $\text{Y}(\text{Ni}_{1-x}\text{Co}_x)_2\text{B}_2\text{C}$ ($0 \leq x \leq 1$) and studied the T_c dependences of these alloys on the concentration of impurity (Co). It was established that a sharp decrease in T_c (from ~ 15 K for the original $\text{YNi}_2\text{B}_2\text{C}$ to ~ 1.2 K for $x \approx 0.2$) occurs with an increase in x . Coehoorn⁷⁰ and Lee *et al.*⁷¹ explained this effect qualitatively within the framework of the rigid band model taking into account the results of band calculations for the matrix, where a decrease in CVE upon introduction of cobalt will induce a decrease in $N(E_F)$.

Another interpretation can be given from the viewpoint of Kaiser’s theory of nonmagnetic resonance states.⁹¹ According to this theory, the change in T_c should be correlated with the resonance scattering of the conduction electrons and Coulomb interaction between localised d states. In this case, the dependence of T_c on the concentration of impurity (x) can be written as follows:⁹²

$$T_c(x) = T_c(0) \exp\left(-\frac{Ax}{1-Bx}\right),$$

where coefficients A and B are functions of the LDOS at the Fermi level for the matrix and impurity [$N_{\text{im}}(E_F)$], respectively, of the parameter of the electron–phonon interaction λ , and effective interatomic Coulomb repulsion U_{ef} . The experimental dependence of T_c can be reproduced if $U_{\text{ef}} = 0.09$ eV, $N_{\text{im}}(E_F) = 11.8$ states per eV atom spin, and the ‘critical’ concentration of impurity (20%) can be found taking $N_{\text{im}}(E_F) = 0.2$ states per eV atom spin and $\lambda = 2.6$ (see Ref. 59). The values of $N(E_F)$ and λ are close in order of magnitude to those of mixed $\text{Lu}_2(\text{Fe}_{1-x}\text{Co}_x)\text{Si}_5$ alloys.⁹³

The effect of Ni substitution by Co and Cu on T_c of $\text{Y}(\text{Ni}_{1-x}\text{M}_x)_2\text{B}_2\text{C}$ was studied by Goldman *et al.*¹⁸ The specimens synthesised contained $\sim 95\%$ of a BCT phase with small amounts of Y_5C_6 , YB_2C_2 , YNi_2 , and Ni_3C . It has been noted that copper possessed limited solubility in the original borocarbide. The lattice parameters (the initial values $a = 3.526$ Å and $c = 10.538$ Å coincide with those found by Schmidt *et al.*⁹⁴ and

Chakoumakos *et al.*⁹⁵) increase or decrease as copper and cobalt, respectively, are introduced as dopants into $\text{YNi}_2\text{B}_2\text{C}$.

The introduction of Co or Cu into $\text{YNi}_2\text{B}_2\text{C}$ results in a decrease in T_c , the effect being more pronounced for Co ($dT_c/dx = -45$ K for Co and $dT_c/dx = -19$ K for Cu in the region $x \leq 0.2$). At high concentrations of dopants the dependence of T_c is affected by multiphase composition of the specimens synthesised.

Several possible reasons for such a strong difference in the dopant effect on T_c of the alloys have been considered, *viz.*, the presence of carbon vacancies; local magnetism of cobalt ions; 'asymmetry' of the shape of the near-Fermi $N(E)$ peak of the matrix, and, finally, the role of the electron–phonon interaction. The assumption of an appreciable concentration of carbon vacancies was based on the presence of a stable boride YCo_2B_2 phase (see Ref. 96). In this case, the number of carbon defects in $\text{Y}(\text{Ni}_{1-x}\text{Co}_x)_2\text{B}_2\text{C}$ must increase with temperature, and the lattice constants should be appropriately changed. However, annealing of borocarbide specimens did not result in noticeable changes in a and c .

The increased dT_c/dx value for Co can be due to its magnetic properties; however, special experiments^{16,90} indicate a nonmagnetic behaviour of Co. Therefore, a relationship between the $T_c(x)$ dependence and the parameters of its electronic spectrum and/or electron–phonon interaction is most probable.

As to the role of the electron states, it should be noted that according to calculations,^{70–72} the E_F value for $\text{YNi}_2\text{B}_2\text{C}$ coincides with the LDOS maximum, *i.e.*, the introduction of either Co or Cu will shift the E_F value along the energy scale favouring an increase in $N(E_F)$ and, correspondingly, suppression of superconductivity. However, the sharp (more than twofold) difference in the effect of Co and Cu impurities on T_c cannot be explained in this case. An attempt to explain the observed effect by the change in the constant of the electron–phonon interaction (λ) cannot be considered as sound, since in this case the 'loosening' of the crystal structure upon introduction of Cu (the increase in the lattice parameters of the solid solution) will determine the increase in λ , whereas the cobalt impurity will have an opposite effect on λ .

Despite the contradictions mentioned above, the experiment confirms directly the principal results of calculations,^{70–72} namely, that E_F coincides with the DOS maximum, which indicates that any attempts to 'chemically modify' the borocarbide composition aimed at increasing its superconducting characteristics¹⁸ are not promising.

Gangopadhyay *et al.*³⁴ and Hoellworth *et al.*⁹⁷ discussed the changes in $N(E_F)$ and the role of the electron–phonon interaction in the formation of superconducting properties of $\text{YNi}_{2-x}(\text{Co}, \text{Cu})_2\text{B}_2\text{C}$ alloys taking into account the results of experimental investigations of magnetic susceptibility (χ)

$$\chi = \chi_P + \chi_L + \chi_{VV} + \chi_c + \chi_i = \chi_{\text{intr}} + \chi_{\text{imp}}, \quad (1)$$

where χ_P , χ_L , χ_{VV} , and χ_c are the Pauli paramagnetic, diamagnetic (of conduction electrons), van Vleck, and diamagnetic (of core electrons) contributions, respectively; χ_i is the contribution of paramagnetic impurities; and χ_{intr} and χ_{imp} are the intrinsic and impurity susceptibilities, respectively.

Gangopadhyay *et al.*³⁴ discussed the role of χ_{intr} and χ_{imp} for $\text{YNi}_2\text{B}_2\text{C}$ doped with cobalt and copper. Assuming that χ_{intr} is independent of temperature and χ_{imp} obeys the Curie–Weiss law, one can write

$$\chi(T) = \chi_{\text{intr}} + \frac{C}{T - T_K}. \quad (2)$$

It turned out that this dependence is valid for a narrow temperature range (see also Refs 97, 98) and appreciably decreases as temperature increases. Similar $\chi(T)$ dependences were also found in the studies of poly- and mono-crystalline specimens of $\text{YNi}_2\text{B}_2\text{C}$.^{99,100}

Assuming that the contributions of the orbital paramagnetism and atomic core diamagnetism are constant, the observed³⁴ $\chi(T)$

dependence can be explained first of all by temperature changes in the Pauli paramagnetism of the conduction electrons χ_P resulting from either rearrangement of the band spectrum or spin fluctuations.^{99,100} The presence of antiferromagnetic spin fluctuations was postulated^{101,102} for $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LuNi}_2\text{B}_2\text{C}$ to account for abnormal temperature dependences of ^{11}B spin-lattice relaxation times and the Knight shift. In a more recent study,¹⁰⁰ the temperature dependence of the magnitude and the sign of χ_P has been interpreted on the basis of the electronic energy spectrum. The results of the experiments on neutron scattering,²¹ NMR,¹⁰⁰ spin relaxation,¹⁰³ and heat capacity¹⁰⁴ also provide no information on spin fluctuations for $\text{YNi}_2\text{B}_2\text{C}$.

The dependence of T_c on the effective DOS calculated for $\text{YNi}_{2-x}(\text{Co}, \text{Cu})_2\text{B}_2\text{C}$ solid solutions from experimental data using the following equation

$$\begin{aligned} \chi_P &= N_A \mu_B^2 S N(E_F) = \\ &= 0.3233 \cdot 10^{-4} S N(E_F) \text{ (states per 1 eV per formula unit),} \end{aligned} \quad (3)$$

where N_A is the Avogadro constant, μ_B is the Bohr magneton, and S is the Stoner parameter, is shown in Fig. 9.

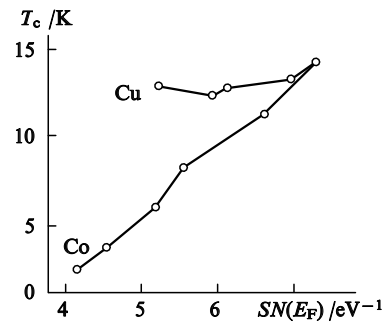


Figure 9. Correlation dependence of T_c on the reduced DOS at the Fermi level $[SN(E_F)]$ for solid solutions $\text{YNi}_{2-x}(\text{Co}, \text{Cu})_2\text{B}_2\text{C}$.

Thus, the reconstructed $T_c[SN(E_F)]$ dependences for Co and Cu impurities are substantially different. The only possible rationale for this fact can be relative strengthening of the electron–phonon interaction in alloys with the $\text{Cu} \rightarrow \text{Ni}$ type of substitution. The results of the investigation of the effect of the uniform compression on T_c for the systems in question¹⁰⁵ can be considered as indirect evidence in favour of the participation of both the electronic and electron-phonon mechanisms in the formation of superconducting properties of intermetallic borocarbides.

The effect of other impurities (Fe, Co, Ru, and Pd) on the superconducting properties of $\text{YNi}_2\text{B}_2\text{C}$ has been considered by Bud'ko *et al.*³² Linear suppression of the superconductivity effect with an increase in x was found in all cases. The data of Mössbauer spectroscopy and experiments on the magnetic susceptibility show that the dopants in the bulk of the initial phase have no local magnetic moments and their effect on the magnitude of the superconducting gap and thermodynamic properties is of local character.¹⁰⁶ Then T_c will be mostly affected by the $N(E_F)$ value, for which the change rate is proportional to the difference between the number of the valence electrons (z) of nickel and that of a substituting element.

Studies of the effects of sublattice doping on the electronic properties of IBC carried out by numerical quantum-chemical methods were started taking the $\text{Y}(\text{Ni}_{1-x}\text{M}_x)_2\text{B}_2\text{C}$ ($\text{M} = \text{Fe}, \text{Co}$, and Ru) solid solutions as an example.⁷³ Solid solutions with two different impurity concentrations ($x = 0.07$ and 0.47) approximated in the framework of the cluster approach by 71-atomic $\text{Y}_{12}(\text{Ni}_x\text{M}_{1-x})_{15}\text{B}_{32}\text{C}_{12}$ fragments with D_{2d} symmetry have been analysed.

The 'cluster' densities of the d states of Ni and substituting elements (Fe, Co, and Ru) in the $\text{Y}(\text{Ni}_{1-x}\text{M}_x)_2\text{B}_2\text{C}$ alloys for

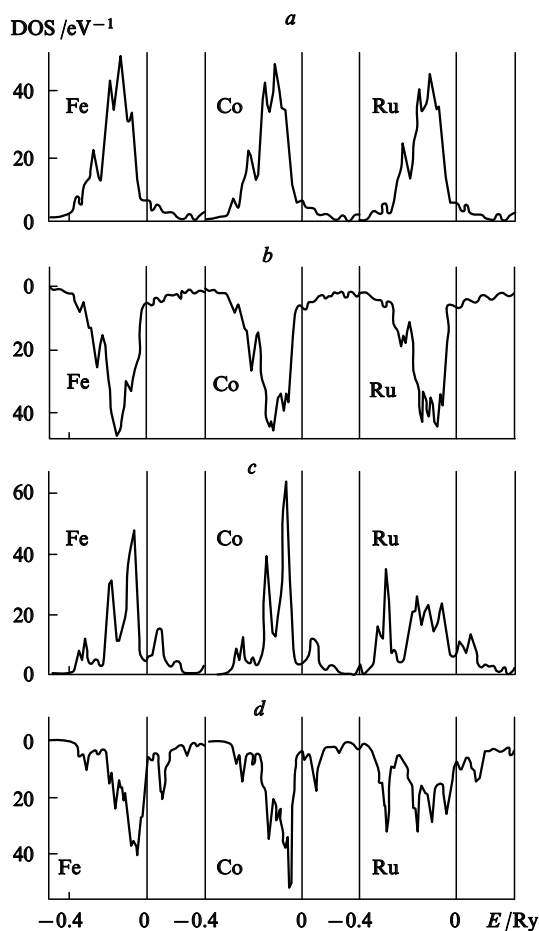


Figure 10. The ‘cluster’ densities of states for Ni (*a, b*) and substituting elements (*M* = Fe, Co, and Ru) (*c, d*) in $Y(Ni_{1-x}M_x)_2B_2C$ alloys for $x = 0.07$ (*a, c*) and 0.47 (*b, d*).

$x = 0.07$ and 0.47 are shown in Fig. 10 and the electronic configurations and atomic charges are listed in Table 7.

As should be expected from the rigid band model, doping the matrix with the *d* elements mentioned should decrease the E_F value and result in partial ‘devastation’ of the near-Fermi $Ni3d$ states with the corresponding reduction of their populations. However, the populations of the $Ni3d$ orbitals remain virtually unchanged, whereas the corresponding cluster LDOS become somewhat broadened. The local densities of states for Ni and dopants differ substantially. Thus, the high-energy region of the subband of *d* states for Fe and Co is vacant. In contrast to $3d$ impurities, the $Ru4d$ states form a broad diffuse subband for all ruthenium concentrations. A low-energy peak (with an energy at the maximum of about -0.4 Ry) corresponding to localised $Ru-B$ bonds in the NiB_4 tetrahedra and a three-peak structure of delocalised states can be seen on the LDOS profile. Additionally, one more LDOS peak appears at the Fermi level. A change in the effective charge of the Ni atoms occurs in the $Y(Ni_{1-x}M_x)_2B_2C$ alloys (Table 7); it is primarily due to breaking down the symmetry of the crystalline environment of these sites upon introduction of dopants and to the change in the population of the extended $4s$ and $4p$ orbitals of nickel.

It is of interest to follow the change in the extent of overlap of the wave functions for individual atoms (the covalent component of the bond) upon doping of YNi_2B_2C . The corresponding bond populations are listed in Table 8. The $B-C$ interaction, which is the strongest in the original crystal, becomes weakened by $\sim 1\% - 4\%$ upon introduction of impurities. The antibonding $Y-C$ state remains almost unchanged, being localised in the plane nets. The $N-B$ bond order is constant in the presence of Fe

Table 7. Mulliken populations of valence orbitals and effective atomic charges in $Y(Ni_{1-x}M_x)_2B_2C$ substitution alloys.

Atom	Orbital population			q_{ef}
	d	s	p	
YNi ₂ B ₂ C				
Ni(1) ^a	0.06	0.38	0.52	+ 0.11
B	—	0.82	2.53	− 0.35
Ni(2) ^b	2.11	0.41	0.39	+ 0.16
Y	0.54	0.06	0.05	+ 2.49
C	—	1.40	4.35	− 1.75
Y(Ni _{1−x} Co _x) ₂ B ₂ C				
Co	8.23	0.33	0.46	+0.05
	8.24	0.33	0.49	0.02
B	—	0.81	2.53	−0.34
		0.81	2.52	−0.33
Ni	9.10	0.41	0.39	+0.17
	9.10	0.42	0.38	0.16
Y	0.54	0.06	0.05	+2.49
	0.54	0.06	0.05	+2.49
C	—	1.40	4.35	−1.75
		1.39	4.36	−1.75
Y(Ni _{1−x} Fe _x) ₂ B ₂ C				
Fe	7.28	0.31	0.45	+0.06
	7.35	0.30	0.41	−0.04
B	—	0.81	2.55	−0.36
		0.80	2.52	−0.32
Ni	9.10	0.41	0.39	+0.17
	9.11	0.42	0.38	+0.16
Y	0.54	0.06	0.05	+2.49
	0.54	0.06	0.05	+2.49
C	—	1.40	4.34	−1.74
		1.40	4.36	−1.76
Y(Ni _{1−x} Ru _x) ₂ B ₂ C				
Ru	7.48	0.25	0.43	+0.10
	7.50	0.24	0.38	0.12
B	—	0.78	2.57	−0.36
		0.75	2.60	−0.34
Ni	9.10	0.41	0.40	+0.16
	9.07	0.43	0.43	+0.13
Y	0.55	0.07	0.05	+2.48
	0.56	0.07	0.06	+2.47
C	—	1.40	4.34	−1.74
		1.39	4.35	−1.74

Note. The values for the atoms of $Y(Ni_{1-x}M_x)_2B_2C$ alloys for $x = 0.07$ and 0.47 are given above and below the line, respectively. ^a The central nickel atom in the cluster. ^b Peripheral nickel atoms in the cluster.

and Co; however, it decreases (by $\sim 3\%$) upon introduction of Ru. The overlap integrals for $M-B$ bonds are larger than those for the $Ni-B$ bond.

The considered processes of rearrangement of the electron states in doped borocarbide alloys are illustrated by the contour plots of the difference charge density.⁷³ These contour plots show that both the covalent $B-C$ bond and the charges on the yttrium atoms weakly ‘respond’ to the change in the composition of the *M* sublattice. The major effects of the electron density perturbation are localised near the substitution centre (in the bulk of the MB_4 tetrahedron). On the whole, the calculations⁷³ make it possible to interpret the chemical bonding in the $Y(Ni_{1-x}M_x)_2B_2C$ solid solutions as a combination of covalent-ionic-metallic interatomic

Table 8. Bond populations (e) in $Y(Ni_{1-x}M_x)_2B_2C$ solid solutions ($M = Fe, Co, \text{ and } Ru$) according to discrete variational embedded-cluster calculations.

Composition, bond	YNi_2B_2C	$Y(Ni_{1-x}Fe_x)_2B_2C$	$Y(Ni_{1-x}Co_x)_2B_2C$	$Y(Ni_{1-x}Ru_x)_2B_2C$
x	0	0.07	0.47	0.07
Ni—B	0.64	0.64	0.62	0.62
Y—C ^a	−0.18	−0.18	−0.18	−0.18
B—C	1.14	1.12	1.13	1.09
M—C	0.66	0.72	0.72	0.68

^a The negative value corresponds to antibonding of the Y—C bond.

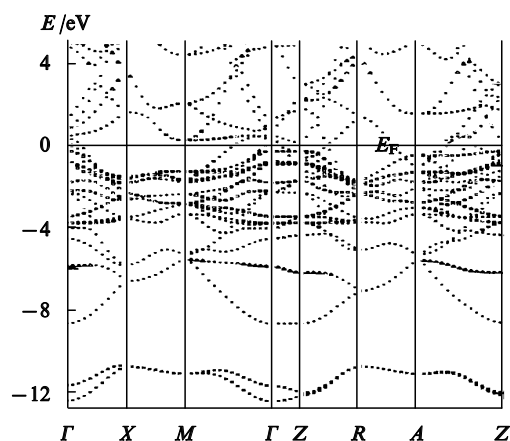
interactions with a substantial spatial anisotropy, where the Y—C interaction in the plane nets and the interaction in M—B layers result from ionic and covalent binding, respectively, and the ‘interlayer’ (YC)—(MB) interactions are due to hybridisation of B and C atomic states. The doping of the M sublattice predominantly modifies the charge states and interspecies bondings in the M—B layers.

It is natural that the applicability of the cluster approach to the correct description of changes in subtle features of the TDOS (especially, near the Fermi surface, *viz.*, in the region of strongly delocalised states), interpretation, and prognosis of superconducting and magnetic properties of multicomponent solid solutions is limited. Band calculations of borocarbide solid solutions of variable composition are needed.

VI. The energy band structure of ‘two-layered’ $LnNiBC$ borocarbides and solid solutions based on them

In addition to the quaternary $LuNiBC$ phase, a series of isostructural solid solutions of variable composition of the general formula $Ln(Ni_{1-x}M_x)BC$ ($Ln = Lu, Y; M = Cu, V$) have been synthesised to date.^{36, 37, 42}

The energy band structure of $LuNiBC$ was calculated by Mattheiss,⁵⁰ Kim,⁶⁸ and Coehoorn.⁷⁰ Let us discuss it in the framework of LAPW calculations.⁵⁰ The character of the $E(k)$ dependence for the near-Fermi bands is the most remarkable when comparing the valence band structures of $LuNi_2B_2C$ (Fig. 3) and $LuNiBC$ (Fig. 11). The flat regions of the $Ni3d$ bands ($G-X$), which virtually coincide with E_F for $LuNi_2B_2C$, appear to be shifted towards higher energies on the energy scale for $LuNiBC$. This results in the formation of the $Ni3d$ resonance in the region of nonbonding states and the DOS at the Fermi level appears to be low ($N(E_F) \sim 1$ electron per cell). The E_F position in the region of the local DOS minimum in the electronic energy spectra of $LuNiBC$ is reproduced in calculations performed by the ASW⁷⁰ and *ab initio* pseudopotential⁶⁸ methods.

**Figure 11.** The band structure of $LuNiBC$.⁵⁰

These peculiarities of the position of the Fermi level in the region of local DOS maximum ($LuNi_2B_2C$) and minimum ($LuNiBC$) are crucial for the explanation of distinctions between the superconducting properties of ‘one-layered’ and ‘two-layered’ IBC having similar crystalline structures and close interatomic distances. If the calculations^{50, 58, 70} of electronic spectrum of $LuNiBC$ are correct, one should expect that the $N(E_F)$ values of solid solutions will be increased as compared to that of an ‘ideal’ crystal (with the corresponding changes in properties) for any change in CVE (for instance, due to the doping of sublattices).

This assumption was tested by Qiu *et al.*^{36, 42} and Gangopadhyay *et al.*³⁷ Thus, YBC , YB_4 , and several other phases were present in the specimens of synthesised $LnNi_{1-x}Cu_xBC$ solid solutions ($Ln = Y, Lu; 0 \leq x < 1$), the amount of tetragonal $YNi_{1-x}Cu_xBC$ phase decreased sharply with an increase in the copper concentration.³⁷ It was thus suggested that compounds $YCuBC$ and $LuCuBC$ are unstable.³⁷ The effect of dopant on the lattice constants of $YNiBC$ ($a = 3.579 \text{ \AA}$, $c = 7.570 \text{ \AA}$) and $LuNiBC$ ($a = 3.495 \text{ \AA}$, $c = 7.663 \text{ \AA}$) is worth noting. The value of parameter a increases most rapidly in the initial stage of doping (up to $x \approx 0.2$), while a linear increase in the parameter c is observed at higher concentrations of copper. The rates of changes in the concentration (c) $d \ln c / dx$ for Y and Lu solid solutions are equal to 0.032 and 0.038, respectively, which is very close to that for $YNi_{2-x}Cu_xB_2C$ ($d \ln c / dx \approx 0.03$).⁴² This indicates a common nature of the observed effect, which can be related to the weakening of covalent M—B interactions upon partial $Cu \rightarrow Ni$ substitution due to the filling of the $Ni3d$ orbitals by an additional electron of copper. The reason for considerable differences in the solubility limits of copper in ‘one-layered’ and ‘two-layered’ IBC, which amount to $\sim 50\% - 60\%$ and 20% , respectively, remain unclear.

An increase in the content of copper results in the increase in T_c of $LnNi_{1-x}Cu_xBC$ solid solutions, the effect for yttrium compounds being more pronounced than that for lutetium compounds. The maximum T_c for $YNiBC$ doped with copper is 8.9 K (at $x > 0.6$) is determined by tetragonal IBC and cannot be ascribed to impurities of other phases [YB_6 ($T_c = 6.0 \text{ K}$), YB_{12} ($T_c = 4.7 \text{ K}$), YC_2 ($T_c = 3.8 \text{ K}$), YB_2C_2 ($T_c = 3.0 \text{ K}$)] found in the specimens.¹⁰⁷ Gangopadhyay *et al.*³⁷ also pointed to the fact that T_c is dependent on the dispersity of the specimens; for instance, annealing of $YNi_{1-x}Cu_xBC$ specimens (for $x > 0.6$) considerably increases their T_c .

Extrapolation of the $T_c(x)$ dependence to $x = 1$, which corresponds to a hypothetical ‘ $YCuBC$ ’, gives $T_c \approx 10 \text{ K}$, which is lower than for ‘ $LuCuBC$ ’. Presumably, the electronic structures of $LuNiBC$ and $YNiBC$ are similar and the $N(E_F)$ value for both compounds must increase upon introduction of copper atoms.

The inverse effect, namely, a decrease in CVE, upon partial substitution of nickel by vanadium in $LuNiBC$, was discussed by Qiu *et al.*³⁶ A series of single-phase $LuNi_{1-x}V_xBC$ solid solutions has been prepared and the solubility limit of vanadium is $x = 0.25$. The temperature dependence of electrical resistance has been measured and it has been found that $T_c(LuNiBC) = 2.96 \text{ K}$ and $T_c(LuNi_{0.8}V_{0.2}BC) = 2.60 \text{ K}$, *i.e.*, $d \ln T_c / dx = -0.5$. Thus, E_F for the matrix does not coincide with the local DOS minimum and the $N(E)$ shape is more complex, since the Fermi level in $LuNiBC$ can be intermediate in energy between the minimum and local

maximum of $N(E)$, hence, $dN(E)/dE > 0$. The study of the effect of external pressure on T_c shows that $dT_c/dP = -0.17 \pm 0.03$ K GPa⁻¹ for both the original and doped IBC. From the viewpoint of the band theory, the effect of external pressure is equivalent either to broadening of the bands (at $E_F = \text{const}$) or to the E_F shift towards the lower-energy region. Hence, if E_F for LuNiBC coincides with the DOS minimum, then the $dN(E_F)/dP$ should be positive for both LuNiBC and LuNi_{1-x}V_xBC. The negative value of dT_c/dP can indicate either a more complex shape of the DOS distribution near E_F than was obtained from the one-electron band calculations or the impossibility to describe the effect of hydrostatic pressure on T_c by a simple correlation with the change in $N(E_F)$.

VII. Electronic structure and some physicochemical properties of intermetallic borocarbides

The nature of IBC is determined by (or is closely related to) their electronic structure and can be rationalised from the viewpoint of theoretical models of EES for intermetallic borocarbides.

1. Superconductivity

The superconductivity of IBC is the property that attracted attention to this class of compounds and gave rise to numerous experimental and theoretical studies. The first calculations of EES of LuNi₂B₂C, LuNiBC, and YNi₂B₂C (see Refs 50, 59, 64, 70, and 71) made it possible to place the IBC with certainty into the class of conventional superconductors with the BCS type of conductivity, to determine specific features of the structure of the near-Fermi energy bands for one- and two-layered IBC, and to relate their conducting properties to specific electron states on the Fermi surface. These concepts are widely used for qualitative interpretation of the results obtained. As has been noted above, the attempts were made to extend them (using the rigid band model) to multicomponent solid solutions. It was assumed, in the simplest case, that $T_c \sim N(E_F)$, which, in turn, is determined by the degree of filling the valence band depending on CVE for the compound of a given composition.

An attempt to find correlations between the parameters of the one-electron energy spectra of solid solutions Y(Ni_{1-x}M_x)₂B₂C (M = Fe, Co, and Ru) (these parameters were obtained in the framework of the cluster approach) and T_c has been undertaken by Zeng *et al.*⁷³ The integrated density of the d states of transition-metal atoms (N_d) in solid solutions of variable composition, which is used in the theory of paired electron correlations and associated with the conditions for the formation of superconducting state, was considered as the 'electronic factor' of superconductivity. The N_d value can be calculated using the following formula

$$N_d = \int_{-\infty}^{E_F} D_d^q(\varepsilon) d\varepsilon, \quad (4)$$

where $D_d^q(\varepsilon)$ is the sum of partial populations of the d states of the q -type atoms

$$D_d^q(\varepsilon) = \sum_i P_{d,i}^q \frac{\delta\pi}{(\varepsilon - \varepsilon_i)^2 + \delta^2}. \quad (5)$$

Here, $P_{d,i}^q$ is the Mulliken population of the atomic orbital d in the cluster orbital ϕ_i with the energy eigenvalue ε_i , δ is the half-width ($\delta = 0.136$ eV) of the Lorentzian function employed to simulate the energy broadening of the discrete cluster levels in the crystal, and summation is performed over all occupied orbitals i .

In the rigid band model, the integrated density of d states for a binary alloy of variable composition A_{1-x}B_x can be written as

$$N_d^{\text{AB}} = (1-x)N_d^{\text{A}} + xN_d^{\text{B}},$$

where N_d^{A} and N_d^{B} are populations of the d states for 'pure' metals A and B. Thus, the corresponding populations for the Ni_{1-x}Fe_x

alloy are usually assumed to be ~ 9 e⁻ (Ni) and ~ 7 e⁻ (Fe). This primitive scheme for the solid solutions under consideration (for instance, Y(Ni_{1-x}Fe_x)₂B₂C) can be refined using formula (6)

$$\bar{N}_d = 9(1-x) + 7x + N_d^0, \quad (6)$$

where N_d^0 describes the effects of hybridisation of the transition metal (Ni), that is substituted, with the nearest environment (Ni–B₄).

Comparison of N_d values obtained from self-consistent calculations on selected clusters and the values of $\bar{N}_d$ parameters of a given model found from Eq (6)[‡] allows one to test the rigid band model.

Calculations performed by Zeng *et al.*⁷³ showed that the N_d and $\bar{N}_d$ values are fairly close for low impurity concentrations ($x = 0.07$) and the T_c vs. N_d correlation dependence is clearly observed. The difference between the parameter of the model $\bar{N}_d$ and the self-consistent N_d value increases substantially as the M content increases.

Direct estimates of T_c based on the results of calculations of the energy band structure of IBC were made by Mattheiss *et al.*,^{50, 64} Pickett *et al.*,⁵⁹ Kim *et al.*,⁶⁸ and Ravindran *et al.*⁷² The constant of the electron–phonon interaction (λ) was found to be approximately equal to 2.6 and the frequency of the Ba_{1g} phonon mode for LuNi₂B₂C is 850 cm⁻¹.⁵⁹ It is assumed that the soft modes of heavier atoms also make contributions to the superconductivity. Taking into account a mixed character of highest filled bands, it is emphasised that the multicomponent nature of the phase is one of the main factors that determine the superconductivity of IBC.

The electron–phonon mechanism of superconductivity in LuNi₂B₂C owing to the interaction between an isolated sp band near the Fermi level and high-frequency Ba_{1g} phonons modulating the angles of NiB₄ tetrahedra was discussed by Mattheiss *et al.*⁶⁴

The T_c value (≈ 15 K) found for YNi₂B₂C using $\lambda = 0.9$, the experimental Debye temperature ($\Theta = 573$ K),⁷⁴ and the calculated $N(E_F)$ value is in good agreement with the experiment.⁷¹

Kim *et al.*⁶⁸ estimated the λ value from the data on measurements of low-temperature electronic heat capacity γ (see Ref. 56) and band calculations using the McMillan formula⁴ and found that $\lambda \approx 0.8-1.1$. The relatively high T_c value for LuNi₂B₂C is primarily determined by considerable contributions of the Ni3d states to $N(E_F)$ ⁶⁸ and the assumed mechanism of the interaction between the high-frequency a_{1g} mode and sp nonmetal bands⁶⁴ cannot play the decisive role, since the contributions of the boron and carbon atomic states to $N(E_F)$ are small. Then, an estimate of the T_c value for the related borocarbide LuNiBC using a rough approximation $T_c \approx N(E_F)$ can be made and the results obtained ($T_c \sim 0.7-2.6$ K) are close to the experimental data.

Despite the above disagreement on the relative role of the electron and vibrational states of individual atoms and atomic groups in the formation of superconducting properties of IBC, all calculations^{50, 59, 64, 68, 71} allow one to consider these compounds as the 3D systems with an intermediate type of the electron–phonon interaction and superconductivity described by the BCS theory.

In this connection the studies of the isotope effect¹⁰⁸ and some electronic properties of IBC¹⁰⁹ should be mentioned. They suggest rather strong electron–phonon interactions in these systems. The phonon anomalies similar to those found in superconducting 3D carbides were found in borocarbides.¹¹⁰ An additional phonon mode associated with the formation of superconducting state was reported by Kawano *et al.*¹¹¹

A progressive suppression of the real part of optical conductivity $\sigma_1(\omega)$ in the far IR region, as should be expected in accord with the BCS theory in the case of appearance of a superconducting gap (Δ), was observed for YNi₂B₂C and LuNi₂B₂C in the

[‡] In this case, the N_d^0 value for the original matrix ($x = 0$) is obtained from the condition $N_d = \bar{N}_d$.

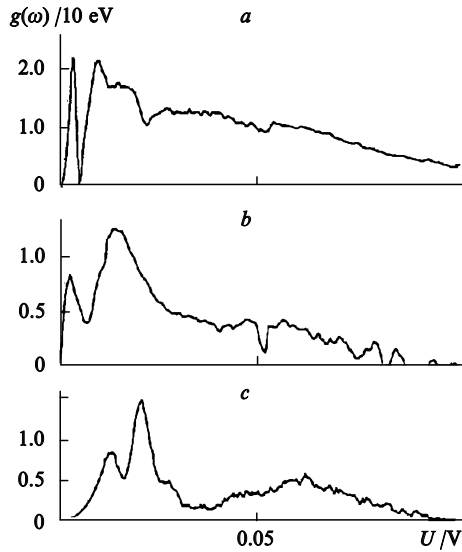


Figure 12. The PCS function of the electron–phonon interaction for $\text{HoNi}_2\text{B}_2\text{C}$ (a), $\text{YNi}_2\text{B}_2\text{C}$ (b), and $\text{LaNi}_2\text{B}_2\text{C}$ (c).¹¹⁴

studies of the temperature dependence of $\sigma_1(\omega)$ at $T < T_c$.¹¹² At $T \approx 6$ K and frequencies 5.6 meV ($\text{LuNi}_2\text{B}_2\text{C}$) and 6.9 meV ($\text{YNi}_2\text{B}_2\text{C}$), the $\sigma_1(\omega)$ values are equal to zero. This makes it possible to estimate the $2\Delta/k_B T_c$ value as ~ 3.9 – 5.2 . Hence, the effect of the formation of the Cooper pairs is assumed to occur with participation of the low-frequency phonon modes (optical phonons).¹¹³

The electron–phonon interaction in a number of IBC was studied by the point contact spectroscopy (PCS),¹¹⁵ which makes it possible to observe directly the interactions of the conduction electrons with elementary excitations in the crystal.

The PCS functions $g(\omega)$ for $\text{HoNi}_2\text{B}_2\text{C}$, $\text{YNi}_2\text{B}_2\text{C}$, and $\text{LaNi}_2\text{B}_2\text{C}$ are shown in Fig. 12. It can be seen that the function $g(\omega)$ for $\text{HoNi}_2\text{B}_2\text{C}$ has two distinct maxima with energies corresponding to the DOS peaks of soft phonons. A similar structure of the function $g(\omega)$ is observed for $\text{YNi}_2\text{B}_2\text{C}$, which indicates an electron-phonon interaction with low-energy phonons ($h\nu \approx 4$ – 9 meV). On the contrary, the corresponding interaction was not observed for nonsuperconducting $\text{LaNi}_2\text{B}_2\text{C}$ in the soft mode region of the phonon spectrum. Bommeli *et al.*¹¹² explain the above distinctions by specific features of the electronic structure (in particular, by the nesting effect on the Fermi surface) of the considered representatives of IBC homologous series.

2. Superconductivity and magnetism

The relationship between superconductivity and magnetism is one of the central problems of modern physical chemistry of crystals. For ternary intermetallic borides, this problem has been discussed in detail in a monograph.¹¹⁶ It has been noted in early studies of the properties of IBC that most $\text{LnM}_2\text{B}_2\text{C}$ phases are magnetic superconductors;^{1–3, 19} therefore, the problems of coexistence and mutual influence of magnetism and superconductivity were considered first in numerous experimental studies.

The results obtained to date make it possible to state that IBC are a unique class of magnetic superconducting materials. It is known that the onset of a magnetic order leads to an abrupt suppression of superconductivity and in the case of coexistence of both effects they are observed at appreciably different temperatures (energies). In this case, the temperature of magnetic ordering (the Neel temperature, T_N) is, as a rule, much lower than T_c for all the known groups of magnetic superconductors. Thus, T_c in Chevrel's phases is higher than T_N (~ 1 K) by an order of magnitude.¹¹⁶ The differences between T_c and T_N for HTSC cuprates containing rare-earth metal ions are even larger.¹⁰⁷

On the contrary, in the case of IBC the magnetic and superconducting states exist in the same temperature range and T_c can be either higher or lower than T_N .

T, K	$\text{ErNi}_2\text{B}_2\text{C}$	$\text{GdNi}_2\text{B}_2\text{C}$	$\text{DyNi}_2\text{B}_2\text{C}$
T_N	6.8	19.0	10.6
T_c	11.0	2.0	6.0

If T_N and T_c values are comparable, then the energy effects of the magnetic ordering and electron–electron interaction through the lattice phonons (formation of the Cooper pairs), *i.e.*, the energies of formation of magnetic structures and the energies of superconducting states, will also be close. Such a unique feature caused an ever increasing number of publications devoted to the investigation of relationship between the magnetism and superconductivity of IBC.

The greatest progress in this line has been achieved in the studies of magnetic structures of IBC. The investigations were mostly carried out by X-ray or neutron diffraction techniques for $\text{PrNi}_2\text{B}_2\text{C}$ and $\text{DyNi}_2\text{B}_2\text{C}$,^{14, 19, 20, 23, 100, 117–132} $\text{ErNi}_2\text{B}_2\text{C}$ and $\text{TbNi}_2\text{B}_2\text{C}$,^{21, 22, 47, 133–135} $\text{TmNi}_2\text{B}_2\text{C}$,^{11, 47, 136–138} $\text{GdNi}_2\text{B}_2\text{C}$,^{25, 45–47} and $\text{CeNi}_2\text{B}_2\text{C}$ and $\text{YNi}_2\text{B}_2\text{C}$.^{47, 139}

As a result, a wide variety of magnetic IBC structures was found; some of them are listed in Table 9. Thus, an antiferromagnetic ordering was found for $\text{LnNi}_2\text{B}_2\text{C}$ ($\text{Ln} = \text{Pr}, \text{Dy}, \text{and Ho}$) at low temperatures. The antiferromagnetic structure is formed due to alternation of antiferromagnetically oriented rare-earth metal layers with ferromagnetic type of intralayer ordering of magnetic moments along the z axis. The magnetic structure of $\text{ErNi}_2\text{B}_2\text{C}$ can be described by the spin density waves (SDW) with the wave vectors $\mathbf{q}(001)$ or $\mathbf{q}(110)$. Several magnetic structures were found for $\text{HoNi}_2\text{B}_2\text{C}$ ($T_c \approx 8$ K). At $T_N \approx 8.5$ K, a helical incommensurate antiferromagnetic structure appears, in which the plane nets of vectors of ferromagnetically oriented moments of are rotated by an angle of $\sim 17^\circ$ with respect to the original antiparallel packing. The wave vector of this incommensurate spin structure is $\mathbf{q}(0, 0, 0.91)$. Another type of incommensurate structure modulated along the x axis by the wave vector $\mathbf{q}(0.55, 0, 0)$ exists at $T_N \approx 6.5$ K (in the region of the reentrant superconducting transition with $T_c \approx 5$ K). The helical structure is destroyed with the formation of a conventional antiferromagnetic order as the temperature decreases. It is important that the magnetic structures are extremely sensitive to the IBC composition.^{140, 141}

Currently, there is no general microscopic theory of superconductors having incommensurate magnetic structures. Only assumptions on the nature of coexistence and relationship between the superconductivity and magnetism have been made.^{10, 14, 23, 47, 117–139}

Table 9. Types of magnetic structures, magnetic moments (μ), the Neel temperatures (T_N/K) critical temperatures (T_c/K), and magnetic wave vectors ($\mathbf{q}$) for several IBC.⁴⁷

Phase	Type of magnetic structure	T_N	T_c	μ, μ_B	$\mathbf{q}$
$\text{PrNi}_2\text{B}_2\text{C}$	AF	4.0	—	0.81	(0, 0, 1)
$\text{NdNi}_2\text{B}_2\text{C}$	AF	4.8	—	2.10	(1/2, 0, 1/2)
$\text{GdNi}_2\text{B}_2\text{C}$	ISS(x)	19.0	—	7.0	(0.55, 0, 0)
$\text{TbNi}_2\text{B}_2\text{C}$	ISS(y)	15.0	—	7.78	(0.555, 0, 0)
$\text{DyNi}_2\text{B}_2\text{C}$	AF	10.6	6	8.47	(0, 0, 1)
$\text{HoNi}_2\text{B}_2\text{C}$	ISS(z)	8.5	8	6.7	(0, 0, 0.91)
	ISS(x)	6.3	—	—	(0.55, 0, 0)
	AF	5.0	5	8.62	(0, 0, 1)
$\text{ErNi}_2\text{B}_2\text{C}$	SDW(x)	6.8	11	7.19	(0.553, 0, 0)
$\text{TmNi}_2\text{B}_2\text{C}$	SDW(z)	1.5	11	3.78	(0.093, 0.093, 0)

Note. The following designations are used: AF is antiferromagnetic structure, ISS(x, y, z) is incommensurate spin structure with the wave vector modulated along the (x, y, z) directions, and SDW(x, y, z) is spin density waves along the (x, y, z) directions.

Thus it has been shown in one of the first studies of $\text{LnM}_2\text{B}_2\text{C}$ ($\text{Ln} = \text{Tm}, \text{Er}, \text{Ho}, \text{and Dy}$)¹⁰ that their properties are similar to those of magnetic superconductors LnRh_4B_4 and LnMo_6S_6 .^{142, 143} In the latter compounds, the high density of local magnetic moments (the long-range spin order) and superconductivity ‘coexist’ owing to the spatial separation of magnetic rare-earth metal ions and transition-metal ions, a weak exchange interaction between the states of these sites, and a low density of the conduction electrons at the sites occupied by the $4f$ elements.

The vast majority of theoretical investigations of EES are devoted to IBC containing nonmagnetic rare-earth metal atoms (Y and Lu) and carried out for a spin-restricted (nonmagnetic) version. Quantitative calculations of the electron states taking into account the spin order were performed only for $\text{GdNi}_2\text{B}_2\text{C}$ assuming the ferromagnetic ordering of magnetic moments.⁷⁰ The first attempt to explain the magnetic order from the viewpoint of one-electron band structure calculations of IBC has been undertaken by Greenwood *et al.*¹⁴⁴ The ordering of magnetic moments was assumed to occur due to an indirect interaction (of the Ruderman–Kittel–Kasuga–Yoshida type) of $4f$ electrons of the rare-earth metal atoms. Then, the onset of magnetic order can be correlated with the maxima of magnetic susceptibility $\chi(\mathbf{q})$ of the conduction electrons, which, in turn, are determined by the distribution of states on the Fermi surface (in particular, by the nesting effect). The calculations¹⁴⁴ showed that the $\chi(\mathbf{q})$ peaks appear near the wave vectors $\mathbf{q} = (0.6, 0, 0)$ and $(0, 0, 0.9)$ along the $\mathbf{a}^*$ axis and near the wave vectors $\mathbf{q} = (0, 0, 0.3)$ and $(0, 0, 0.9)$ along the $\mathbf{c}^*$ axis. These wave vectors correspond to the observed incommensurate SDW for $\text{HoNi}_2\text{B}_2\text{C}$.¹⁹

It should be noted again that most of the problems of the fundamental theory of superconducting magnetic IBC remain unexplored to date. They include, in particular, the problems of the onset of the magnetic order in superconducting materials, conditions of compatibility of and competition between these phenomena, the nature of the exchange interaction between magnetic ions and the conduction electrons, the role of the spin-orbital interaction, *etc.*

3. The electric field gradient

The electric field gradient (EFG) reflects the asphericity of the charge density distribution near the nucleus in question and is directly related to the electron density distribution in the crystal, the nature of the chemical bond, and the symmetry of the nearest environment of the nuclei. It is possible to determine the EFG value by studying the quadrupole effects in NMR spectra¹⁴⁵ and the Mössbauer effect.¹⁴⁶ Experimental estimates of EFG for compounds in question were performed for the ^{155}Gd nuclei in $\text{GdNi}_2\text{B}_2\text{C}$ and $\text{GdCo}_2\text{B}_2\text{C}$ (see Ref. 70) and ^{57}Fe for $\text{Y}(\text{Ni}_{1-x}\text{Fe}_x)_2\text{B}_2\text{C}$ alloys.⁷³

The electric field gradient at the ^{155}Gd nuclei reflects first of all the asphericity of the $6p$ electron density distribution within a radius of $\sim 2 \text{ \AA}$.¹⁴⁷ The positive contributions to the V_{zz} EFG obtained for $\text{GdNi}_2\text{B}_2\text{C}$ and $\text{GdCo}_2\text{B}_2\text{C}$ points to considerable contribution of the $6p_x, p_y$ orbitals localised in the plane of $\text{Gd}-\text{C}$ nets to the charge density.

A quantitative EFG analysis was carried out using ASW calculations of the low-temperature $\text{GdNi}_2\text{B}_2\text{C}$ phase under the assumption of ferromagnetic spin order.^{70, 148} The values of local magnetic moments at the Gd , Ni , B , and C atoms were 7.27, 0.03, 0.00, and $-0.01 \mu_B$, respectively. The contributions of the populations (n_i) of the $\text{Gd } 6p$ and $5d$ orbitals to the EFG and the radial charge densities $\langle r^{-3} \rangle_i$ were calculated using the following equations¹⁴⁸

$$V_{zz}(6p) = 7.74 \left[\frac{1}{2} (n_x + n_y) - n_z \right] \langle r^{-3} \rangle_{6p}, \quad (7)$$

$$V_{zz}(5d) = 5.54 \left[\frac{1}{2} (n_{x^2-y^2} + n_{xy}) - \frac{1}{2} (n_{xx} + n_{yy} - n_{3z^2-r^2}) \right] \langle r^{-3} \rangle_{5d}.$$

Table 10. Orbital populations (n_i), radial charge densities ($\langle r^{-3} \rangle_i$), and EFG components (V_{zz}) at ^{155}Gd nuclei for ferromagnetic $\text{GdNi}_2\text{B}_2\text{C}$ according to the ASW calculations.

Parameter	Spin ‘up’	Spin ‘down’
$n_x = n_y / e$	0.173	0.165
n_z / e	0.147	0.132
$n_{z^2-y^2} / e$	0.216	0.148
n_{xy} / e	0.304	0.278
$n_{xz} = n_{yz} / e$	0.235	0.178
$n_{3z^2-r^2} / e$	0.285	0.227
$\langle r^{-3} \rangle_{6p} / e a_0^{-3}$	25.9	29.0
$\langle r^{-3} \rangle_{5d} / e a_0^{-3}$	1.83	1.44
$10^{21} V_{zz}(6p) / \text{V m}^{-2}$	5.21	7.41
$10^{21} V_{zz}(5d) / \text{V m}^{-2}$	0.0	0.16

The values obtained are listed in Table 10. It can be seen that the $\langle r^{-3} \rangle_{6p}$ values are much larger than $\langle r^{-3} \rangle_{5d}$, *i.e.*, that the V_{zz} values are determined mainly by the asphericity of the $6p$ charge density. The calculated V_{zz} value ($12.8 \times 10^{21} \text{ V m}^{-2}$) virtually coincides with the experimental one ($11.9 \times 10^{21} \text{ V m}^{-2}$) obtained from the analysis of the Mössbauer spectra.¹⁴⁸

Mulder *et al.*¹⁴⁸ emphasise that the V_{zz} value for $\text{GdNi}_2\text{B}_2\text{C}$ is comparable to the EFG value for the known magnetic materials $\text{Ln}_2\text{Fe}_{14}\text{B}$, $\text{Sm}_2\text{Fe}_{17}\text{N}_3$, and LnCo_5 (see Refs 149–151) and is remarkable in connection with the macroscopic magnetic anisotropy of IBC. However, the V_{zz} contribution of isostructural BCT phases ($\text{GdNi}_2\text{Si}_2\text{C}$, $\text{GdCo}_2\text{Si}_2\text{C}$) is small and negative.¹⁴⁷ It is suggested¹⁴⁸ that carbon atoms filling the vacancies of ThCr_2Si_2 -like sublattice play the key role in the formation of IBC. The role of the carbon atoms is thought to be analogous to that of the nitrogen atoms, whose insertion into the bulk of intermetallic $\text{Sm}_2\text{Fe}_{17}$ results in redistribution of the electron density around the samarium nucleus in such a way that the EFG in the formed nitride $\text{Sm}_2\text{Fe}_{17}\text{N}_3$ increases by $\sim 100\%$.¹⁵²

The EFG values at the nuclei of transition-metal atoms in alloys of composition $\text{Y}(\text{Ni}_{1-x}\text{M}_x)_2\text{B}_2\text{C}$ ($\text{M} = \text{Fe}, \text{Co}, \text{and Ru}$; $x = 0.07$ and 0.47) were calculated in the framework of the cluster approach;⁷³ the following individual components responsible for the formation of the EFG tensor at the nuclei were estimated: V_{zz}^{val} , *i.e.*, the EFG dependent on the asymmetric distribution of valence electrons of the atom under consideration,

$$V_{zz}^{\text{val}} = \left\langle \frac{\rho(3z^2 - r^2)}{r^5} \right\rangle, \quad (8)$$

and V_{zz}^{nuc} , which includes the contribution of point charges Q_v and polarisation of inner shells

$$V_{zz}^{\text{nuc}} = \sum_v \frac{Q_v(3z_v^2 - r_v^2)}{r_v^5}, \quad (9)$$

where the summation is performed over the atoms of the calculated fragment.

Generally, one should also take into account the contribution of V_{zz}^{host} , which describes the effect of the crystal ‘residue’ (‘external’ with respect to the cluster selected) and whose nature is similar to that of V_{zz}^{nuc} . In several studies (see, for instance, Ref. 70), the V_{zz}^{host} value is assumed to be negligible by analogy with the results of calculations of ionic compounds.¹⁵³ The V_{zz}^{val} , V_{zz}^{nuc} , and V_{zz} values are listed in Table 11.

The EFG for transition metals is known to be determined by the asphericity of the distribution of d and p electrons.¹⁵⁴ The positive V_{zz}^{val} values (see Table 11) show that the contributions of $d_{x^2-y^2}$, d_{xy} , p_x , and p_y orbitals of transition metals (in the xy plane) dominate over those of d_{z^2} , d_{xz} , d_{yz} , and p_z orbitals oriented along the z axis. The small concentration differences in V_{zz}^{val} indicating the local nature of the EFG formation also worth noting. Estimates of the quadrupole splitting value proportional to the

Table 11. The EFG components ($e a_0^{-3}$) at the transition-metal nuclei in $Y(Ni_{1-x}M_x)_2B_2C$ ($M = Fe, Co,$ and Ru) alloys according to discrete variational calculations.

Central atom in the cluster	x	V_{zz}^{val}	V_{zz}^{nucl}	V_{zz}	$10^{17} V_{zz}$ / $V \text{ cm}^{-2}$
Ni	0.00	0.74	-0.65	0.09	0.87
Fe	0.07	0.61	-0.65	-0.04	-0.39
Fe	0.47	0.50	-0.63	-0.13	-1.26
Co	0.07	0.27	-0.65	-0.37	-3.59
Co	0.47	0.24	-0.64	-0.40	-3.89
Ru	0.07	1.96	-0.65	1.31	12.7
Ru	0.47	1.95	-0.63	1.32	12.8

EFG value for iron in $Y(Ni_{1-x}Fe_x)_2B_2C$ alloys appeared to be in reasonable agreement with those obtained by Mössbauer spectroscopy.³³

4. Atomic properties

Physicochemical characteristics of the solids determined by the total energy of their electron–nuclear system (E_{tot}) or by their cohesion energy (E_{coh}) are usually considered as their atomic properties. Direct calculations of E_{tot} and E_{coh} using modern quantum-chemical methods make it possible to determine many of the properties of crystals, namely, the equilibrium volumes and lattice parameters, bulk moduli, critical pressures (breaking stress of a chemical bond), and a number of thermodynamic parameters.^{155, 156}

To date, these parameters have been calculated only for YNi_2B_2C in the framework of the LMTO approach.⁶⁹ Thus, calculation of the contributions of the atoms of different types (the so-called structural energies ΔE)⁷² makes it possible to understand, in particular, the role of individual elements in the formation of the crystal structure of IBC. It has been found that ΔE values for Y and Ni are negative, whereas they are positive for the metalloid atoms (with respect to E_{tot} of neutral atoms), which implies that metallic components play the key role in the phase formation of IBC. Despite the destabilising (positive) energy of carbon, its incorporation into the structure results in an appreciable increase in the bonding energy of yttrium, *i.e.*, in the overall stabilisation of the phase. This is confirmed by calculations of the heat of formation of YNi_2B_2C : $\Delta H = -153.82$ Ry per formula unit.

Ravindran *et al.*⁷² reported the solution of the equation of state for YNi_2B_2C (which makes possible studying the P – V dependences^{157, 158}) as a universal relationship between the volume of the crystal and its total energy. Theoretical values of the bulk modulus ($B_0 = 1.071$ kbar) and its first derivative have been obtained. Their comparison with the corresponding values for YRh_3B indicates a greater plasticity of YNi_2B_2C , which is likely associated with its layered structure.⁷² Unfortunately, thermomechanical characteristics of IBC have not virtually been studied.

In our opinion, systematic calculations of the atomic characteristics of IBC of different composition and structure must be an effective method of attacking the problems of thermobarochemistry and theoretical material science of IBC and related compounds.

VIII. Spectroscopic studies of the electronic structure of intermetallic borocarbides

Spectroscopic methods make it possible directly to investigate the distribution of partial and total densities of filled and free states in a wide energy interval using X-ray emission, X-ray absorption, and X-ray photoelectron spectra (XES, XAS, and XPES, respectively). It is natural that the first band structure calculations were followed by spectroscopic studies of IBC. The main problems of such studies were testing the correctness of suggested theoretical

models and determining specific features of the distribution of the electron states in excited electronic subsystems.

1. X-Ray photoelectron spectra

The XPES method was first used in studies of the distribution of the YNi_2B_2C electron states (Fig. 13).^{159, 160} As can be seen, the XPES contains a peak of maximum intensity (~ 1.4 eV lower than the Fermi level) corresponding to the distribution of the $Ni3d$ states, and local maxima with energies (E) 4.6, 6.2, 9.2, and 13 eV corresponding to s and p energy bands of boron and carbon. The doublet structure of the $Y4p$ core level is detected at $E \approx 25$ eV. The edge structure of the near-Fermi photoelectron emission matched to the YNi_2B_2C DOS obtained from LAPW calculations^{50, 59} and corrected for the effective cross-sections of photoionization of the individual states¹⁶¹ is shown in the inset. The calculations reproduce the spectral structure sufficiently well. The narrowing of the width of the experimental peak (of the $Ni3d$ type) and the shift of its maximum (by ~ 0.25 eV) towards lower bonding energies are the most pronounced differences between the calculated and experimental spectra. In addition, the DOS peak with an energy equal to E_F , predicted by quantum-chemical calculations, is not detected in the experiment.

The discrepancies between the results of calculations of the nonexcited states of YNi_2B_2C and its XPES can be explained using the resonance emission experiments.¹⁵⁹ The XPES were studied in the range of photon energies $h\nu = 64 - 74$ eV, *i.e.*, near the excitation threshold of $Ni3p$ core levels. In this case, a satellite peak with energy $E \approx 8$ eV is clearly seen on the high-energy side of the main spectral maximum.

This phenomenon, which is known for many metals, alloys, and compounds as resonance photoemission,^{162–166} is accounted for by excitation of the $Ni3p$ core level and interference of direct processes of excitation of $3d$ photoelectrons and the processes involving super-Kronig–Coster transitions $3p^63d^{10}4s \rightarrow 3p^63d^84s + e$, where e is a free electron.

Thus, the experimentally measured width of the $3d$ band for metallic nickel is by about 30% smaller than that obtained from LEDF calculations of the ground state, and a satellite is observed in the spectrum (~ 6 eV lower than E_F) due to the effects of electron correlation in the d band.^{162, 163} The reason for the appearance of the satellite for NiO (~ 10 eV lower than E_F)¹⁶⁵ is analogous. Thus, the indicated discrepancies between the calculations and XPES of YNi_2B_2C can be associated with the redistribution of the ‘spectral’ density between the energy interval of localisation of the band of nonexcited states and lower-energy region (the appearance of the satellite due to the effect of electron correlation).

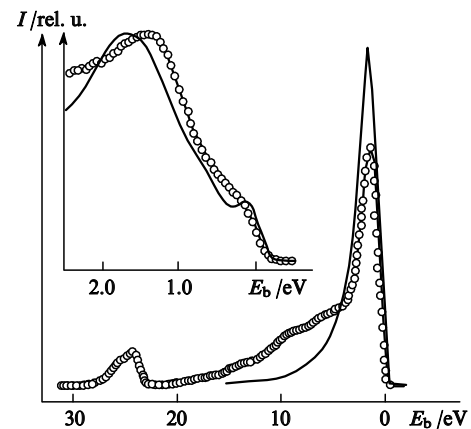


Figure 13. X-Ray photoelectron spectra of YNi_2B_2C ($h\nu = 60$ eV). The high-energy near-edge structure of photoemission ($h\nu = 20$ eV) is shown in the inset. Solid lines correspond to the theoretical XPES spectra obtained from the band LAPW calculations.

Peculiarities of the distribution of free states near the Fermi level in $\text{YNi}_2\text{B}_2\text{C}$ were studied¹⁶⁰ by the inverse XPES method also known as X-ray bremsstrahlung (isochromat) spectroscopy (XBIS). The XBIS spectrum obtained¹⁶⁰ corresponds mainly to the $\text{Ni}3d$ conduction band shifted by ~ 1.5 eV with respect to E_F and to a partially unfilled $\text{Y}4d$ band with its centre ~ 6 eV above the E_F . For both XPES and XBIS, the suppression of spectral intensity near E_F is observed. This can be connected with narrowing of the near-Fermi conduction bands due to the interaction with low-energy excitations (the appearance of a pseudogap as a result of electron–phonon interactions,^{167,168} the interaction of electrons with spin fluctuations¹⁶⁹).

The main reason for discrepancies between the results obtained by the XPES method and the band theory, namely, redistribution of ‘spectral’ density towards higher bonding energies near E_F for $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LuNi}_2\text{B}_2\text{C}$, is discussed by Fujimori *et al.*¹⁷⁰ It has been suggested to explain the transfer of the ‘spectral’ density from the near-Fermi region of coherent quasi-particle excitations to the region of incoherent excitations (more distant from the E_F) by renormalisation of the mass of the conduction band; the macroscopic description of this effect should take into account the electron–electron interactions.

2. X-Ray emission spectra

The XES studies of the partial DOS distribution were carried out for $\text{YNi}_2\text{B}_2\text{C}$ and LuNiBC (see Ref. 171) and for $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LaNi}_2\text{B}_2\text{C}$ (see Ref. 172).

The BK_α and CK_α emission spectra of $\text{YNi}_2\text{B}_2\text{C}$ and LuNiBC and the LDOS of B and C atoms calculated by Mattheiss⁵⁰ are presented in Fig. 14. As can be seen, the positions of the main spectral peaks are in agreement with the distribution of the $\text{B}2p$ and $\text{C}2p$ states. The contributions from low-energy bands (mainly of the $2p$ type) of nonmetals are not detected in K_α XES, since they are forbidden by the dipole selection rules; the spectra exhibit the presence of a density of boron and carbon $2p$ states near E_F for $\text{YNi}_2\text{B}_2\text{C}$, and their presence in this region is associated with the effect of $\text{B}2p$ – $\text{Ni}3d$ – $\text{C}2p$ hybridisation.¹⁷¹

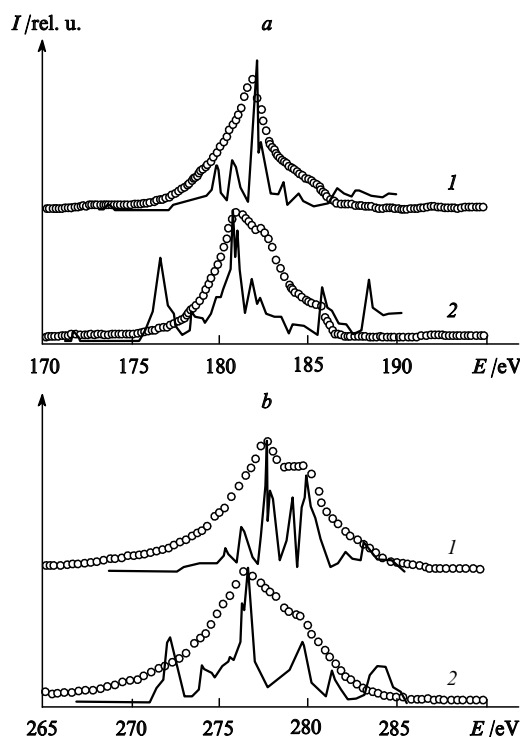


Figure 14. The BK_α (a) and CK_α (b) X-ray emission spectra of LuNiBC (1) and $\text{YNi}_2\text{B}_2\text{C}$ (2). Solid lines correspond to local DOS of the B and C $2s$ and $2p$ AOs according to the LAPW calculations.⁵⁰

Fluorescence (B, C) K_α XES of polycrystalline specimens of $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LaNi}_2\text{B}_2\text{C}$ have been analysed by Shin *et al.*¹⁷² After comparing the parameters of the BK_α and CK_α spectra of both IBC, the authors have noted that the BK_α lines appeared to be more sensitive to structural distortions on going from $\text{YNi}_2\text{B}_2\text{C}$ and $\text{LaNi}_2\text{B}_2\text{C}$, which implies that the metal–nonmetal hybridisation occurs mainly due to the $\text{B}2p$ states. Comparison of intensities of the BK_α XES of IBC near E_F shows that this value for the superconducting $\text{YNi}_2\text{B}_2\text{C}$ is $\sim 10\%$ larger than that for $\text{LaNi}_2\text{B}_2\text{C}$ and, hence, $\text{B}2p$ states play an important role in the formation of superconducting properties of IBC.

3. X-Ray absorption spectra

Pellegrin *et al.*¹⁷³ studied the structure of the bottom edge of the conduction band of polycrystalline $\text{LnNi}_2\text{B}_2\text{C}$ ($\text{Ln} = \text{Y}, \text{Sm}, \text{Tb}, \text{Ho}, \text{Er}, \text{Tm}, \text{Lu}$) specimens by $\text{BK}(1s \rightarrow 2p)$ and $\text{NiL}_{2,3}(2p_{2/3} \rightarrow 3d, 4s)$ XAS. It has been found that the shape of the NiL spectra is nearly the same for all IBC studied, *i.e.*, that the degree of filling of $\text{Ni}3d$ and $4s$ bands is independent of the nature of the Ln atoms. Hence, the observed differences in T_c for these phases are not related to the position of E_F with respect to the centre of the $\text{Ni}3d$ band, but are determined by the effect of the magnetic unpairing of the Cooper pairs. The lines of the NiL XAS of IBC were found to be shifted (by ~ 1 eV) toward the high-energy region relative to metallic nickel, which is accounted for by the chemical shift of the $\text{Ni}2p$ level in borocarbides due to a partial $\text{Ni} \rightarrow \text{B}, \text{C}$ charge transfer, which also involves the density of $\text{Ni}4s$ electrons.

For BK XAS, on the contrary, pronounced distinctions depending on the lanthanide type were observed between spectral lines in the region 4–7 eV above E_F , which might be due to the lanthanide effect on the degree of distortion of the NiB_4 tetrahedra.

Matching the BK and $\text{NiL}_{2,3}$ absorption spectra using a unified scale (Fig. 15) indicates an appreciable covalent overlap of Ni – B outer states. Thus the four clearly seen extrema of the $\text{NiL}_{2,3}$ spectrum (see Fig. 15, points *b*, *c*, *d*, and *e*) have their isoenergetic analogues in the structure of the BK spectrum and reflect a rather strong $\text{Ni}3d$ – $\text{B}2p$ interaction. The peak of the BK spectrum corresponds to the $\text{C}2p$ – $\text{B}2p$ covalent interaction.

Comparison of the absorption spectra and partial densities of unfilled states indicates¹⁷³ that the one-electron methods of the band theory reproduce the electronic energy distributions in this spectral region fairly well. An appreciable broadening of XAS spectral bands as compared to the results of calculations can be due to the electron–photon interaction.

The XAS method was also used for the determination of cerium valence in $\text{CeNi}_2\text{B}_2\text{C}$ and solid solutions $\text{Y}_{1-x}\text{Ce}_x\text{Ni}_2\text{B}_2\text{C}$.¹⁷⁴ As has been mentioned above, in its crystallographic

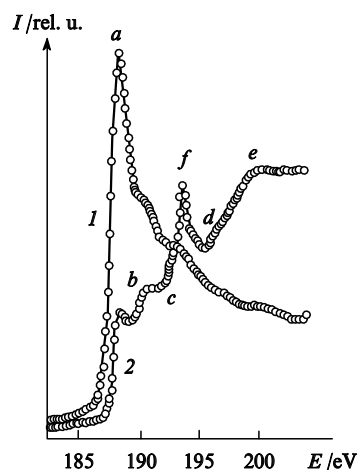


Figure 15. The near-edge structure of the BK (1) and NiL (2) absorption spectra of $\text{ErNi}_2\text{B}_2\text{C}$.

characteristics $\text{CeNi}_2\text{B}_2\text{C}$ is an exception to the morphological series of IBC, namely, its lattice constant a is larger, whereas the lattice constant c is smaller than those expected from the lanthanide compression rule. Presumably, the above anomaly is associated with the variable valence of Ce; an indirect confirmation of this assumption was obtained in the experiments on magnetic susceptibility in the series of phases $\text{CeNi}_2\text{B}_2\text{C}$, $\text{NdNi}_2\text{B}_2\text{C}$, and $\text{GdNi}_2\text{B}_2\text{C}$.^{175, 176}

X-Ray absorption spectra of $\text{Y}_{1-x}\text{Ce}_x\text{Ni}_2\text{B}_2\text{C}$ alloys ($x = 0, 0.05, 0.1, 0.25$, and 1.0) were obtained in the energy region $5680\text{--}5820\text{ eV}$ corresponding to the L_{III} edge of Ce absorption at 300 and 10 K . The absorption spectrum contains two resolved peaks at $E \approx 5723$ and 5731 eV assigned to the $\text{Ce}4f^1$ and $\text{Ce}4f^0$ configurations, respectively. The relative intensities of these maxima change with temperature, which directly indicates a fluctuation of the valence state of cerium. Decomposition of spectral lines into individual components according to the procedure suggested^{177, 178} makes it possible to estimate the averaged cerium valence ($\langle v \rangle$). The $\langle v \rangle$ values obtained 3.15 and 3.21 (at $T = 300\text{ K}$ and 10 K , respectively) are smaller than 3.33 , which is usually obtained for the ions with a formal valence of 4 by the XAS method. The standard underestimation of $\langle v \rangle$ as compared to the value of the formal valence is due to the final state effect.¹⁷⁹ In $\text{Y}_{1-x}\text{Ce}_x\text{Ni}_2\text{B}_2\text{C}$ solid solutions, cerium also has a variable valence ($\langle v \rangle = 3.18$). It is of interest to note that the $\langle v \rangle$ value decreases at elevated temperature and increases at low temperature ($T = 10\text{ K}$) as the cerium concentration in the solid solution increases. Allen *et al.*¹⁷⁴ explained the distinctions in the temperature dependence of $\langle v \rangle$ for Ce in $\text{CeNi}_2\text{B}_2\text{C}$ and $\text{Y}_{1-x}\text{Ce}_x\text{Ni}_2\text{B}_2\text{C}$ solid solutions diluted with respect to Ce by co-operative effects.¹⁷⁷

Additional information on the valence states of Ce can be obtained using the X-ray fluorescence spectroscopy of core levels.

IX. Conclusion

Over a rather short period elapsed from the beginning of intensive studies of IBC, a considerable body of information on the physicochemical properties of this group of compounds has been accumulated. The available data are dissimilar. Intermetallic borocarbides are a unique class of multicomponent superconducting magnetic materials. For this reason, their low-temperature electrophysical and magnetic characteristics have been studied in most detail.

Much less information on phase equilibria and phase diagrams of IBC is available, while their thermodynamic and thermomechanical properties have not virtually been studied. The latter is also true for the problems of targeted synthesis of IBC and the effect of various structural defects on the properties of these compounds. A systematic accumulation of information on the above lines is required to develop the fundamentals of material science of IBC.

Only the principal results of the studies of the electronic structure of intermetallic borocarbides have been covered in this review. Currently, prominent specific features of electron distributions and chemical bonding in IBC have been reliably established. The mechanism of the formation of several physicochemical properties of these compounds has been explained from the viewpoint of their electronic structure.

It should be noted that most of the available data refer to nonexcited electronic subsystems of ideal quaternary phases in the nonmagnetic state. Taking account of a swift increase in the experimental information on the properties of IBC, particular attention of theoreticians in the near future will most likely be drawn to describing the microscopic nature of the origin of magnetic order, conditions of its coexistence with superconductivity, relationship between the superconductivity and the valence state of lanthanides, possible external effects (pressure or temperature) on the spin subsystems.

Setting up research in the field of theoretical material science of IBC associated with problems of constructing phase and magnetic phase diagrams, computer simulation of new multicomponent phases, their solid solutions, studies of the influence of various impurities and structural defects on the properties of IBC appears to be no less urgent.

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The concept of electronegativity. The current state of the problem

A R Cherkasov, V I Galkin, E M Zueva, R A Cherkasov

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Abstract. A systematic account is given of the current ideas about atomic and group electronegativities and the trends in the development of the concept of electronegativity are analysed. Attention is concentrated on the latest approaches to the definition of electronegativity — the concept of 'orbital' electronegativities and the density functional theory. A procedure is proposed for the determination of 'inductive' electronegativities, which permits a correct theoretical calculation of the electronegativity of a substituent from the electronegativities of individual atoms and the steric structure. It is shown that the approach developed has a series of important advantages — for example, it makes it possible to calculate the group electronegativities of isomeric substituents avoiding the principle of the equalisation of electronegativities. A survey of literature data and generalisation of the method proposed by the authors have made it possible to formulate the concept of electronegativity as an unchanging fundamental immanent characteristic of a chemical element. The bibliography includes 222 references.

I. The electronegativity of atoms

The history of the study of electronegativity (EN) has been described in a series of theoretical, methodological, and retrospective communications.^{1–6} The concept and the term 'electronegativity' itself were introduced in 1932 by Pauling, who characterised it as the force with which an atom in a molecule attracts electrons. In Pauling's studies, the electronegativity of atoms was determined on the basis of thermodynamic data from the energies of the single bonds in which they are involved:⁷

$$\Delta E(AB) = E(AB)_{\text{exp}} - \frac{1}{2}[E(AA) + E(BB)], \quad (1)$$

where $\Delta E(AB)$ is the additional energy of the interaction of the atoms A and B above the additive covalent contribution. Pauling observed that atomic additivity is characteristic of the function $\Delta E^{1/2}$ and that it may serve as a characteristic of the difference between the electronegativities (χ) of the atoms involved in the formation of the bond

$$|\chi_A - \chi_B| = 0.208 \Delta E^{1/2} \text{ (eV)}.$$

Having adopted EN for hydrogen as $\chi_H = 2.1$, Pauling calculated the values of χ for a large number of atoms. The data which he obtained served as the basis for the first electronegativity scale. Virtually the same scale may be obtained by using in Eqn (1) the geometrical mean value of the covalent component of the bond energy.⁸

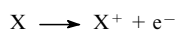
The fruitfulness of Pauling's idea and the practical importance of his scale were convincingly confirmed in studies by various investigators who published the results of thermochemical studies (see, for example, Batsanov's communication⁸ and the literature quoted therein).

Later some investigators modified the computational scheme itself, whilst others redetermined the values of EN found by Pauling on the basis of their own experimental data and found new values of χ . As a result, Pauling's scale was significantly expanded and, what is particularly important, the EN for atoms in different valence states were determined. One of the most significant gaps in Pauling's original concept, which postulated a single value of χ for each atom regardless of its hybridisation, was thus abolished. Nevertheless, none of the subsequent studies introduced fundamental changes into Pauling's system of EN and into the method for their determination.

Furthermore, the main cause of the appearance of other approaches to the calculation of χ from physical characteristics of atoms and molecules was believed for a long time to be the impossibility of a thermodynamic description of the values of EN for all the elements in all the their chemical manifestations owing to the lack of the energies of individual bonds.⁸

Pauling's EN scale came to be generally employed and became a kind of reference standard for new methods of calculation of χ , many of the newly created scales being adjusted to Pauling's scale.⁹ Furthermore, some of the modern investigators believe that Pauling's original EN scale is not only the most successful but is also adequate¹⁰ and that his method is still one of the fundamental ones for the determination of EN.

Another no less familiar approach to the determination of electro-negativities was developed in 1934 by Mulliken,¹¹ who determined 'absolute' electronegativities, having expressed them in terms of half the sum of the ionisation energies of a neutral atom:

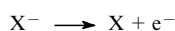


(first ionisation potential I) and a negative ion

A R Cherkasov, V I Galkin, E M Zueva, R A Cherkasov
Kazan State University, ul. Kremlevskaya 18, 420008 Kazan, Russian Federation. Fax (7-843) 231 51 86. Tel. (7-843) 231 51 86 (A R Cherkasov).
E-mail rafael.cherkasov@ksu.ru (R A Cherkasov)

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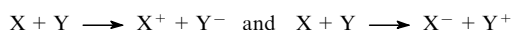
Uspekhi Khimii 67 (5) 423–441 (199); translated by A K Grzybowski



(electron affinity F) in the absence of the overlap of the electron shells of the interacting atoms:

$$\chi_M = \frac{I + F}{2}. \quad (2)$$

Mulliken considered two neutral systems X and Y having identical electronegativities. In this case, the energy changes in the two disproportionation reactions



should be identical. The energies of the first and second reactions are $I_X - F_Y$ and $I_Y - F_X$, so that, after recalculation for a single valence electron, one obtains Eqn (2) in which EN is expressed in energy units.

Pauling's and Mulliken's scales proved to be linearly related (different workers give different parameters of the corresponding linear regression),^{9, 12–15} although the dimensions of the EN are in fact not the same. Furthermore, as already mentioned, the EN of atoms on Pauling's scale are regarded as unchanging, whereas the EN on Mulliken's scale should depend on the hybridisation of the atom (like the ionisation potential and the electron affinity). This factor served subsequently as a basis for the creation of scales containing the EN for atoms in different valence states.⁸ At the same time, some workers have noted that Mulliken's system does not have a rigorous theoretical basis.^{3, 9} The use of ionisation potentials and electron affinities makes the Mulliken EN not only easy to obtain but also readily explicable, reflecting the average power of the atom to retain its own valence electron (described by I) and to attract the electron of its partner involved in the bond (described by F).

However, in a series of subsequent studies, only one of the parameters of the Mulliken equation was employed. For example, Vereshchagin¹⁵ assumed that the EN of an atom is expressed directly by its electron affinity F , because EN reflects the 'tendency' of the atom in the molecule to attract electrons. On the other hand, in practice, procedures for the calculation of EN involving the use of the ionisation potential (IP) of the atom came to be most widely used.¹⁶ Thus the employment of average IP for the calculation of EN by the equation

$$\chi = -\frac{I_n}{n} + F,$$

where I_n is the ionisation potential of an n -valent atom and F its electron affinity, made it possible to find the values of χ satisfactorily correlated with the EN found by Pauling.¹⁷

Martynov and Batsanov¹⁸ put forward the hypothesis that, from the physical standpoint, EN could be usefully determined as the average energy per valence electron and expressed in terms of the arithmetical mean of all the IP of all the valence electrons

$$\left(\sum_{i=1}^m I_i \right) / m. \quad \text{Allen}^{19} \text{ identified the average energy of a single}$$

valence electron with the weighted mean of the energies of s and p electrons (ε_s and ε_p respectively):

$$\chi_{\text{spec}} = \frac{m\varepsilon_s + n\varepsilon_p}{m + n},$$

where χ_{spec} is the 'spectroscopic' EN.

In a later review,³ he notes that the ionisation potential of a valence electron should in fact be regarded as an objective physical characteristic reflecting the EN of an atom and formulates the equation quoted above as

$$\chi_{\text{spec}} = \frac{mI_s + nI_p}{m + n},$$

where I_s and I_p are the IP for s and p electrons respectively.

The employment of the first IP of atoms (in Mulliken's procedure the values of I averaged in a certain way) or of the last IP for the calculation of EN^{20, 21} leads to results which agree with those obtained by Pauling.⁸ This situation can be evidently accounted for by the fact that both the electron affinity and different IP functions and hence EN itself are determined by the same factor — the individual electronic structure of the atom.

This idea constitutes in essence the basis of another widely employed procedure for the determination of EN — χ is found from geometrical relations of the type

$$\chi = aZR^{-n} + b, \quad (3)$$

where a , n , and b are constants, Z is the effective nuclear charge, and R is the covalent atomic radius.

The 'geometrical' EN scale was first put forward by Gordy,²² who identified EN with the electrostatic potential generated by the effective nuclear charge Z on a covalent sphere with a radius R :

$$\chi = 0.62 \frac{Z}{R} + 0.5. \quad (4)$$

The effective nuclear charge Z is the charge of a nucleus partially shielded by electrons:

$$Z = Z^* - \sigma,$$

where Z^* is the formal nuclear charge and σ is the shielding constant.

There are several ways of determining σ , among which Slater's semi-empirical method is the most familiar. According to this method, the electron shells have their own values of σ_i , the sum of which determines the shielding constant of the atoms σ .

According to Gordy,²² $\sigma = 1$ for inner electrons and 0.5 for valence electrons. Thus Eqn (4) assumes the form

$$\chi = 0.31 \frac{n+1}{R} + 0.5, \quad (5)$$

where n is the number of valence electrons.

The calculation of EN by Gordy's procedure is simple; it is also quite important that this method makes it possible to express electronegativity in terms of fundamental characteristics of the atom — Z and R , demonstrating the 'periodic' character of χ which distinguishes EN, according to the view of many investigators, from other quantitative characteristics of intramolecular interactions.¹⁵ Even within the framework of the same 'geometrical' system, different parameters a and b in Eqn (3) are characteristic of elements belonging to different Periods.

The fact that in Gordy's method the electrostatic potential was first employed to calculate EN must be included among its undoubted advantages. This idea subsequently proved very fruitful.⁹

Allen¹⁹ proposed that the Periodic Table be considered in a three-dimensional form and that the spectroscopic electronegativities of the elements be introduced as the third dimension. In Allen's view, this will make it possible to rationalise the diagonal subdivision of the Periodic Table into metals and nonmetals. With the aid of $\Delta\chi_{\text{spec}}$, it is possible to arrange systematically the properties of an extensive range of familiar materials: ionic crystals, covalent compounds, metals, minerals, inorganic and organic polymers, semiconductors, etc.

An ideologically similar approach has been used by Sproul,^{23, 24} who proposed a simple graphical procedure for the determination of the nature of bonds in binary two-component molecules A_nB_m . By plotting the electronegativity difference $\chi_A - \chi_B$ against the average value $\bar{\chi}$ for a wide range of compounds A_nB_m , Sproul observed that the points on the resulting plot form three different regions corresponding to the ionic, metallic, and covalent nature of the bonds between A and B. Regardless of the EN scale employed, the nature of the distribution and separation of the points was reproduced every time.

Strictly speaking, the conclusion that the electronegativities of partner atoms involved in the bond determine the nature of the latter followed from the work of Pauling himself. However, on the basis of empirical data, Sproul showed that the best graphical separation is achieved when Allen's¹⁹ and Nagle's²⁵ scales are employed. Nagle considered the ratio $(n/\alpha)^{1/3}$, where n is the number of valence electrons and α the polarisability of the isolated atom, as a measure of the polarisability of isolated atoms. Since it is known that $\alpha^{1/3}$ for an isolated atom is proportional to its radius,^{26,27} Nagle's EN scale, like that of Gordy, can be assigned to the class of 'geometrical' scales.

There are quite a few approaches to the determination of χ in which the number of valence electrons²⁸ or directly the number of the Group^{14,29} are used.

Returning to the history of the development of 'geometrical' systems, we shall consider the widely familiar study by Pritchard and Skinner,³⁰ who devised a more rigorous approach to the calculation of the parameter Z in Eqn (4) and obtained, within the framework of Gordy's method, an EN scale which agrees well with Pauling's scale.

Luo and Benson³¹ identified EN with the energy of attraction of a valence electron at a distance equal to the covalent radius from the nucleus;

$$\chi_{LB} = \frac{m+n}{R},$$

where m and n are the numbers of s and p electrons respectively and R is the covalent radius. They created a scale of χ_{LB} values, which they called 'covalent potentials'. The Luo–Benson scale is one of the most familiar and frequently employed in the interpretation of experimental EN data.³² On the basis of the results of the analysis of the frequency distribution of elements with respect to a range of values of χ , Filippov and Gorbunov³³ isolated from the set of known EN data the 'covalent potential' scale and recommended it as the most convenient for practical use.

Neng and Guo³⁴ proposed another modern EN scale reflecting the properties of the outer valence electrons of isolated atoms. They defined EN as the average nuclear potential of the last valence electron:

$$\chi = \frac{Z^*}{\langle r \rangle_{nl}}.$$

Here $\langle r \rangle_{nl}$ is the average radius, which serves as a specific measure of the distance from the valence electron to the nucleus (the averaging was carried out not only with respect to the orbital radius but also with respect to the possible effects of the nuclear core) and Z^* is the nuclear charge acting on the valence electron separated by the distance $\langle r \rangle_{nl}$ from the nucleus and strictly speaking not identical with Slater's nuclear charge. The EN scale introduced by these investigators³⁴ for free atoms is correlated with Mulliken's scale.

The relation

$$\chi_A - \chi_B = k(f_{AB} - 0.5),$$

where k is the scaling factor, f_{AB} is the orbital factor determined by the distances from the atoms A and B to the centre of the bond orbital (r_A and r_B respectively), i.e.

$$f_{AB} = \frac{r_A}{r_A + r_B}$$

and $f_{AB} - 0.5$ is a measure of the difference between the forces of attraction of electrons by atoms, serves as the basis for the creation of the first nonempirical scale within the framework of the quantum-mechanical FSGO (floating spherical Gaussian orbital) method.³⁵

It is noteworthy that the nonempirical FSGO method yields reasonable and reliable values of EN, which are correlated with those on Pauling's scale, but a lot of calculation is then necessary.

The method for the estimation of EN in terms of electron density is very close to the FSGO method:³⁶ the scale obtained on this basis takes into account the topological properties of the electron distribution density in the molecule. The H–X systems (where X is an atom or group of atoms) with the distances r_H and r_X to the bond critical point (BCP) are considered within the framework of this method. The parameter F_X may serve as an equivalent of the EN of the atom X:

$$F_X = \frac{r_H}{n_X \rho(r_i) r_{HX}},$$

where n_X is the number of valence electrons given up by the atom X to the molecule HX and $\rho(r_i)$ is the electron density at the BCP. If the values of F_X are adjusted to the scale with the boundary values $\chi(\text{Li}) = 1.0$ and $\chi(\text{F}) = 4.0$, then χ_X can be found from the equation

$$\chi_{\tilde{X}} = 1.938 F_X^{-0.2502}.$$

The values obtained in this way are correlated both with those calculated by Pauling and with the χ_{FSGO} .

We may note that, in systems analogous to H–X the electronegativity of the atom X is expressed in terms of the change in the H–X bond length on ionisation.³⁷ Marriott *et al.*³⁸ considered derivatives of HX and showed that the charge density on the hydrogen atom, obtained within the framework of *ab initio* calculations, may be used as a simple measure of the electronegativity of X.

The study of Allred and Rochow³⁹ initiated the overall direction of the development of the 'geometrical' methods for the calculation of EN. They were the first to represent EN as the force of the interaction of an unshielded atomic nucleus and a valence electron separated by a distance corresponding to the covalent radius R :

$$\chi = 0.36 \frac{Z_{\text{ef}}}{R^2} + 0.74.$$

The value of Z_{ef} is determined in accordance with Slater's rule. Numerical coefficients adjust χ to Pauling's scale.

Evidently the method for the description of EN as a 'force' corresponds best to its initial definition by Pauling and comparison of the values found by Allred and Rochow with those derived for other systems demonstrated the high quality of their approach.^{8,9} The Allred–Rochow EN system is one of the best known and most frequently employed. For example, Allen identifies it, together with Pauling's system, as the best founded and most acceptable at the present time.³ Employment in the Allred–Rochow equation of experimental values of Z_{ef} obtained from X-ray diffraction data makes it possible to put forward an EN scale⁴⁰ which agrees with Pauling's scale.

The 'force' approach to the determination of EN was later developed in many investigations.^{8,41,42} Boyd and Markus⁴³ proposed a theoretical method for the calculation of EN based on a nonempirical electrostatic model, according to which electrostatic forces, which determine χ , act between the effective nuclear charge and electrons at a certain distance r from the nucleus:

$$\chi = c N r^{-2} \left[1 - \int_0^r D(r) dr \right],$$

where c is the normalising coefficient which adjusts the EN to Pauling's scale, N is the atomic number, and $D(r)$ is the radial density function. Application of the Hartree–Fock wave function enabled the authors to obtain electro-negativities which are satisfactorily correlated with the values on empirical scales.⁹

The force acting on an electron (and hence EN) can be determined⁴² within the framework of the inverse quadratic dependence on the radius R using the ionisation potential of the valence electron I and the effective principal quantum number n^* :

$$\chi = 0.241 \frac{n^*(I/R)^{1/2}}{r^2} + 0.775$$

(R is the Rydberg constant).

Sanderson's 'geometrical' system,^{44–54} based on the inverse cubic law, relates the EN of an atom to its volume electron density (ED), which is determined by the atomic number N and the covalent radius R :

$$\text{ED} = \frac{3N}{4\pi R^3}.$$

Sanderson suggests that a dimensionless quantity, which he called the 'stability ratio' (SR), be used as a measure of ED. It is obtained by dividing the ED for the atom by the ED for the inert gas in the given Period (the value of R for the latter is interpolated). The stability ratios thus obtained, characterising according to Batsanov⁸ not isolated atoms (as postulated by Sanderson himself) but atoms in molecules, form an intrinsic electronegativity scale (SR), which can be adjusted to Pauling's scale by means of the following equation:^{8,9}

$$\chi = (0.21\text{SR} + 0.77)^2.$$

The values of SR are correlated satisfactorily with experimental data.⁹

More than 20 different 'geometrical' EN systems are known.⁵⁵ It is assumed that the increase in the accuracy of such systems is associated with the increase in the power exponent n in Eqn (3). However, Batsanov⁸ has noted that the accuracy increases also with increase in the constant term b . The increase is caused by the parallel increase in the difference between the dimensionalities of the thermochemical and geometrical EN.

In order to reduce this difference to a minimum, Batsanov proposed a new geometrical EN system. Having adopted as a basis the Cottrell–Sutton formula

$$\chi = 0.5 \left(\frac{Z}{R} \right)^{1/2} + 0.2$$

(one of the earliest geometrical systems), he put forward the following relation whereby the maximum approach of the values of χ to Pauling's scale is achieved:

$$\chi = \alpha \left(\frac{Z^*}{R} \right)^{1/2},$$

where α is a correction factor:

$$\alpha = \frac{1 + 0.1n}{1 + 0.01(n^*)^3},$$

n being the number of the Group of the element in the Periodic System.

By modifying this equation, it is possible to calculate the EN of atoms in the crystalline state, which is necessary for the interpretation of the nature of the bonds in binary and complex compounds.

As noted above, several tens of EN scales, based on different properties of atoms and molecules, which are not always identical, are known. As a rule each scale is satisfactorily correlated with several other EN scales. This apparently reflects the identity of their nature despite the fact that the values of EN proposed by different workers may differ both in dimensionality and in the methodology of their determination and even in the physical significance attributed to them.

We may note that the criteria of the validity of a particular approach to the determination of EN are lacking, which is perhaps the principal problem as regards the concept of EN. For this reason, investigators test the correctness of any new EN system by comparing it with the scales already available. The necessary correspondence can be achieved with by no means all the scales and investigators have to be satisfied as a rule by a more or less acceptable reproduction of a proportion of them.

Indeed the question arises which physical (or chemical) characteristic or property should be regarded as the most adequate expression of χ , how should EN be measured, and what is its dimensionality. In order to answer these questions, it is essential to understand what EN actually is. Paradoxically, despite the more than adequate, from the scientific point of view, age of the concept of EN, controversy as to 'what is electronegativity' has not been resolved even now. The majority of investigators tend to adopt Pauling's original treatment: 'EN is the force with which an atom in a molecule attracts electrons'. However, the current content of this concept is much wider. Since EN is undoubtedly an individual atomic characteristic, the question naturally arises what individual property of the atom determines its power to attract electrons in the molecule. Finally, is this property additive and to what extent? Evidently the property must be characteristic of an individual free atom (the majority of approaches are based precisely on this idea), but at the same time it can remain unchanged or vary in proportion to the initial value on formation of bonds. It has to be said that an exact unambiguous answer has not been obtained to the majority of these questions to this day.

II. The electronegativity of groups

The development of the concept of EN has inevitably led to the appearance of the idea of the EN of a group (substituent).

In 1951, Sanderson put forward the postulate according to which the EN of a molecule is equal to the EN of any atom in it and proposed a method for the averaging of the EN on the basis of their geometrical mean.⁹ Sanderson's total equalisation principle initiated the overall direction of the development of the concept of EN and made it possible to calculate the EN of groups and substituents from the atomic χ .

If EN is a characteristic not only of an atom but also of a group, the question of the quantitative determination of the group EN is legitimate. According to Pauling's classical definition, the latter is the force with which the group attracts valence electrons in the molecule.

The EN of groups of atoms were first calculated by Pritchard and Skinner³⁰ in a study of the thermochemical characteristics of disproportionation reactions of mercury derivatives.

Finemann⁵⁶ later modified Pauling's classical method for the determination of the EN of hydrocarbon radicals:

$$\Delta E = E(\text{AR}) - \frac{1}{2}[E(\text{AA}) + E(\text{RR})],$$

where A is an atom and R a radical. The quantity $\chi_{\text{Me}} = \chi_{\text{C}}$ was adopted as the standard.

Subsequently this thermodynamic approach was developed and partially applied in practice. The results of the analysis of the thermodynamic parameters of various reactions and experimental bond energy data have been described in detail in a monograph.⁸

When Pauling's method is employed, account is frequently taken of the results of other physicochemical studies. Thus the following equation has been employed:^{57,58}

$$D(\text{AB}) = [D(\text{AA})D(\text{BB})]^{1/2} + k|\chi_{\text{A}} - \chi_{\text{B}}|^2.$$

Here the force constant k is optimised on the basis of the values of χ_{B} obtained from the parameters of NMR spectra. Examples of a similar use of hydrolysis⁵⁹ and basicity constants, oxidation potentials, *etc.*¹⁵ are known.

1. Determination of electronegativity from correlations with physical properties

The concept of EN is directly related to ideas concerning bond energies. The energy of chemical bonds determines in its turn many physical characteristics of compounds, for example spectroscopic characteristics. Thus the numerous correlations between EN and various spectroscopic parameters, frequently employed in finding new values of χ , have a physical justification.

It has been noted^{8,15} that it is most useful to employ bond force constants, which are determined solely by the energies of the interactions between atoms. Such a relation was first established by Gordy,⁶⁰ who expressed the force constant k as a function proportional to the product of the EN of the atoms involved in the bond. Furthermore, the force constant k_{AB} of the A–B bond can be expressed, as in Pauling's method, in terms for the corresponding values for homogeneous bonds, k_{AA} and k_{BB} , and the difference between the EN of the atoms A and B:⁶¹

$$k_{AB} = (k_{AA}k_{BB})^{1/2} + (\chi_A - \chi_B)^2.$$

However, since the force constants are difficult to obtain, correlations between EN and the vibrational frequencies of atoms have come to be most widely employed.

As early as 1954, Bell *et al.*⁶² found a linear relation between the vibrational frequency of the P=O bond in the compounds ABCP(O) and the sum of the EN of the groups A, B and C. Subsequently this approach was extended⁶³ to the carbonyl derivatives ABC=O.^{64,65}

Relations between the vibrational frequency of a functional group and not only the EN of the substituents but also the EN of the atom attached to the group are widely known. Thus it has been shown⁶⁶ that there is a linear relation for the compounds CH₂=CHX between the frequencies of the out-of-plane deformation vibrations of the CH₂ groups and the Pauling EN of the atoms X. A similar dependence on the EN of a halogen atom is characteristic of the $\nu(\text{H}-\text{Hal})$ stretching vibrations.

Subsequently similar relations were discovered not only for the compounds HR^{67,68} but also for the methyl derivatives CH₃X.⁶⁹ Correlations between the EN and the vibrational frequency of the OH,⁷⁰ CN, CH, *etc.*¹⁵ groups have also been obtained. It has been shown⁷¹ that the vibrational frequencies of the –CH₂– fragment in the molecules A–CH₂–B are directly related to the sum of the electronegativities of A and B. On the other hand, a dependence of ν on χ^2 has been found for these systems.⁷² Similar relations have been noted also in a series of other investigations (see, for example, a monograph¹⁵ and the literature quoted therein). Relations between ν and $\chi^{1/2}$ have been established for the vibrational frequencies of the C–Si bonds in silane derivatives.⁷³ Vereshchagin¹⁵ has noted that the correlations between the parameters of vibrational spectra and EN can be extended to compounds of any complexity.

A large number of studies have been devoted to relations between the EN of atoms and groups and NMR spectroscopic data. Spin–spin coupling constants, particularly for olefinic derivatives, are used to calculate the unknown values of χ .^{74,75} Numerous linear relations between EN and vicinal constants have been discovered.¹⁵ The chemical shifts of protons have also been considered as characteristics of EN. For example, an expression relating the difference between the proton shifts of methylene and methyl groups to the EN of the substituent X has been established:⁷⁶

$$\chi = 1.71 + 0.02315[\delta(\text{CH}_3) - \delta(\text{CH}_2)].$$

Inamoto and coworkers^{77,78} have shown that the chemical shifts in the ¹³C NMR spectra of certain aliphatic (EtX) and aromatic (PhX) derivatives reflect the influence of the EN of the corresponding substituent X. In order to account for experimental NMR data, a new 'inductive' parameter of the substituents has been proposed. It is calculated by a formula similar to Gordy's equation [Eqn (4)]:

$$i = \frac{Z_{\text{ef}} + 1}{n_{\text{ef}}}.$$

The relations describing the influence of the EN of the substituent on the shielding of the nuclei continue to be used widely even to this day in ¹H,⁷⁹ ¹³C,^{80–82} ¹⁹F,^{83,84} ¹³P,⁸⁵ ¹¹⁹Sn,^{15,86} *etc.* spectroscopy.

Correlations between EN and the shifts of the absorption maxima of compounds in UV spectra, ³⁵Cl NQR spectroscopic frequencies, and other physicochemical parameters are known.

2. Theoretical approaches to the quantitative estimation of group electronegativities

The experimental methods described above have undoubtedly played and continue to play an important role in the quantitative estimation of Group EN. At the same time, it is evident and reasonable that procedures for the calculation of EN of groups using the EN of their substituent atoms are theoretically of greatest interest among all the diverse approaches to the solution of this problem.

The majority of studies in this field may be assigned to two principal aspects. The first identifies the donor–acceptor properties of the substituent with the nature of its central atom (CA). Thus the problem of the determination of the group EN (χ_g) reduces to finding a value of the EN at the first (central) atom of the group modified depending on the environment:

$$\chi_g = \chi(\text{CA}) + \delta\chi(\text{CA}).$$

Thus, in Gordy's method,²² on passing from the calculation of the EN of atoms to that of the EN of groups the number of valence electrons n in Eqn (5) is replaced by the effective quantity n^* , reflecting the 'electron atmosphere' of the first atom. The latter is calculated from the EN of the first atom and a series of independent parameters introduced by various investigators in a fairly arbitrary fashion.^{87,88} The corresponding equation has the form

$$\chi = a \frac{n^* + 1}{R} + b$$

A similar 'geometrical' approach to the determination of the EN of the central atom as a measure of the EN of the group is used in the Luo–Benson method of 'covalent potentials' (U_X):^{31,88–92}

$$U_X = \frac{n_X}{R_X}$$

where n_X is the number of valence electrons of the central atom and R_X is its covalent radius.

The fundamental difference between this method and others consists in the fact that the covalent radius of the central atom (R_X) is considered as the variable. Since this experimental physical quantity characterises the size of the atom in the 'covalent' molecule, *i.e.* the atom in the energetically optimal valence state and not the free state, one can postulate that the calculated values of R_X are reliable. This hypothesis has been confirmed by the satisfactory correlation between U_X and the results of other workers.^{91–93}

The contribution of the environment of the central atom to the overall EN of the group is calculated within the framework of certain approaches on the basis of a kind of similarity of the additive scheme, which admittedly does not have a rigorous physical and mathematical justification. Thus the following equation has been proposed for the calculation of the EN of the group AX_m.⁹⁴

$$\chi(\text{AX}_m) = \chi(\text{A}) + \frac{m}{6}[\chi(\text{X}) - \chi(\text{A})].$$

If the substituents at A were different, similar relations were employed. For example, the EN of the group CX¹X²X³ (Refs 64, 65) was calculated by the equation

$$\chi(CX^1X^2X^3) = 0.5\chi(C) \sum \frac{\chi^2(X)}{12\chi(H)}.$$

The other aspect, developed in Sanderson's studies,^{44–54} is based on the principle of the equalisation of electronegativities which he postulated. In this approach the group EN is considered as a function of the averaging of the EN of all the atoms constituting the substituent. Apart from the geometrical-mean function, proposed by Sanderson himself,^{95,96} the arithmetical-mean^{8,15} harmonic-mean,⁹⁷ *etc.*⁹⁸ functions were examined.

All the theoretical methods specified above for the determination of the group EN are linked by the idea that the EN of a free atom changes when the latter forms a covalent bond. Thus an internal electronegativity, equalised *in situ*, is attributed to the 'bound' atom. It can be determined also by its environment, among other factors. The *in situ* EN of atoms determine in their turn the donor–acceptor properties of the group itself.

A logical development of the entire EN theory consisted in the fact that an intrinsic and unique value of EN was assigned to each atom, as had been done in the original study by Pauling, after which the EN of the atom in different valence states were introduced, and finally there arose the concept of the *in situ* EN of the bound atom, which depends on its environment, *i.e.* on the state of the atom in the molecule.

Consequently any attempt to designate the relation between the 'free' EN and the EN *in situ* involves the principal problem in chemistry — what is an atom in a molecule? In practice the consideration of the EN of chemical groups and the atoms in them makes it necessary to take into account the distribution of electron density.

III. The concept of 'orbital' electronegativities and the equalisation principle

As noted above, Mulliken's definition of EN¹¹ postulates the dependence of EN on the valence state of the atom, which made it possible to abandon the idea of the existence of a unique EN for each atom regardless of its hybridisation. The need to take into account the orbital in which the valence electron is located then arises.

While studying this problem Hinze and Jaffe^{99–101} introduced the concept of the 'orbital' EN and developed a semi-empirical method for the calculation of the ionisation potential (I_v) and the electron affinity (F_v) for any valence state v . This made it possible to find the EN by Mulliken's method taking into account the corresponding valence states of the atoms:

$$\chi_M = \frac{I_v + F_v}{2}. \quad (6)$$

The calculated values proved to be linearly related to those determined by Pauling's method.

It is noteworthy that quantum-mechanical calculations are used to evaluate the orbital EN for pure s , p and d states. In order to obtain the EN of an atom, they are added together in conformity with the degree of hybridisation of the atom:¹⁵

$$\chi = n_s\chi_s + n_p\chi_p + n_d\chi_d + \dots$$

The orbital EN (χ_l) may be expressed¹⁰² also in terms of the radius of the valence shell and the quantum number l :

$$\chi_l = \frac{l}{R}.$$

If χ_1 , χ_2 , and χ_3 are the EN of the s , p , and d orbitals respectively, then the atomic EN is expressed as follows:

$$\chi_a = 0.43 \sum \chi_l + 0.24.$$

It has also been suggested that the orbital EN be calculated by Mulliken's method with the aid of the modified Eqn (6):^{103–107}

$$a = \frac{I_v + F_v}{2} = \frac{I_0 + P_0 + P^+ + P^-}{2},$$

where I_0 and P_0 are respectively the ionisation potential of the free atom and the energy of the transition of the free atom to the given valence state and P^+ and P^- are the energies of the promotion of the cation and anion formed from the atom in the valence state v .

Special mention should be made of the study of Iczkowski and Margrave,¹⁰⁸ which to a large extent determined the subsequent development of the ideas about the orbital EN. In 1961, these workers first represented the energy of an isolated atom (E) as a function of the filling of the electron shell:

$$E(\delta) = E_0 + a\delta + b\delta^2 + c\delta^3 + d\delta^4, \quad (7)$$

where E_0 is the energy of the ionised core, δ is the partial charge of the atom, and a , b , c , and d are empirical coefficients, which depend on the nature of the atom and its valence state.

According to the authors themselves, it is sufficient to restrict Eqn (7) to second-order terms (at least for s and p elements):

$$E(\delta) = E_0 + a\delta + b\delta^2. \quad (8)$$

If it is assumed that $E_0 = 0$, $E(1) = I$, and $E(2) = I + F$, then the values of a and b expressed in Mulliken terms are obtained:

$$a = \frac{3I - F}{2}, \quad b = \frac{F - I}{2}.$$

Iczkowski and Margrave regarded $E(\delta)$ as a continuous and differentiable function of δ and identified the EN of an isolated atom with the first derivative of the energy with respect to the occupation number of the valence orbitals:

$$\chi = \frac{dE}{d\delta}. \quad (9)$$

In this representation, the EN of an atom may be expressed as a linear function of δ :

$$\chi(\delta) = a + 2b\delta. \quad (10)$$

It was subsequently proposed that a more rigorous three-term equation be employed:¹⁰⁹

$$\chi(\delta) = a + b\delta + c\delta^2$$

with empirical coefficients differing markedly from those in Eqn (10) (here the contribution of the quadratic terms is relatively small). Nevertheless the linear Eqn (10) has in fact come to be most widely used and has become best known. On substituting into it the parameters a and b expressed in the Mulliken form, it is possible to obtain the following expressions for the EN of a cation, a neutral atom, and an anion respectively:

$$\chi(0) = \frac{3I - F}{2}, \quad \chi(1) = \frac{I + F}{2}, \quad \chi(2) = \frac{3F - I}{2}.$$

On the one hand, the identity of the equation for the EN of a neutral atom $\chi(1)$ with the Mulliken expression served, according to Iczkowski and Margrave, as confirmation of the correctness of their approach. On the other hand, Mullay⁹ noted that such results yielded an additional theoretical justification of Mulliken's scale itself, which may possibly make it the best among all others.

It is noteworthy that Iczkowski and Margrave were not the first to relate the *in situ* EN of an atom to its partial charge δ . As early as 1951, Sanderson⁹⁵ suggested, on the basis of the principle of the total equalisation of electron density, a simple scheme for the calculation of δ . Here the *in situ* χ was calculated as the geometrical mean.

Nevertheless, it was in fact Eqns (9) and (10) that became the 'starting' point for the further development of the theory and methods for the calculation of EN.

Hinze *et al.*¹¹⁰ developed ideas concerning orbital EN and identified the donor–acceptor properties of an isolated atom with the EN of its valence orbital. Having adopted as a basis the definition of Iczkowski and Margrave, who expressed the EN of an isolated atom in terms of the potential acting on the valence orbital [Eqn (9)], the authors suggested that similar relations be used for the orbital EN (χ_{aj}):

$$\chi_{aj} = \frac{\partial E_a}{\partial n_j}, \quad (11)$$

where E_a is the energy of the atomic orbital j and n_j is its population.

Next, having postulated that the function $E_a(n)$ is continuous and differentiable and having restricted it to the quadratic dependence on n , they obtained a linear equation relating the EN of the orbital to its population:

$$\chi_{aj} = a_a + 2b_a n_{aj}. \quad (12)$$

This equation is analogous to Eqn (10). According to the data of Whitehead *et al.*,¹¹¹ the parameters a_a and b_a may be expressed, as in Eqn (10), in terms of the ionisation potential and the electron affinity, but in this case not of the atom but of the corresponding orbital j . Furthermore, Whitehead showed that the parameters a_a and b_a can be determined by using the parameters of the population of all the valence orbitals of the atom other than j .

As mentioned above, Eqns (10) and (11) identify the EN (the EN of an isolated atom and the orbital EN) with the potential, which possesses *a priori* the equalisation property. This factor reasonably led the creators of the theory of orbital EN to the idea of their equalisation. In conformity with Meek's hypothesis,¹⁰⁵ the orbital EN of the atoms A and B are equalised on formation of the bond A–B:

$$\frac{\partial E_A}{\partial n_A} = \frac{\partial E_B}{\partial n_B},$$

hence the functions of the charges on each of these atoms also become equal:

$$a_A + 2b_A n_{Aj} = a_B + 2b_B n_{Bj}.$$

Thus, bearing in mind that two electrons participate in the formation of the bond, *i.e.* $n_{Aj} + n_{Bj} = 2$, the equation obtained can be used to establish the charge distribution. On the basis of the foregoing, an iterative method for the calculation of the EN of haloalkyl groups has been developed;¹¹⁰ with its aid, it has been possible to calculate certain group χ .

Subsequently Huheey^{112, 113} proposed a simple scheme for the determination of the EN of groups based on the Iczkowski–Margrave Eqn (10), but in this instance operating with the values of a_A and b_a taken from the studies of Hinze, Whitehead, and Jaffe. On the basis of Sanderson's study, Huheey postulated the equality of the EN of the group and its constituent atoms. Thus the following expression was obtained for the substituent AB_n :

$$\begin{aligned} \chi_{AB_n} = \chi_A = \chi_{B_1} = \dots = \chi_{B_n} &= a_A + 2b_A \delta_A = \\ &= a_B + 2b_B \delta_{B_1} = \dots = a_B + 2b_B \delta_{B_n}. \end{aligned}$$

Having solved these equations, it is possible to obtain, as in the method of Hinze, Whitehead, and Jaffe, the charges and the group EN. The solutions can then be found for a neutral group, a cation, and an anion (subject to the condition that $\delta_g = \Sigma \delta = 0, +1$, and -1 respectively). Having applied his approach, Huheey calculated the EN of almost 100 substituents and, what is no less important, analysed the significance of the coefficients in the equation relating the EN of a group (atom) to the charge and identified a_A with the intrinsic value of the EN of the atom and b_A with the sensitivity of the EN to a change in the charge.

A similar approach, based on the hypothesis of the equality of a_A and b_A , *i.e.* $\chi_a = a_a + b_a \delta_a = a_a(1 + \delta_a)$, and the principle of

the total equalisation of the EN, made it possible to obtain the following expression for the group EN:⁹

$$\chi = (N + \delta_g) / \sum_1^N \frac{n_i}{\chi_{ai}}, \quad (13)$$

where $N = \Sigma n_i$ is the total number of atoms, n_i is the number of atoms in the group, and χ_i is the EN of the i th atom on Pauling's scale before the formation of the molecule.

Subsequently Mullay¹¹⁴ established another relation between the coefficients a_a and b_a , namely $b_a = 1.5a_a$, and expressed the *in situ* orbital EN in the following manner:

$$\chi_{aj} = a_a(1 + 1.5 \sum \sigma_a). \quad (14)$$

The EN of a chemical group AB is then determined as the EN of its central atom on which an effective charge $d_j \ll 0$ is accumulated at the expense of the orbital j , ensuring a bond between the central atom and the rest of the molecule. Subject to the condition of the conservation of electroneutrality ($\delta_A + \delta_B = 0$) and the equalisation of the orbital EN ($\chi_A = \chi_B$), it is possible to obtain an expression for the calculation of group EN analogous to Eqn (13):³

$$\chi_g = \frac{N + 1.5 \sigma_g}{\sum_1^N n_i / \chi_i}.$$

The group EN obtained within the framework of this method, which takes into account the hybridisation of the valence orbital and the effective charge on the group, have reasonable values.

Subsequently this approach was improved: a term taking into account the interatomic electronic repulsion of the valence orbitals was added to Eqn (14):^{115, 116}

$$\chi_{aj} = a_{aj}(1 + 0.5 \sum \delta_{ai} + 1.5 \sum \delta_{aj}).$$

Thus the concept of orbital EN became the basis of the modern concept of EN, with the aid of which not only have the new easy methods for the calculation of EN been created but its physical nature has been to a large extent elucidated. Certain principal postulates of this concept of EN have been subjected to serious criticism at various times;³ the very legitimacy of identifying the EN solely with orbitals has been questioned;⁹ in some investigations, it has been shown that the idea of using orbitals in discussing EN is not always necessary.¹¹⁷ The arbitrary nature of the assumption of the continuity and differentiability of the relation between the energy of the system (atom, molecule) and the number representing the filling of the orbitals by valence electrons [the function $E(q)$], the assumption constituting the basis of the theory of orbital EN, has also been noted.⁶ This hypothesis is strictly speaking invalid for an isolated atom: in this case, the values of the argument q can only be discrete.

Slater¹¹⁸ emphasised that in the fundamental equations of the X_α SCF method there are no limitations associated with the requirement that q is integral because atomic and electronic systems obey Fermi statistics, a characteristic feature of which is fractional energy level occupation numbers. At the same time, he justified the expansion of the function $E(q)$ in the series

$$E(q) = E(0) + \left(\frac{\partial E}{\partial q}\right)q + \frac{1}{2!} \left(\frac{\partial^2 E}{\partial q^2}\right)q^2 + \frac{1}{3!} \left(\frac{\partial^3 E}{\partial q^3}\right)q^3 + \dots \quad (15)$$

Eqn (15) is analogous to the empirical Iczkowski–Margrave Eqn (7). Comparison demonstrates the correspondence between the coefficients a and b in the Iczkowski–Margrave equation and the first and second derivatives of the energy with respect to the occupation number in the Slater formula.

Klopman^{119–121} also showed that it is possible to expand the energy in a series analogous to the series in Eqn (7). Within the

framework of the theory of atomic spectra, he expressed the energy of a free atom by the equation

$$E_a = \sum_i B_a^i + \frac{1}{2} \sum_{ij} A_a^+ \delta_{ij} + \frac{1}{2} \sum_{ij} A_a^- (1 - \delta_{ij}), \quad (16)$$

where B_a^i is the energy of the i th electron in the atomic spin-orbital in the electron shell with the quantum number l , A_a^+ and A_a^- are the energies of the interaction of electrons with identical and opposite spins respectively, and δ_{ij} is the Kronecker parameter.

If the electrons are in the same orbital, $A_a^+ = A_a^- = A_a$ and Eqn (16) assumes the form

$$E_{a_j} = n_{a_j} B_a^j + \frac{1}{2} n_{a_j} (n_{a_j} - 1) A_a. \quad (17)$$

Having put $a_a = B_a^j - A_a/2$ and $2b_a = A_a/2$, we obtain from Eqn (17) an expression for EN:

$$\chi_{a_j} = \frac{\partial E_{a_j}}{\partial n_{a_j}} = B_a^j - \frac{A_a}{2} + \frac{A_a}{2} n_{a_j},$$

which corresponds fully to the Hinze–Jaffe formula (12).

Later Mullay¹¹⁴ showed that the relation between the Klopman parameters B_a^j and A_a is linear. This enabled him to express the orbital EN by employing only one of the parameters:

$$\chi_{a_j} = A_a(0.5 + 0.15N s_j).$$

Here N is the number of valence electrons and s_j is the fraction of the s character of the orbital j .

From this expression, the author obtained a formula whereby a series of values of EN on Pauling's scale were determined:

$$\chi_{a_j}^0 = 1.67 \frac{G_j Z_{\text{ef}}^2}{n_{\text{ef}}^2} + 041,$$

where G_j is a function which depends linearly on the p character of the orbital j and Z_{ef} and n_{ef} are the effective nuclear charge and the effective principal Slater quantum number.

Furthermore, it should be noted that Klopman confirmed within the framework of his approach the validity of the equalisation principle for orbital EN, having described them not only in atomic but also in molecular terms:¹²²

$$\frac{\partial E_m}{\partial n_j^i} = \frac{\partial E_m}{\partial n_k^i},$$

where E_m is the energy of the molecule, n_j^i the electron density of the orbital j corresponding to the i th electron, and n_k^i the electron density of the orbital k corresponding to the i th electron. Thus Klopman concluded that all the orbitals in the molecule are equipotential and actually proposed the term 'molecular orbital EN'.

The total equalisation principle, which became an indissoluble component of the concept of orbital EN, has been subjected to a many-sided criticism.^{3, 9, 15} One of its main deficiencies is the impossibility of a differentiated determination of the EN of isomeric groups, although their donor–acceptor properties should undoubtedly differ. Some investigators have noted that the equalisation principle, possessing undoubted simplicity, does not reflect a series of fundamental chemical ideas, for example the resonance electrostatic effects.^{15, 112, 1113, 123, 124} There exists also the view that, under conditions where the electron density is displaced, the total equalisation principle does not work at all because the electrostatic potential arising under these conditions inhibits further displacement of electron density and at best one can only speak of a partial equalisation of the EN.

Thus Pritchard¹²³ suggested that the real difference between the electronegativities of bound atoms, taking into account the overlap of the orbitals, reaches $\sim 10\%$ of the initial difference $\Delta\chi$.

Quantum corrections for this overlap were subsequently introduced,¹⁵ which permitted an additive calculation of the electron distribution in a series of fluoromethane derivatives.

Whilst modifying this method for the determination of EN, Huheey¹²⁵ proposed 80% equalisation of electron density and introduced a corresponding coefficient of 0.8 into the calculation.

The method involving the incomplete equalisation of the EN has also been developed in other investigations^{126, 127} based on the electrostatic model postulating the expansion of the energy in a power series. The authors multiplied the atomic charges (obtained by minimising the total energy) by an arbitrary constant, which takes into account the potential arising when electrons are displaced and also the influence of remote atoms. The iterative procedure for the calculation of EN was performed until constant values of the latter called the 'residual' EN were obtained. A rigorous determination of such EN became possible only subject to the removal of the condition involving the restriction of the dependence of E on q to the quadratic term.¹²⁸

Thus the concept of orbital EN undoubtedly promotes the development and understanding of the problem of EN as a whole, permitting the theoretical justification and the binding into a single whole of many general ideas and postulates (for examples, Mulliken's definition of EN, Sanderson's principle of the equalisation of EN, the dependence of EN on the valence state of the atom, the dependence of the energy of the atom on the charge, *etc.*). At the same time, one cannot fail to mention also a whole series of important problems remaining open to discussion, such as the possibility of the continuous expansion of E in terms of q for an isolated atom, the legitimacy of the total equalisation of EN and the specific equalisation algorithm (geometrical mean, arithmetical mean, *etc.*), the physical significance of the *in situ* EN of an atom in a molecule, and certain others, which have not so far received an adequately rigorous justification.

Many of these problems have been solved within the framework of the density functional theory (DFT), which has recently appeared and has undergone an extremely dynamic development. It permitted the current interpretation of many facts which have been insufficiently rigorously justified and treated.

IV. Electronegativity and the density functional theory

Any property characterising the state of a molecule is a function of parameters the values of which manifest the individuality of the given compound. The density functional theory considers a molecule as a set of nuclei and electrons. The parameters employed are the number of electrons N and the energy of the interaction of the nuclear core with the i th electron $v(r)$ at any point in the molecular system (its nuclear potential):¹²⁹

$$v(r) = \sum_n \frac{Z_n}{r_{n_i}},$$

where n is the index of the nucleus, Z_n is the nuclear charge, and r_{n_i} is the distance from the nucleus n to the i th electron.

If $N = \text{const}$, the energy of the system is determined as the functional $E[N, v(r)]$, and the task of describing the interaction between the nuclei and electrons consists in finding an analytical expression for the energy E as a function of the independent parameters N and $v(r)$.

The function of the distribution of electron density of the ground state $\rho(r)$, simultaneously determining N and $v(r)$ and hence containing all the information about the system itself and its energy, is introduced within the framework of the DFT in accordance with the Hohenberg and Kohn theorems:¹²⁹

$$E(N, v) = E(\rho) = \int \rho(r) v(r) dr + F(\rho).$$

By applying the variational principle to the functional $E_{\text{el}}[\rho(r)]$ (E_{el} is the electronic energy of the system), it is possible to obtain

the Euler equation, which is analogous to the Schrodinger equation:

$$v(r) + \frac{\partial F(r)}{\partial \rho(r)} = \mu,$$

where $F(r)$ is the sum of the electron kinetic energy and the electron repulsion energy, $\rho(r)$ is the electron density functional, and μ is the Lagrange multiplier, called the electron chemical potential, which has the same value throughout the entire system and is determined as the partial derivative of the energy E with respect to the number of electrons N at a constant external potential v :

$$\mu = \left(\frac{\partial E(r)}{\partial \rho(r)} \right)_{v(r)} = \left(\frac{\partial E}{\partial N} \right)_{v(r)}.$$

Thus $\mu[Nv(r)]$ is a global characteristic, which, together with the energy, is a fundamental property of the ground state of the system.

The development of the ideas of both the DFT and of the entire modern concept of EN has to a large extent been determined by the studies of Parr and Pearson and coworkers.^{130–136}

Parr and coworkers¹³¹ made the fundamentally important assumption that the negative chemical potential and the EN are identical:

$$\chi = -\mu = \left(\frac{\partial E}{\partial N} \right)_v. \quad (18)$$

Subsequently Parr and Pearson¹³² determined the second derivative of the energy with respect to the number of electrons as the absolute hardness (η)

$$\eta = \frac{1}{2} \left(\frac{\partial^2 E}{\partial N^2} \right), \quad (19)$$

reflecting the ‘resistance’ of the chemical potential μ (or the electronegativity χ) to a change in the number of electrons:

$$\eta = \frac{1}{2} \left(\frac{\partial \chi}{\partial N} \right) = \frac{1}{2} \left(\frac{\partial \mu}{\partial N} \right). \quad (20)$$

Correspondingly the softness of the system is defined as the reciprocal of the hardness:

$$S = \frac{1}{2\eta}. \quad (21)$$

Having postulated a quadratic dependence of the energy of the system on the number of electrons (in the absence of overlap of the valence orbitals), the electronegativity of the atom χ^0 and its hardness η^0 can be expressed in terms of the ionisation potential I and the electron affinity F :

$$\chi^0 = \frac{I + F}{2}, \quad \eta^0 = \frac{I - F}{2}. \quad (22)$$

Thus the definition of EN within the framework of the DFT agrees with Mulliken’s ideas about the ‘absolute’ EN, while the parameter η , defined by Eqn (20), is³² the ‘absolute’ hardness.

1. The principle of hard and soft acids and bases

The concepts of chemical hardness and softness were first introduced in the study of the properties of Lewis acids (electron acceptors) and bases (electron donors). Pearson^{133–135} divided them into soft (readily polarisable) and hard (poorly polarisable). He also formulated the principle of ‘hard and soft acids and bases’ (HSAB), according to which hard acids combine preferentially into complexes (react) with hard bases, whilst soft acids combine similarly with soft bases.^{133, 134} This principle has been widely applied in various branches of chemistry, but a quantitative

characteristic of the ‘hardness’ of acids and bases was lacking for a long time.⁶ The definition of hardness η within a framework of the DFT readily elucidates the physical significance of this parameter. According to the Klopman theorem, the ionisation potential I and the electron affinity F can be expressed in terms of the energy of frontier orbitals: the highest occupied (HOMO) and the lowest unoccupied (LUMO):^{134, 136, 137}

$$-E_{\text{HOMO}} = I, \quad -E_{\text{LUMO}} = F.$$

Thus the hardness of the system is determined by half the difference between the energy levels:

$$\eta = \frac{E_{\text{HOMO}} - E_{\text{LUMO}}}{2}. \quad (23)$$

Clearly a ‘hard’ molecule should have a large energy gap between the LUMO and the HOMO, while a ‘soft’ molecule should have a small gap, which in fact explains the difference between their polarisabilities.

Another important postulate put forward by Pearson¹³⁸ is the principle of maximum hardness, according to which the system tends to acquire the maximum hardness. This principle, like the HSAB principle, was initially based on experimental relations and only then received a mathematical justification within the framework of DFT.^{136–140} According to Eqn (22), the quantity η increases with increase in ionisation potential and with decrease in electron affinity. Thus the system endeavours not to give up its electrons and not to accept extraneous ones, *i.e.* to remain stable.

Pearson’s principle of maximum hardness combines a whole series of familiar empirical relations, rules, and concepts: the octet principle postulated by Lewis and Langmuir, the 18 electron rule. Hückel’s $(4n + 2)$ aromaticity rule for organic systems, and the Wade–Mingos $(2n + 2)$ rule for inorganic systems, as well as the concept of the maximum thermodynamic stability of the molecule in the case where all its bonding orbitals are fully occupied whilst the antibonding orbitals are unoccupied.¹³⁷ The view that chemical hardness is a quantitative characteristic of the stability of electronic systems and can be used instead of the overall energy has been generally established in the literature.^{141–151}

Together with the chemical potential (EN) and hardness, yet another parameter, playing an important role in the modern studies of reactivity and selectivity, namely the Fukui function $f(r)$, defined by Parr and Yang¹⁵² (see also Refs 148–153),

$$f(r) = \left(\frac{\partial \mu}{\partial v(r)} \right)_N = \left(\frac{\partial \rho(r)}{\partial N} \right)_{v(r)},$$

has been introduced within the framework of the DFT.

Yang *et al.*¹⁵⁴ established that a high local reactivity corresponds to a large Fukui function at a point r in the molecule. This means that $f(r)$ is an important reactivity index. The Fukui function is an intramolecular characteristic which can be used to determine intramolecular reactivity indices, in particular the local hardness and the local softness $s(r)$. The latter is defined as follows:

$$s(r) = \left(\frac{\partial \rho(r)}{\partial \mu} \right)_{v(r)} = \left(\frac{\partial \rho(r)}{\partial N} \right)_{v(r)} \left(\frac{\partial N}{\partial \mu} \right)_{v(r)} = f(r)S,$$

where S is the global softness [see Eqn.(21)], which can be calculated in terms of the local softness $s(r)$ values:

$$S = \int s(r) dr.$$

Evidently the local characteristics of the molecule should determine the selectivity of the reactions involving it.^{155–158} Thus in the interaction with a hard reagent, a ‘locally hard’ atom should serve as the preferred reaction centre, whilst in a reaction with a soft reagent a ‘locally soft’ atom should be used for this purpose.

Thus the DFT yields a satisfactory qualitative justification of Pearson's HSAB principle and leads to the possibility of a quantitative estimation of the corresponding parameters.

2. The density functional theory and the electronegativity equalisation principle

The density functional theory justifies not only the continuity of the expansion of the energy E in a power series in terms of the charge q but also confirms the validity of the total equalisation of the EN, which follows from the variational principles for the electron density of the ground state.^{159, 160} Furthermore, the DFT identifies EN with the chemical potential μ , which is characterised, by definition, by the equalisation property, like any other potential.

The mathematical formalism of the principle of the total equalisation of EN, based on the ideas of the DFT, has become the basis for the creation of a wide variety of approaches, which makes it possible to calculate the partial charges on atoms,^{161–167} to model the chemical bond,^{6, 168–170} to interpret the reactivities of various compounds,^{164, 171–176} etc. We shall examine the approaches concerning the mathematical interpretation of the principle of the equalisation of EN and the method for the determination of the EN of atoms and groups based on it.

Thus using the mathematical procedures of the DFT, Parr and Bartolotti¹⁷⁷ justified not only the principle of the total equalisation of EN proposed by Sanderson but also his method of averaging EN on the basis of the geometrical mean.

In describing a bound atom, the authors examined its valence state as the ground state perturbed by the environment and proposed the following scheme for the formation of a molecule.

The initial hypothetical molecule AB, consisting of an atom A with the parameters μ_A^0 , ρ_A^0 , N_A^0 , and v_A^0 and an atom B with the parameters μ_B^0 , ρ_B^0 , N_B^0 , and v_B^0 , possesses intrinsic values of μ_{AB}^0 , ρ_{AB}^0 , $N_{AB}^0 = N_A^0 + N_B^0$, and $v_{AB}^0 = v_A^0 + v_B^0$. Before charge transfer, the atoms A and B are in the valence states A* and B* characterised by the parameters μ_A^* and μ_B^* , ρ_A^* and ρ_B^* , N_A^0 and N_B^0 , and v_A^* respectively. After charge transfer, the atoms A and B are in states to which the parameters μ_A , ρ_A , N_A and μ_B , ρ_B , N_B correspond. Under these conditions, one can write for the molecule (in accordance with the total equalisation principle)

$$\begin{aligned}\mu_{AB} &= \mu_A + \mu_B, \\ \rho_{AB} &= \rho_A + \rho_B, \\ N_{AB} &= N_A + N_B = N_A^0 + N_B^0.\end{aligned}$$

Thus $\Delta N_A - N_B^0 = N_B - N_B^0$, which is proportional to $\mu_A^* - \mu_B^* = \mu_A^0 - \mu_B^0$ corresponds to the charge transfer. Under these conditions, the equalised EN is determined as the geometrical mean of the EN of the neutral atoms before charge transfer:

$$\mu_{AB}^2 = \mu_A^2 = \mu_B^2 = \mu_A^* \mu_B^* \simeq \mu_A^0 \mu_B^0.$$

Bearing in mind that the chemical potential μ is identified with EN, we obtain for the molecule AB

$$\chi_{AB} = (\chi_A \chi_B)^{1/2}.$$

At the same time, according to the definitions of the chemical potential (EN) and the absolute hardness within the framework of the DFT [Eqns (18)–(20)], one can formulate the following expression for the *in situ* EN:

$$\chi = \left(\frac{\partial E}{\partial N} \right)_{v(r)} = \chi^0 + 2\eta^0 \Delta N, \quad (24)$$

where χ^0 is the intrinsic orbital EN of the atom, η^0 is its absolute hardness, and ΔN is the number of electrons participating in the charge transfer. Thus it is easy to show that the charge transfer along the bond AB is determined by the values of EN and of the hardness of the atoms A and B:

$$\Delta N = \frac{\chi_A^0 - \chi_B^0}{2(\eta_A^0 + \eta_B^0)}. \quad (25)$$

Eqns (24) and (25) were first obtained already by Huheey and Watts,^{178, 179} who used instead of the hardness η the charge capacity parameter $k = 1/2\eta$, characterising the power of the atom to delocalise the partial charge, *i.e.* the 'softness'.

The stabilisation energy corresponding to the given charge transfer can be expressed in terms of the same parameters:¹³²

$$\Delta E = \frac{(\chi_A^0 - \chi_B^0)^2}{4(\eta_A^0 + \eta_B^0)}. \quad (26)$$

Like Pauling's original formula, Eqn (26) demonstrates the proportionality of the polar component of the energy to the square of the difference between the EN of the partner atoms involved in the bond.

Komorowski *et al.*¹⁸⁰ identified ΔE with the power of the atoms A and B to effect charge transfer [they introduced the CTA (charge-transfer affinity) parameters] and emphasised that the polarity of the bond is determined not only by the EN of the atoms A and B but also by their hardnesses and it is not permissible to neglect them, as had been done in Eqn (26). Furthermore, whilst considering the pair interactions of the substituents with the reference reaction centre, the authors found an interesting linear relation between the inductive constants (σ_F) of the substituents and the corresponding CTA parameters. On the one hand, this makes the latter adequate characteristics of the groups and, on the other, it demonstrates the impossibility of a direct (disregarding the hardness) comparison of the inductive constants σ and the electronegativities χ . In their description of the *in situ* polarity of the bond AB, Allen and coworkers^{3, 181, 182} neglected the hardnesses of A and B and introduced the bond polarity index BPI, directly related to the difference between the EN. Komorowski and coworkers^{180, 183} find in the BPI a contradiction both with Pauling's original concept and with its DFT-based justification.

On passing from a simple diatomic molecule AB to a system comprising atoms Yang *et al.*¹⁸⁴ obtained the following expression for the averaging of atomic EN taking into account the electroneutrality principle ($\sum \Delta N_i = 0$) and the total EN equalisation condition ($\chi_i = \chi$):¹⁰

$$\chi = \frac{\sum_i \chi_i^0}{\sum_i \eta_i^0} \bigg/ \frac{1}{\sum_i \eta_i^0}. \quad (27)$$

This equation may be formulated also using the values of the softness of atoms:¹⁷⁶

$$\chi = \frac{\sum_i \chi_i^0 s_i}{\sum_i s_i}. \quad (28)$$

Similar relations of type (27) and (28) have been obtained independently by different workers in the study of equalised EN based on the DFT-justified approaches.^{185–188} At the same time, in describing the EN of bound atoms, many investigators indicate the need to take into account their interaction and to introduce the corresponding corrections.

Mortier and coworkers^{161–163, 173} proposed a scheme for the equalisation of the *in situ* EN taking into account the influence of the charge on the neighbouring atom q_B on the electronegativity χ_A :

$$\chi_A = \chi_A^0 + \Delta \chi_A + 2(\eta_A^0 + \Delta \eta_A) + \sum \frac{q_B}{r_{AB}}.$$

The last term (the Madelung potential) includes the interatomic distance parameter r_{AB} , which takes into account the influence of the geometrical parameters of the molecule on the equalisation of the EN of its constituent atoms.

The interaction of the atomic charges is taken into account within the framework of the Rappe–Goddard model¹⁶ by

introducing into Eqn (18) an additional parameter containing the Coulombic integral J_{AB} , which describes the potential between A and B:

$$\chi_A = \chi_A^0 + 2\eta_A^0 + \sum J_{AB}q_B.$$

A similar additional term has also been used by Wells.¹²

As already mentioned, Eqn (25) makes it possible to calculate the charge transfer in the bond. Such a calculation is frequently used to determine the ionicity parameters, but the values thus obtained are lower by approximately a factor of two compared with the traditional estimates by Pauling's method.⁶ This is associated with the failure to take into account the interaction between the atoms. Urusov⁶ therefore proposed an approach, called the 'model of interacting spheres' according to which the electron density of the molecule is regarded as a superposition of the electron densities of atoms with the effective charges $q+$ and $q-$. This approximation makes it possible to some extent to take into account the repulsion between the electrons of different atoms and their attraction to the 'foreign' nucleus. Within the framework of this method, an expression has been obtained for the ionicity parameter:

$$\Delta N = \frac{\chi_A^0 - \chi_B^0}{\eta_A^0 + \eta_B^0}.$$

It yields values twice as high as those found by Eqn (25). Furthermore, in Urusov's view,⁶ the EN equalisation principle can be applied more accurately and correctly in the model of interacting spheres than in the DFT.

Special mention should be made of a study¹⁸³ the authors of which developed a quantum-chemical method for expressing the *in situ* EN and the hardness without the direct employment of the EN equalisation principle. They assumed that the EN of a molecule χ_m can be divided into the additive contributions of its constituent atoms χ_a :

$$\chi_m = -\frac{dE_m}{dN} = -\sum \frac{dE_m}{dN_a} \frac{dN_a}{dN} = \sum \chi_a K_a, \quad (29)$$

where $\chi_a = -(dE_m/dN)$ is the EN of the bound atom and $K_a = dN_a/dN$ is the index of the Fukui function.¹⁸⁹

On passing to group EN, one can write¹⁸⁰

$$K_g = -\frac{dN_g}{dN} = \sum \frac{dN_a}{dN} = \sum K_a;$$

since $\sum N_a = N$, it follows that

$$\chi_g = \frac{\sum \chi_a K_a}{\sum K_a}. \quad (30)$$

Evidently this expression is virtually identical with Eqns (27) and (28) based on the EN equalisation principle; the Fukui index K_a is related to the softness s_i in Eqn (28) by the expression $s = K_a/\eta_m$,¹⁸³ where η_m is the hardness of the molecule. Furthermore, the authors showed that the *in situ* χ_a can be replaced in Eqn (30) by χ_a^0 — the EN of free atoms (groups):

$$\chi_g^0 = \frac{\sum \chi_a^0 K_a}{\sum K_a}.$$

Evidently on passing to a molecule, *i.e.* for $\sum K_a = 1$, the expression obtained reproduces formula (29).

As noted by Komorowski *et al.*¹⁸⁰ themselves, the approach presented presupposes any level of additivity — the EN of the molecule can be divided not only into the contributions of atoms but also into those of groups or even into 'mixed' contributions:

$$\chi_m = \sum \chi_a K_a + \sum \chi_g K_g.$$

An orbital additive level of representation of formula (29) is also possible.

We may note that Liu and Parr,¹⁹⁰ who examined the chemical potential (EN) at the orbital level, arrived at analogous conclusions and relations, but they employed the classical DFT apparatus (and evidently the principle of the total equalisation of EN).

Together with the methods based on the DFT postulates, it is necessary to point out another remarkable approach — Bader's quantum topological model, which also operates with the electron density function $\rho(r)$ and the concepts of EN and hardness but is characterised at the same time by a series of fundamental differences and characteristic features.^{191–194}

Bader's concept of topological atoms is based on the subdivision of molecular space into nonoverlapping atomic regions separated by boundary surfaces corresponding to zero electron density flux.

This procedure also presupposes the classification of the interatomic interactions (chemical bonds) in terms of types of the so called 'bond critical points' (BCP) at which the condition presented above holds. It was then found that the position of the BCP and the electron density at this point reflect the polarity of the corresponding bond and make it possible to determine the EN for both atoms and groups.^{36, 195, 196} One of the most significant arguments in support of this approximation is the fact that the atoms in the given valence state and the molecular fragments frequently retain an unchanged form, volume, polarisability, and other characteristics as part of the composition of various compounds. This in fact determines their chemical individuality.

Using atomic characteristics obtained on the basis of Bader's method (atomic volumes and the BCP parameters) combined with classical DFT equations, Komorowski *et al.*¹⁹⁷ calculated the EN and hardnesses for a large number of chemical groups.

In concluding this Section, we may emphasise that the DFT, supported by a single theoretical basis, integrates the methods for the quantitative expression of the donor–acceptor properties of chemical systems and combines Mulliken's ideas concerning absolute EN,¹¹ the Iczkowski and Margrave expansion of the energy of an isolated atom,¹⁰⁸ the Hinze–Jaffe concept of orbital EN,^{99–101, 110} Sanderson's principle of the total equalisation of EN,⁹⁵ the HSAB concept, *etc.* The global and local characteristic parameters introduced within the framework of the DFT (hardness, softness, Fukui index, *etc.*) permit an adequate description of quantitative data on the reactivities and selectivities of the interaction of diverse compounds.

At the same time, the different interpretations involved in the determination of the *in situ* EN on the basis of the OFT-justified approaches have been attributed by Allen³ to the deficiencies of the DFT definition of EN given by Parr and Pearson. Furthermore, he subjected to a well argued, in our view, criticism Mulliken's expression for EN, which has become the criterion of the validity of a whole series of approaches, including the DFT. Furthermore, Allen believes that it is illegitimate to identify EN with the chemical potential and he therefore does not accept the idea of the equalisation of EN. Parr postulates in his turn that Allen's criticism has arisen mainly from a discrepancy in the understanding of the electronic state of a bound atom.¹⁹⁰

In our view, the essential feature of the contradictions has a deeper origin. One is not dealing with deficiencies in the Mulliken definition of EN and with the disagreements of various workers as regards the state of an atom in a molecule. Both in the beginning and now there is no clear idea as to what EN is (and hence as to what is the exact mathematical form of its description). Indeed the entire data described in the previous Sections indicate that the authors of different concepts of EN have no unanimous view concerning its nature even at the atomic level. Strictly speaking, the current state of this question does not even allow one to consider EN as a physical quantity. It is merely a qualitative and, in a certain sense, a conceptual notion more in the nature of a 'property' or a 'capacity' and having no rigorous dimensionality and mathematical expression. Despite this initial contradiction,

the ideas concerning EN have developed and the concepts of the EN of first a group and later of a molecule appeared. Indeed, if EN is identified with the energies of HOMO and LUMO, the EN (chemical potential) of a molecule can be easily calculated. However, it does not then become in any way better founded and more unambiguous.

The chemical potential of a molecule is known to depend on external factors such as the solvent,^{198, 199} the external field,¹⁵⁹ *etc.* Consequently one should not speak of the EN of a molecule as a characteristic individual quantity. And, whereas in relation to Lewis acids and bases the molecular EN together with hardness can be used for the interpretation of the properties of complex formation, in the general case its physical significance is not entirely clear. Even hardness itself, used together with EN as an independent parameter, is evidently not such a parameter because both χ and η are expressed with the aid of the same parameters — the ionisation potential I and the electron affinity F .

Another piece of evidence for the ambiguity of the parameters χ and η is the interrelation (and in a series of approaches also the identity), mentioned in this review, of the parameters a and b in the quadratic equations relating E and q , subsequently identified with EN and hardness. Furthermore, it is logical to postulate (and this has already been noted above) that the parameters I and F are themselves determined by identical factors involving the elementary structure of the atom and constitute merely one of the many manifestations of EN as a more fundamental property.

In our view, EN has received an unduly extensive and hence diffuse treatment, which does not reflect its initial physical significance. The reason is that, as a fundamental characteristic determining the electronic properties of atoms and molecules, EN cannot be measured in a way other than through these (measured) properties, *i.e.* cannot be determined directly. This is in fact why fundamental importance is frequently attributed to a measured parameter (for example, the ionisation potential).

We believe that the vital problem at the present stage of development of EN is that of the ‘return to sources’: it is necessary to restrict the concept of EN as a fundamental unchanging property of a chemical element and to create on this basis simple and understandable methods for the quantitative determination of the electronic properties of atomic-molecular *ensembles* (substituents, groups, molecules, *etc.*). The next Section of the review is devoted to one of such possible approaches.

V. The concept of ‘inductive’ electronegativities

A wide variety of numerous methods for the estimation of EN have been developed (the main ones were described in previous Sections of the review). Several tens of EN scales have been created on their basis and these are widely employed in the analysis of physicochemical properties and reactivities of compounds.

At the same time, the general methods for the estimation of EN from reactivity data have been scarcely employed. In our view, such direct approaches are in fact the most interesting and promising for the estimation of the electronic properties of atoms and groups, just as inductive, steric, and other constants of substituents are determined on the basis of the principle of the linearity of free energies.^{14, 15, 200, 201}

The view that the values of EN and inductive constants reflect a general fundamental property, determining the distribution of electron density in the molecule, has been firmly established in the literature.¹⁵ This is confirmed by the existence of numerous correlations of inductive constants and EN with the same parameters. Furthermore, numerous examples of the employment of EN of atoms and groups for the quantitative interpretation of the reactivities of molecules, especially in the chemistry of organo-metallic compounds, are known.¹⁵

In this connection, attempts have frequently been undertaken to relate the quantities σ and χ , but the correlations obtained were

of a local character, which rules out the establishment of a functional interrelation between these parameters.²⁰²

1. A new model of the inductive effect

In a series of communications^{203–206} we proposed a new method of determining the EN of ‘inductive’ atoms and groups from the inductive constants of substituents, which are directly related to the reactivity of molecules.

The method has been developed on the basis of a new model of the inductive effect, which makes it possible to calculate with a high degree of accuracy the inductive constants of various substituents at any reaction centres. The calculated Taft inductive constants for 427 substituents are linearly related to the corresponding experimental data with a correlation coefficient of 0.99.²⁰⁶

Using the model of the inductive effect, it is possible to solve a series of important theoretical problems associated with that of inductive interactions, such as the inductive influence of alkyl substituents,²⁰⁷ the inductive effect in the chemistry of organoelement compounds,²⁰⁸ *etc.*, which cannot be done within the framework of any other approaches. Some of the rules derived in the new model made possible a new look at the problem of the quantitative determination of EN and of its physical significance.²⁰⁹ The principal results obtained by means of the approach which we have developed have been surveyed in a review.²⁰²

The fundamental postulate of the model of the inductive effect involves the consideration of inductive constants at the atomic level of additivity:

$$\sigma^* = \sum_i^n \frac{(\sigma_a)_i}{r_i^2}, \quad (31)$$

where σ^* is the inductive constant of the substituents on Taft’s scale, n is the number of atoms in the substituent, $(\sigma_a)_i$ is an empirical quantity, which we introduced, defining the inherent power of the i th atom of the substituent to exhibit the inductive effects and depending on the chemical nature of the element and its valence state, and r_i is the distance from this atom to the reaction centre for which a tetracoordinate carbon atom was chosen in constructing the model.

Evidently this approach is in essence formal. However, the high quality of the correlations between the calculated inductive constants and experimental data shows that the constants σ_a really reflect the ability of atoms to exhibit the inductive effect. As a consequence of this, the question of the factors responsible for such ability, *i.e.* the physical significance of the elementary constants σ_a , is of current interest.

In order to solve this problem, we investigated the quantitative dependence of the constants σ_a on various physical and geometrical parameters and established in this connection a series of important rules.

In particular, an expression relating the quantity σ_a to the difference between the EN of the given element and carbon (the reaction centre) and the square of the covalent radius of the element in the corresponding valence state was obtained:

$$\sigma_a = 7.840(\Delta\chi + 0.45)R^2. \quad (32)$$

This relation explains satisfactorily both the magnitude and the sign of the inductive constants.

In order to eliminate the systematic correction of 0.45 from Eqn (32), we adopted a value of 2.1 for the ‘inductive’ EN of the carbon atom. Eqn (32) then assumes a simpler form:

$$\sigma_a = 7.840\Delta\chi R^2. \quad (33)$$

This value of the ‘inductive’ EN of carbon ($\chi_C = 2.1$) differs appreciably from the corresponding value on Pauling’s scale ($\chi_C = 2.55$), which is not fortuitous. The value which we proposed reflects the real donor–acceptor properties of carbon manifested in its reactivity. An argument in support of this claim is the fact

that the data obtained are based on concrete characteristics of the reactivity of molecules — inductive substituent constants. That the EN of carbon on Pauling's scale are somewhat too high is indicated also by the fact that the quantity $\chi_C = 2.55$ presupposes the existence of electron-accepting properties in carbon in relation to iodine ($\chi_I = 2.4$) and phosphorus ($\chi_P = 2.2$) and this is not the case. Furthermore, the insignificant polarity of the C–H bond indicates the similarity of the electronegativities of carbon and hydrogen atoms, which is also inconsistent with their values on Pauling's scale ($\chi_H = 2.1$).

By analysing Eqn (33), it is possible to understand the physical significance of inductive interactions. The constant σ_a , reflecting the ability of the atom to exhibit the inductive effect, depends not only on the EN — the driving force of the shift of electron density — but also on the area of its valence shell (R^2), *i.e.* its ability to delocalise the charge generated. Thus the inductive effect of a particular element (substituent) is determined by the 'difference between the potentials' ($\Delta\chi$) of this element and the reaction centre and by the 'capacity' of the latter.

We may also note that Eqn (33) makes it possible to express the EN of the element in terms of its constant σ_a and the square of the covalent radius.

$$\Delta\chi = a\sigma_a R^{-2}$$

Evidently this method of expressing EN is in essence identical with the 'geometrical' EN systems, while the empirical constants σ_a are similar, in terms of their physical nature, to the effective nuclear charges of atoms. Furthermore, we obtained a correlation, with a similar significance, between the constant $\sigma_a(C)$ of the element E, linked to a carbon atom as the reaction centre, and the dipole moment μ of the C_{sp^3} –E bond:²⁰³

$$\sigma_a(C) = 9.370 R^2 \frac{\mu}{l}, \quad (34)$$

where l is the bond length.

Since $\mu/l = q$, one can postulate that the superposition of relations (33) and (34) will 'disclose' the correspondence of the difference between the EN of the partner atoms in the formation of the bond ($\Delta\chi$) to the partial charge q arising on them:

$$q = 0.836\Delta\chi.$$

We have already mentioned analogous relations between the atomic charges in the X–H and X–Me systems, calculated by quantum-chemical methods, and the EN of the element χ quoted by Marriott *et al.*³⁸ Relations between q and χ are also known for alkali metal halides.⁸

The fact that Eqns (31) and (33) make it possible to express the inductive constant of the substituent via the fundamental physical and geometrical parameters of its constituent atoms in accordance with the additive scheme

$$\sigma^* = 7.840 \frac{\sum \Delta\chi_i R_i^2}{r_i^2} \quad (35)$$

is particularly remarkable. This method of determining inductive constants permits the solution of many theoretical problems concerning the quantitative determination of the inductive effect (for a more detailed system, see the relevant review²⁰²).

It is remarkable that Eqn (35) relates two terms — the driving force for the displacement of electron density (EN) and the ability to delocalise the charge generated (R_i^2/r_i^2 , actually the softness). However, these parameters are frequently used as independent parameters for the description of reactivity within the framework of the DFT (see, for example, Langaenaeker and coworkers^{210–213}). Thus an analogy may be traced in which the parameter R_i^2/r_i^2 acquires the significance of an 'effective softness'.

Furthermore, the reproducibility and stability of the solutions indicate the constancy of the physical nature of the additive model of the inductive effect. This permits the analysis of the physical significance of the established rules on the basis of fundamental

physical laws. Thus the evident analogy between the mathematical procedures of the model under discussion and the familiar equations of the theory of electrostatic induction is noteworthy. In particular, within the framework of this theory the flux of the electrostatic induction vector $\vec{N}$ through a spherical surface is defined as follows:

$$\vec{N} = \frac{q}{4r^2} R_s^2, \quad (36)$$

where R_s is the radius of the sphere, q is the point charge, and r is the distance from the centre of the sphere to this charge.

If the inductive influence of the substituent is considered within the framework of the fundamental equation (31) taking into account Eqn (34) obtained, then, for the inductive constant of a monatomic substituent on Taft's scale, it is defined by

$$\sigma^* = 9.370 \frac{q}{r^2} R^2, \quad (37)$$

where q is the charge arising on the atom when the latter forms a covalent bond, r is the distance from the atom to the reaction centre, and R is the covalent radius of the atom.

The similarity of Eqns (36) and (37) imparts to the inductive constant of a monatomic substituent the physical significance of the flux of the electromagnetic induction vector, passing through the surface of the corresponding atom and generated by the charge on the reaction centre. The physical significance of the inductive effect has been analysed.²⁰⁹ Without going into the details of this investigation, we shall only mention that the following expression has been established for the calculation of the charge arising on the i th atom in a nonconjugated molecule:

$$q_i = 0.172 \sum_j \frac{\Delta\chi_{i-j}(R_i^2 + R_j^2)}{r_{i-j}^2}, \quad (38)$$

where the values of q_i are expressed in units of the elementary charge e , while the distances r_{i-j} between the i th and j th centres and the radii of the atoms i and j are expressed in Å.

We may note a clear analogy between the relation obtained and Eqn (25) expressing the charge in terms of the EN and the hardness of the partner atoms involved in the bond. In the model of the inductive effect, the charge and its inductive constant are directly proportional to $\Delta\chi$ and the ability of the system to delocalise the charge [the ratio $(R_i^2 + R_j^2)/r_{i-j}^2$]. In the DFT, the quantity q is also directly proportional to $\Delta\chi$ and inversely proportional to the sum of the hardnesses $\sum\eta$, *i.e.* actually to the ability to delocalise the charge mentioned above.

We shall demonstrate by the following example the possibility of calculating the partial charges in the molecule on the basis of the relations which we have obtained. Table 1 presents the effective atomic charges (δ) in the molecules of hydrogen halides obtained by Sanderson's method,²¹⁴ the reduced dipole moments of the hydrogen halide molecules μ/l , and the charges q calculated by Eqn (38). Evidently δ and q are fairly close. Furthermore, the reduced dipole moments of the H–Hal molecules and the distribution of their electron density are correlated with the calculated value of q :

$$\frac{\mu}{l} = (-1.351 \pm 0.071) + (19.523 \pm 0.645)q.$$

Table 1. The charges on the atoms in the molecules of hydrogen halides calculated by Sanderson's method and within the framework of the new model of the inductive effect together with the reduced dipole moments.

Molecule	δ / e	q / e	$(\mu/l)/\text{\AA}$
HF	0.16	0.177	2.09
HCl	0.09	0.108	0.81
HBr	0.06	0.099	0.56
HI	0.04	0.084	0.26

Thus one may say that the empirical rules established within the framework of the model developed permit a fairly adequate estimation of the shift of electron density in molecules.

2. Determination of the 'inductive' electronegativities of atoms and groups

The results of our investigations have shown that the model developed elucidates to a considerable degree the nature and physical significance of the inductive effect, relating it to the fundamental laws of electrostatics and electromagnetic induction. This leads in its turn to new possibilities for the quantitative theoretical estimation of the intramolecular distribution of electron density and of the reactivities of organic and organoelement compounds.

Furthermore, the expressions obtained for the inductive constant [Eqns (33)–(35)] permit the converse procedure involving the calculation of the group 'inductive' EN.^{215–217}

Thus we found the values of χ for a series of the commonest atoms in different valence states by a converse recalculation based on Eqn (33). We created in this way a scale of 'inductive' EN. The values obtained reproduce Pauling's scale with an adequate accuracy (with the exception of the carbon atom) and are quite well correlated with a series of other familiar scales.²¹⁵

Proceeding to the determination of group EN on the basis of Sanderson's total equalisation principle, we postulated that the $\Delta\chi_i$ in Eqn (35) for the atoms of the substituent is a constant quantity reflecting the EN of the entire substituent. One can then write

$$\Delta\chi = \frac{\sigma^*}{7.84 \sum R_i^2/r_i^2}.$$

Comparison of this expression and Eqn (33) yielded the final formula for the calculation of group 'inductive' EN.

$$\Delta\chi_g = \frac{\sum_i^n \Delta\chi_i R_i^2/r_i^2}{\sum_i^n R_i^2/r_i^2}. \quad (39)$$

It is remarkable that an evident analogy with Eqn (33) for the group EN in the DFT is observed in this case too. This confirms yet again the legitimacy of identifying the parameter R_i^2/r_i^2 with the effective softness of the atom.

Equation (39) permits the calculation of the group EN for any groups, substituents, or ligands at any reaction centres from the fundamental characteristics of their constituent atoms. At the same time, it is evident that this expression for the group EN has a series of undoubted advantages.

Firstly, it makes it possible to reveal in an analytical form, other conditions being equal, the decisive role of the central atom of the substituent. It is in fact in this instance that the parameter r_i is a minimum and the contribution of the corresponding term is the most significant. Furthermore, the expression presented makes it possible to obtain the values of EN of both groups and individual atoms on a single scale, because the latter can be regarded in this case as monatomic substituents.

Secondly, the 'inductive' EN of the most diverse nonconjugated substituents,²¹⁶ calculated in terms of the approximation of a carbon reaction centre within the framework of Eqn (39), are correlated satisfactorily with the known scales based on the principle of the total equalisation of EN (for examples, the scales of Mullay,¹¹⁵ Sanderson,²¹⁸ and De Proft *et al.*²¹⁹). A fairly good qualitative correspondence is observed with other χ scales (correlation coefficients of 0.91–0.95).²¹⁶ In contrast to other equations, Eqn (39) takes into account the steric structure of the substituent, which permits a correct calculation of the group EN for isomeric fragments, avoiding one of the most significant deficiencies of the principle of the equalisation of EN.

Thirdly, in analysing the expression for the group EN one cannot disregard the question of the dependence of the EN of the substituent on its conformation. The existence of this dependence for the inductive effect has been frequently noted and is not open to doubt.¹⁵ Electronegativity has never been considered in this context, although the EN of the substituent and its inductive influence have the same physical nature.

Fourthly, Eqn (39) makes it possible to discover the relation between the three principal characteristics of substituents — the inductive (σ^*) and steric (R_s) constants and the group EN (χ_g).

The following expression defining the steric constant has been proposed within the framework of the model of the frontal steric effect which we have developed:^{220–222}

$$R_s = 30 \lg \left(1 - \sum_i^n \frac{R_i^2}{4r_i^2} \right), \quad (40)$$

where R_i is the radius of the i th atom of the substituent and r is the distance from this atom to the reaction centre.

The scale of the constants R_s thus obtained is satisfactorily correlated with various experimental scales (for example, E_s , E_s^0 , and V), describing adequately the steric effects of various substituents. The model permits the calculation with a high degree of accuracy of the steric effect of any substituent at any reaction centre.

Equation (40) may be simplified by taking into account the fact that, for low values of x , the function $\log(1-x)$ is linear. For the vast majority of substituents (with the exception of unduly bulky ones), the sum in brackets is small and one can therefore write

$$R_s = \text{const} \sum_i^n \frac{R_i^2}{r_i^2}. \quad (41)$$

Since the difference between the atomic and covalent radii of the elements (used respectively in the steric and inductive models) is as a rule insignificant, the following final formula relating the fundamental physical parameters of the substituent is obtained from Eqns (35) and (41):

$$\sigma^* = A \Delta\chi_i R_s, \quad (42)$$

where $A = \text{const}$.

In order to confirm the correctness of this expression and to determine the normalised value of the multiplier, we calculated the group EN also for a series of other groups frequently encountered in organic and organoelement compounds and not containing multiple bonds. Within the framework of regression analysis, all the values of $\Delta\chi_i$ obtained were compared with the corresponding constants σ^* and R_s . The theoretical values of the latter for substituents at a carbon reaction centre were taken from Cherkasov *et al.*²⁰² This yielded a relation²¹⁶ confirming the validity of the above considerations at an experimental level and indicating the universality of relation (42):

$$\sigma^* = (0.067 \pm 0.034) + (0.435 \pm 0.024) \Delta\chi_i R_s \quad (43)$$

(the correlation coefficient is 0.9868 for 64 points).

The exact value of the normalising coefficient in expressions of type (43) can vary somewhat on passing from one reaction series to another depending on the nature of the specific reaction centre.²¹⁷

The existence of relation (43) makes it possible to justify Eqn (39), avoiding the direct employment of the equalisation principle.

Since the steric constant R_s , defined by Eqn (41), is additive, we can write

$$R_{si} = B \frac{R_i^2}{r_i^2}, \quad (44)$$

where $B = \text{const}$ and R_{si} is a parameter describing the shielding of the reaction centre by the i th atom of the group.

Using Eqns (44) and (45), it is possible to express the inductive constant of the substituent in the following form:

$$\sigma^* = \text{const} \sum_i^N \Delta\chi_i R_{si}.$$

However, bearing in mind Eqn (43), the inductive constant of the substituent can be expressed in terms of the EN of the group and its steric shielding constant:

$$\sigma^* = \text{const} \Delta\chi_g R_{sg}. \quad (45)$$

Thus, taking into account Eqns (35) and (45), we obtain an expression for the group EN, more correctly for the difference between the EN of the substituent and the reaction centre $\Delta\chi_g = \chi_g - \chi_{RC}$, which agrees fully with Eqn (39), but this time does not involve the employment of the principle of the total equalisation of EN:

$$\Delta\chi_g = \frac{\sum_i^n \Delta\chi_i R_i^2 / r_i^2}{R_{sg}} = \frac{\sum_i^n \Delta\chi_i R_i^2 / r_i^2}{\sum_i^n R_i^2 / r_i^2}. \quad (46)$$

It is remarkable that Eqn (45) is analogous also to the relation between the principal characteristics of the substituent — the inductive constant σ , the group EN, and the steric shielding constant R_s — obtained on the basis of the total equalisation principle.

Taking into account the relations obtained, one may conclude that the mathematical principle of the total equalisation of the EN of all the atoms constituting the substituent is capable of yielding correct results as a computational method. The problem consists only in the need to establish the optimum algorithm for the averaging of the atomic EN, taking into account the chemical nature of the atoms and the steric structure of the substituent. Evidently, our approach is fully consistent with these requirements.

3. The 'inductive' electronegativities of substituents at different reaction centres

In the expression which we obtained for the 'inductive' EN, there are parameters which depend on the choice of the specific reaction centre — the distance from the i th atom of the substituent to this centre and the difference between their EN. It therefore appeared logical and useful to calculate using Eqn (39) the values of $\Delta\chi_g$ for the commonest nonconjugated substituents at different reaction centres.²¹⁷

We compared them with the corresponding 'inductive' EN [$\Delta\chi_g(C)$] which we had obtained earlier in terms of the approximation of a carbon reaction centre²¹⁶ using a linear regression of the type

$$\Delta\chi_g(E) = a\Delta\chi_g(C) + b. \quad (47)$$

This made it possible to show that there is a rigorous linear relation between the $\Delta\chi_g$ for substituents at different reaction centres; the correlation coefficients are 0.98–0.99. The coefficients a then proved to be virtually unity and the coefficients b were found to be equal to the difference between the EN of carbon and the element E ($\chi_C - \chi_T$), whence it follows that χ_g is a constant quantity. This leads to the unambiguous conclusion that the 'inductive' EN of the substituents χ_g are constant regardless of the nature of the reaction centre, which is consistent with the established view concerning the universal nature of the concept of 'electronegativity'.

The method which we have developed takes into account the evident dependence of the difference between the EN of the group and the reaction centre $\Delta\chi_g$ on the nature of the latter, but the 'inductive' EN themselves do not vary under these conditions, in contrast to the constants σ characterising the electronic pair interaction between the substituent and the reaction centre.

In analysing the relations obtained, the question arises of the universality of the relation between the inductive constant, the group EN, and the steric constant [Eqn (45)] and of its dependence on the nature of the reaction centre. Thus, we showed previously²⁰² that, on passing from one reaction centre to another, the constants R_s vary in proportion, but the inductive constants are not linearly related in the general case. Furthermore, the linear relation established in the above investigation between the $\Delta\chi_g(E)$ presupposes the existence of a significant constant term in relations of type (47). In order to estimate the universality of Eqn (45) and to determine its normalising multiplier, we tested experimentally the validity of Eqn (45) on a wide range of different reaction centres E. The constants σ and R_s were taken from Cherkasov and coworkers.^{202, 220}

Analysis of the data obtained demonstrated the validity of a rigorous linear relation between the parameters investigated and the constancy of the slopes in all the correlation equations. Consequently Eqn (45) is universal and valid regardless of the choice of the reaction centre. Having averaged the values of a obtained, it is possible to formulate the following final expression:

$$\sigma^* = -2.1\Delta\chi_g R_s.$$

Thus the methods for expressing the steric (R_s) and inductive (σ) constants as well as EN in terms of fundamental physical and geometrical parameters [Eqns (35), (40), and (46)] which we have proposed not only permit a correct theoretical calculation of these characteristics but also reveal their genetic interrelation.

The possibility of a simple description of the electronic steric influence of substituents within the framework of the models developed is determined by the fact that they are based on extensive experimental data — inductive and steric constants. This 'extremely empirical' basis of the theoretical approaches which we have developed constitutes a significant argument in support of their adequacy. This is also indicated by the agreement between the experimental substituent constants and their values calculated by Eqns (35) and (44).

The concept of 'inductive' EN revealed a series of new aspects of the application of group EN: its interrelation with conformations, the absence of a dependence on the nature of the reaction centre, and 'the genetic relationship' with the inductive and steric constants. The quantitative interrelation of the 'inductive' EN and the partial atomic charges, which we have discovered, as well as consistency with other known methods for the calculation of EN must be specially emphasised. This makes it possible to throw light on certain controversial questions and to emphasise new aspects in the concept of EN.

Thus the expression for group EN [Eqn (46)] has been obtained within the framework of the approach which we have developed by two independent procedures, one of which presupposes the equalisation of the EN of the substituent atoms. On the one hand, this makes it possible to explain the existing diversity of the views on the principle of the equalisation of EN. As a mathematical computational procedure, it undoubtedly 'works', although Eqn (46) presupposes a more complex equalisation formula than simple geometrical, arithmetical, *etc.* averaging. On the other hand, the existence of an expression which permits the calculation of the EN of the group from the EN of its constituent atoms taking into account the geometry of the system throws doubt on the usefulness of employing the principle of the equalisation of EN. We agree with the criticism by Allen,³ who pointed out that the equalisation of the *in situ* EN conflicts with the constancy of the chemical nature of the atom and who rejected the identification of EN with the chemical potential.

We have already emphasised that the 'inductive' EN have been obtained from the corresponding empirical atomic constants σ_a . This suggests that the calculated 'inductive' EN of atoms reflect their real electron-donating (electron-accepting) properties. However, since σ_a is an inherent unchanging atomic characteristic (this in fact permits its employment in additive calculations), we arrive inevitably at the conclusion that EN

should also be a constant quantity for an atom, regardless of its environment (and, incidentally, regardless of any external factors in general).

$$\chi = \frac{\sigma_a}{R} = \text{const.}$$

Thus one may conclude that the transition from the set of accumulated methods for the determination of χ (including also procedures within the framework of our approach) and also of procedures for the treatment of the term 'electronegativity' itself to a qualitatively new representation of its essential nature, not as a concept but as a property determined solely by the nature of the element and its valence state, has been achieved.

VI. Conclusion

Within the limited space of a review article, we were unable to cover the entire wide variety of the studies carried out in the field of the quantitative determination of EN and its practical employment.

From our point of view, the entire experience gained in the course of the historical development of the concept of EN has shown that it is a universal property of a chemical element, which depends solely on its nature and valence state and remains unchanged on formation of a molecule. Indeed, in all the existing scales, with all their diversity, the EN of chemical elements are constant quantities within the limits of each scale, differing only as regards the valence state. They describe satisfactorily the physical and chemical properties of diverse molecular systems. On the other hand, the majority of the scales, which have been frequently created on the basis of significantly (sometimes also fundamentally) different approaches, are satisfactorily correlated, emphasising the universality of EN as a property of a chemical element.

On the other hand, all the known methods for the 'averaging' or equalisation of EN when the donor — acceptor properties of groups and molecules are considered nevertheless operate in one way or another with 'intrinsic' (or 'null') values of the EN of their constituent chemical elements. Thus the basic sets of EN are entirely sufficient for an adequate quantitative description of the electronic properties of any atomic ensembles, while the equalisation principle (whatever the specific algorithm on which it is based) is only a successful instrument for such description. The attribution to it of a real physical significance actually leads to the blurring of the concept of EN and to its replacement by other (perhaps similar) concepts.

One should add to the foregoing that electronegativities are introduced methodologically as constants: an intrinsic unchanging value of χ is assigned to each abstract atom or substituent; their sets constitute EN scales.

Thus EN is a fundamental property of an atom — its power to attract electrons, which is manifested on formation of a molecule. We suggest that it is just as fundamental and unchanging as the chemical nature of an element and its nuclear charge and mass are constant in any molecules. As a fundamental property in a similar category, EN should be regarded, in our view, as a characteristic of a chemical element which depends on its nature and valence state. In its turn, EN generates the remaining electronic properties of atoms and molecules — ionisation potential, electron affinity, chemical potential, charge distribution, hardness, softness, etc, (the group EN should be included here also), which are determined by the balance of the EN of the chemical elements constituting the given system.

These properties may vary and may be equalised, but EN itself should remain unchanged. As soon as we allow a dependence of the EN of the element on its environment in the molecule, its charge, etc, we inevitably blur the very concept of EN, replacing it by other derived quantities (for example, the chemical potential) which are perhaps logically non contradictory. Yet another important cause of such 'mixing' of concepts is the fact that EN may be measured only in terms of measured properties, as a

consequence of which an unjustifiably great importance is attributed to the measured parameter. Pauling's definition of EN is most correct in this connection: 'EN is the force with which an atom in a molecule attracts electrons'.

However, when account is taken of the postulate, described above, of the constancy of EN as a fundamental property of a chemical element in a given valence state, we tend to understand by the term 'atom in a molecule' in Pauling's formulation the state of the atom in the initial instant of the interaction. From our point of view, such an interpretation is simpler, logical, and rational if only because it is definite and unambiguous. Pauling's definition, which is essentially correct, therefore requires refinement in each specific instance. We believe that it can be formulated as follows: 'EN is the ability of an element to attract electrons on formation of chemical bonds, which depends on its nature and valence state'.

This revised definition of EN is the most complete and unambiguous and makes it possible to distinguish it from other similar parameters characterising the electronic state of atomic-molecular systems, and implies the constancy of EN as a fundamental property of an element in the given valence state.

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

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

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

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

^e — *Mendeleev Chem. J. (Engl. Transl.)*

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

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

^h — *Organomet. Chem. (Engl. Transl.)*

Reactions of carbonyl compounds with α,β -unsaturated nitriles as a convenient pathway to carbo- and heterocycles

Yu A Sharanin (deceased), M P Goncharenko, V P Litvinov

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Abstract. Published data on the methods for synthesis of carbo- and heterocyclic compounds based on reactions of α,β -unsaturated nitriles with carbonyl compounds and activated phenols are surveyed. It is demonstrated that all these reactions occur *via* nucleophilic addition of the carbanion generated from a carbonyl compound to the double bond of an unsaturated nitrile (the Michael reaction). The main routes of transformation of the adducts into carbo- and heterocyclic compounds are considered. The methods for regioselective preparation of fused 4*H*-pyrans or 1,4-dihydropyridines by varying conditions of cyclisation of Michael adducts are discussed. The bibliography includes 249 references.

I. Introduction

Reactions of carbonyl compounds with α,β -unsaturated nitriles can yield carbo- and heterocycles that are difficult to synthesise by other methods. Unsaturated nitriles activated by electron-withdrawing substituents react with carbonyl compounds under mild conditions; in some cases, this makes it possible to isolate intermediate compounds and to conduct highly regio- and stereoselective reactions that require simple experimental equipment. The use of initial compounds with various substituents in the molecules permits the synthesis of a broad range of heterocyclic derivatives including substituted 4*H*-pyrans, pyridines, 2-pyridones, and pyridine-2-thiones. It should be noted that the compounds produced in this way contain easily modifiable functional groups, and, therefore, they present interest for fine organic synthesis and for the chemistry of pesticides and medicines. The reactions of carbonyl compounds with ylidene derivatives of malononitrile, cyanoacetamide, and ethyl cyanoacetate have been considered in several reviews^{1–6} and monographs.^{7–9} How-

ever, due to the vigorous development of this field of organic chemistry, the information available from these sources needs to be supplemented. In this review, we generalise and describe systematically the data on the methods for the synthesis of carbo- and heterocycles based on reactions of carbonyl compounds with unsaturated nitriles.

II. General regularities and classification of the reactions

Reactions of carbonyl compounds **1** with α,β -unsaturated nitriles **2** occurs most often as the Michael nucleophilic addition of the methylene group of the carbonyl compound to the activated double bond of the nitrile. The reaction involves a base, the role of which is to generate the corresponding carbanion. In addition, the base stabilises the resulting adduct as salt **3**. This process is generally illustrated by Scheme 1.¹⁰

The resulting salt **3** or **4** can undergo a number of subsequent transformations, their routes depending on the structures of the initial reagents and on the particular conditions. Thus, the reaction in question possesses great synthetic potential, because its regioselectivity can be modified by varying the substituents and reaction conditions. In some cases, the process follows pathway (*a*) with elimination of nitrile derivative **5** and formation of α,β -unsaturated dicarbonyl compounds **6**, *i.e.* **1** and **5** exchange their methylene fragments. This reaction is reversible, and heterocyclic compounds can be synthesised both by reaction of **1** with **2** and **5** with **6**. If one of the substituents (for instance M) is a good leaving group, it is eliminated giving rise to a multiple bond [path (*b*)]. The alkene **7** thus formed, depending on its structure, is either removed from the reaction area or undergoes intramolecular cyclisation to give carbo- or heterocyclic compounds. Acidification of the salt **3** gives adduct **8**, which can be converted into the nitrile **7** upon elimination of MH.

The most frequently encountered variant of the subsequent transformations of the compounds **3** and **8** is intramolecular cyclisation.¹¹ Depending on the natures of substituents X, Y, and Z, this can afford diverse, as a rule six-membered, carbo- and heterocycles. Some of the adducts **3**, **7**, and **8**, can be isolated, especially those derived from cyclic dicarbonyl compounds or tetracyanoethylene, which cyclise under more rigorous conditions. These adducts can also eliminate a nucleofugal fragment.

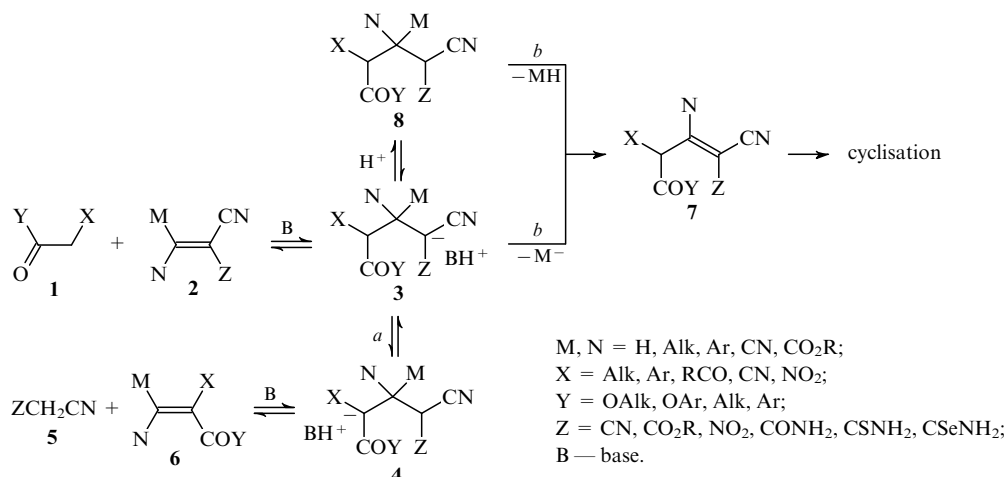
Yu A Sharanin (deceased), M P Goncharenko T G Shevchenko Lugansk State Pedagogical Institute, ul. Oboronnaya 2, 348011 Lugansk, Ukraine. Fax (7-064) 255 33 68. Tel (7-064) 253 83 94.

V P Litvinov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 135 88 37.

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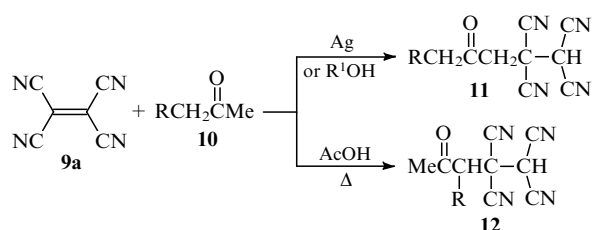
Uspekhi Khimii 67 (5) 442–473 (1998); translated by Z P Bobkova

Scheme 1

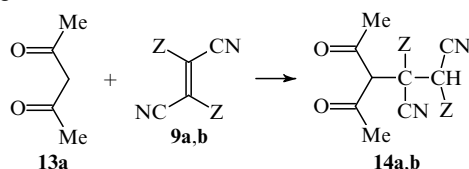


III. Synthesis of Michael adducts

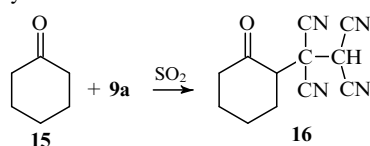
In this Section the formation of stable Michael adducts in the reactions of carbonyl compounds with unsaturated nitriles is described, the conditions and stereochemical aspects of these reactions are generalised, and decomposition of these adducts with elimination of nucleofugal groups is considered. The Michael adducts derived from carbonyl compounds and tetracyanoethylene (TCE) are the most stable.^{3,4} It has been found that reaction of TCE **9a** with ketones **10** catalysed by 'molecular silver' or alcohols occurs selectively involving the methyl group and yields acyclic adducts **11**.¹² To activate the methylene group and obtain the isomeric product **12**, the reaction needs to be conducted with heating in the presence of acetic or trichloroacetic acid.¹² The structures of the adducts **11** and **12** were confirmed by their cyclisation into pyridines and pyrans under the action of acids.¹³



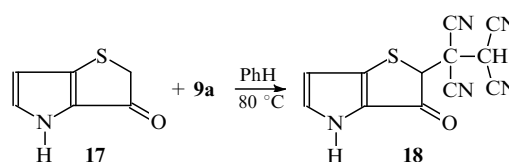
Acetylacetone **13a** reacts with TCE in the presence of silver in benzene at room temperature to give easily cyclisable adduct **14a** in 70% yield.¹⁴ When the same compounds react in ethanol without a catalyst, the yield of **14a** is 88%.¹⁰ Dicyanofumarate **9b** gives similar adducts **14b**.¹⁰



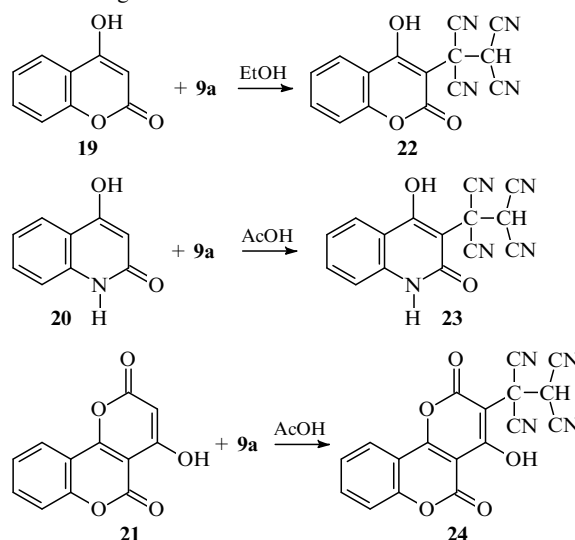
Data on isolation of stable products of addition of cyclohexanone **15** to TCE in the presence of SO₂ have been reported; the yield of adduct **16** reaches 95%.³



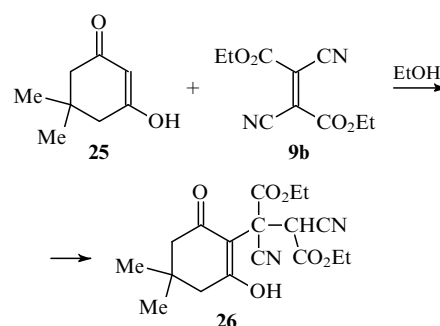
4*H*-Thieno[3,2-*b*]pyrrol-4-one **17** reacts with TCE in boiling benzene giving rise to stable adduct **18**, which has been reported¹⁵ not to undergo subsequent cyclisation.



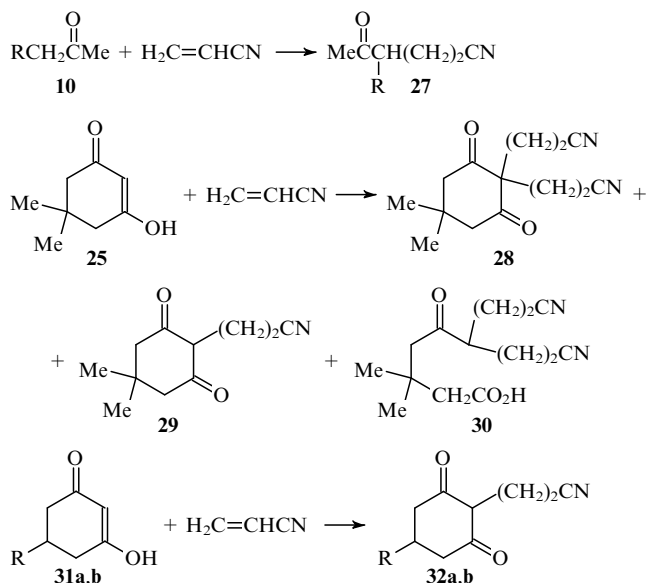
Tautomeric forms of cyclic 1,3-dicarbonyl compounds, such as 4-hydroxycoumarin **19**, 4-hydroxy-2-quinolinone **20**, and (4-hydroxy-2,5-dioxo-2*H*,5*H*-pyrano)[3,2-*c*][1]benzopyran **21**, also react with TCE to give stable Michael adducts. The adduct **22** was prepared in ethanol, while compounds **23** and **24** were synthesised in glacial acetic acid.¹⁶



The reaction of the dicyanofumarate **9b** with dimedone **25** results in the formation of adduct **26** existing in the enol form.¹⁰

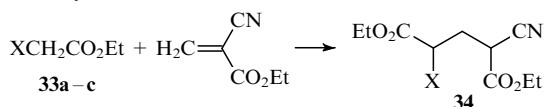


Under the Michael reaction conditions, the ketones **10** are cyanoethylated by acrylonitrile at the methylene group yielding stable compounds **27**, which are intermediates in the synthesis of cyclic diketones (see Section IV).¹⁷ The addition of dimedone **25** to acrylonitrile in boiling dioxane gives rise to stable Michael adducts **28** and **29** and acid **30**, the latter being the major product. However, variation of the reaction conditions permits the adduct **28** to be prepared in 85% yield. Alkaline hydrolysis of this adduct in a 10% solution of potassium carbonate affords the acid **30** in 74% yield.¹⁸ The reaction of cyclohexanone **31a** or its methyl analogue **31b** with acrylonitrile affords adducts **32** in yields of more than 60%.²⁰ The structure and chemical properties of these products, in particular, cyclisation to give pyridines, have been studied.^{19, 20}



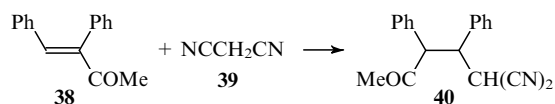
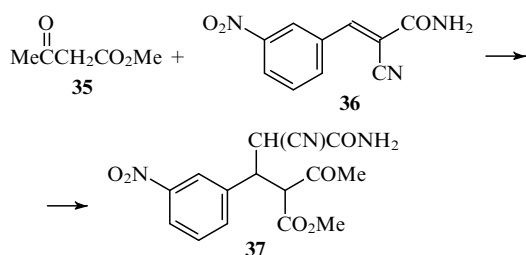
R = H (a), Me (b).

Ethyl acetoacetate **33a** adds to ethyl 1-cyanoacrylate in the presence of highly basic secondary amines yielding adduct **34**.²¹ Ethyl cyanoacetate **33b** and ethyl nitroacetate **33c** behave in a similar way.

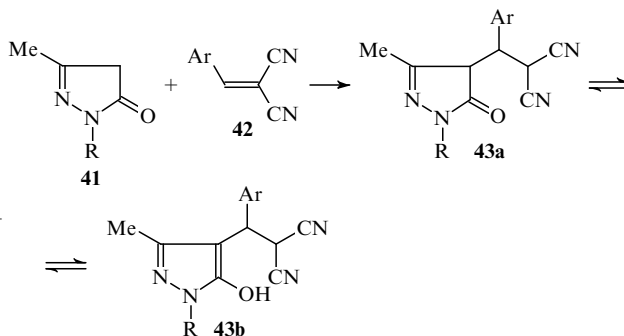


X = AcO (a), CN (b), NO₂ (c).

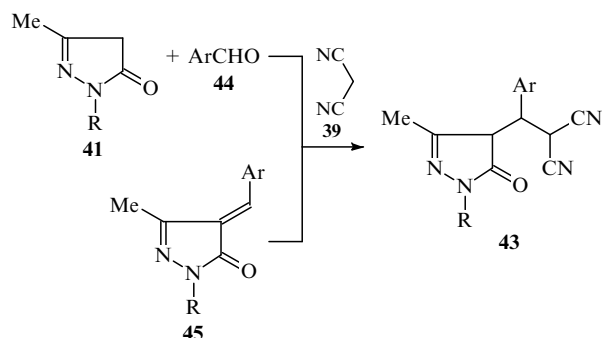
Arylidene derivatives of malononitrile and its analogues are widely used in reactions with carbonyl compounds. The Michael adducts formed in these reactions are normally unstable and readily undergo intramolecular cyclisation. However, the reaction of methyl acetoacetate **35** with 2-cyano-3-(3-nitrophenyl)acrylamide **36** in methanol in the presence of piperidine affords stable Michael adduct **37** in 88% yield.²² Similar open-chain products are formed when unsaturated ketone **38** is made to react with malononitrile **39**; adduct **40** does not cyclise even in sodium alkoxide solutions.²³



Apparently due to steric rigidity, heterocyclic carbonyl compounds are more readily converted into Michael adducts than acyclic 1,3-dicarbonyl compounds. The reaction of N-substituted 3-methyl-5-pyrazolones **41** with arylidenemalononitriles **42** can serve as an example of a well studied reaction of this type. A large number of adducts **43** with various aryl substituents have been synthesised in this way.^{11, 24–27} It was found that in DMSO solutions these compounds exist mostly in the enol form **43b**.²⁵

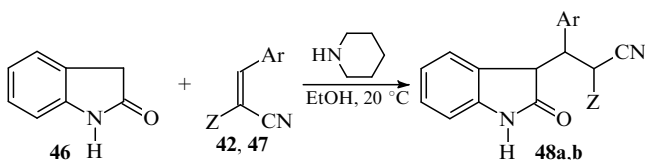


The adducts **43** have also been obtained by condensation of aromatic aldehydes **44**, malononitrile **39**, and pyrazolones **41**²⁷ and by the addition of malononitrile **39** to 4-arylidene-3-methyl-5-pyrazolones **45**.^{25, 27}



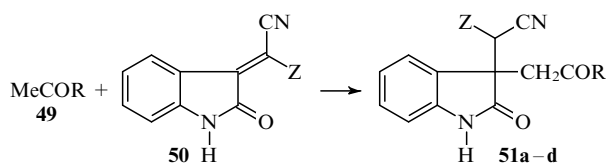
In addition, adducts of the type **43** are formed upon interaction of benzylidenemalononitrile **42** with 3-hetaryl-substituted 5-pyrazolone derivatives.²⁸

Stable Michael adducts are also produced when oxindole **46** reacts with arylidene derivatives of malononitrile **42** or cyanoacetamide **47**.²⁹ The adducts **48** do not cyclise into the corresponding pyrans even on treatment with strong bases; this was attributed²⁹ to the low degree of enolisation of the indoline fragment.



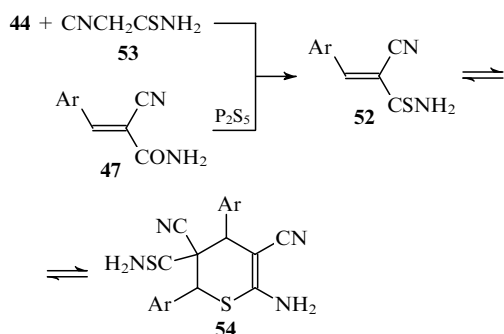
Z = CN (**42**, **48a**); Z = CONH₂ (**47**, **48b**).

Apparently, this also accounts for the fact that adducts **51a–d** formed from ketones **49** and 3-cyanomethylidene derivatives of oxindole **50** are quite stable and do not cyclise to pyrans without preliminary reduction.³⁰

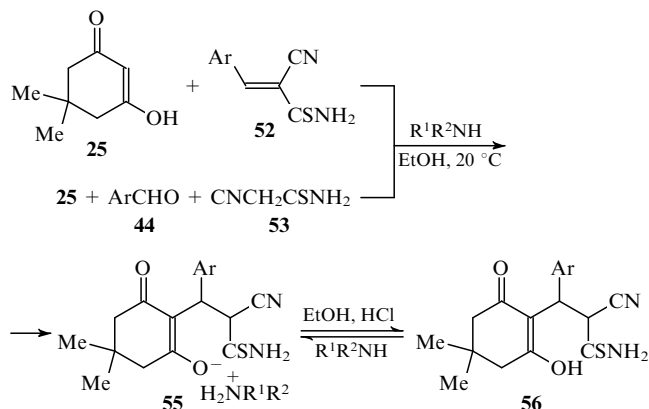


Z = CO₂Et, R = Ph (**a**); Z = CN, R = Me (**b**);
Z = CO₂Et, R = Me (**c**); Z = CN, R = Ph (**d**).

The reaction of dicarbonyl compounds with arylidene derivatives of cyanothioacetamide also possesses great synthetic potential. In this case, the presence of several reaction centres ensures the existence of various routes for cyclisation of the intermediate Michael adducts and, as a consequence, the possibility of regio-controlled synthesis of a number of oxygen-, nitrogen-, and sulfur-containing heterocycles. Arylidene cyanothioacetamides **52** are prepared by reactions of the aromatic aldehydes **44** with cyanothioacetamide **53**^{31,32} or by reactions of the corresponding amides **47** with phosphorus pentasulfide in pyridine.³³ They tend to dimerise according to the Diels–Alder reaction pattern to give 2H-thiopyrans **54**, which exist in solutions as a ring–chain equilibrium with the compounds **52**; this equilibrium shifts to the left on increasing the temperature.³² Some thioamides **52** have been reported to exhibit tuberculostatic activities.³³

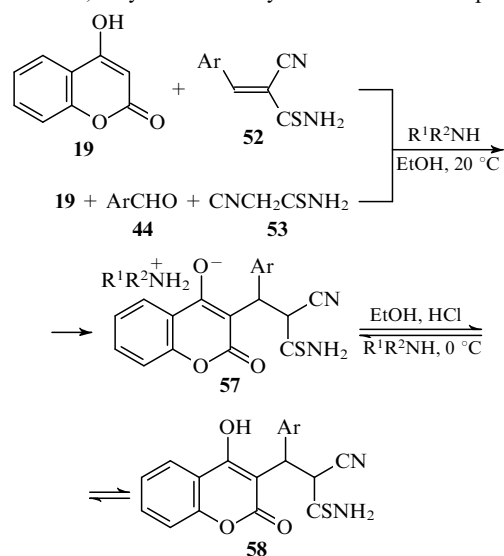


The reaction of dimedone **25** with arylidene cyanothioacetamides **52** in the presence of an equimolar amount of secondary amines in anhydrous ethanol at 20–25 °C affords Michael adducts, which are isolated from the reaction mixture as poorly soluble enol salts **55**.^{34–36} The corresponding aromatic aldehydes **44** and cyanothioacetamide **53** can be used in this reaction, instead of the compounds **52**, under the same conditions.³⁶ On treatment with hydrogen chloride in ethanol at 0 °C, these salts are reversibly converted into free adducts **56**, which exist solely in the enol form.³⁶

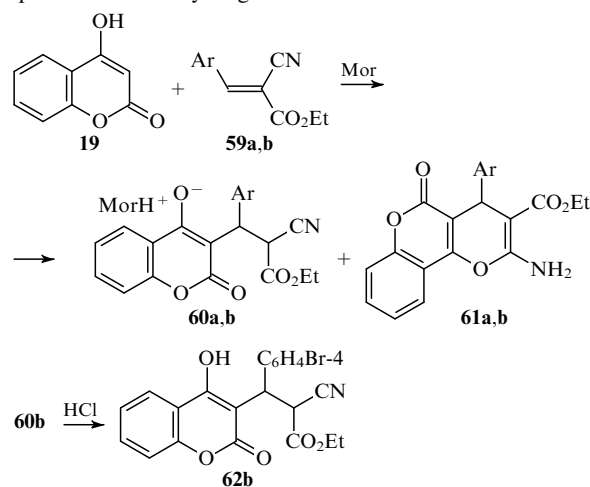


4-Hydroxycoumarin **19** reacts with arylidene cyanothioacetamide **52** in a similar way. When the reaction is carried out in ethanol in the presence of equimolar amounts of secondary amines at 20–25 °C, salts **57** are formed; these salts are also produced when 4-hydroxycoumarin **19** reacts with the aromatic aldehydes **44** and cyanothioacetamide **53**.³⁷ When gaseous hydro-

gen chloride is passed through an ethanolic solution containing the salts **57**, they are reversibly converted into compounds **58**.³⁷

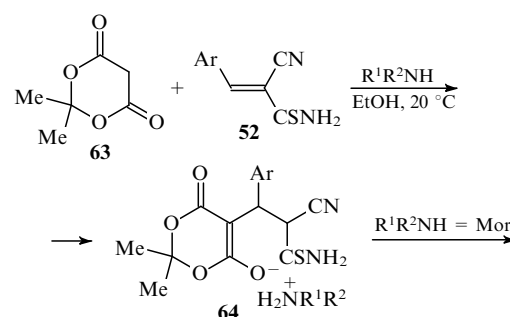


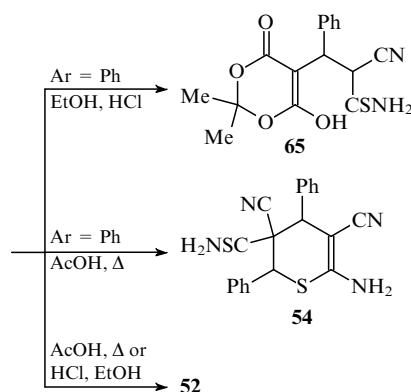
When 4-hydroxycoumarin **19** is made to react with ethyl arylidene cyanoacetates **59** in the presence of an equimolar amount of morpholine, a mixture of enolates **60** and the products of their subsequent cyclisation, 4H-pyrans **61**, is formed; according to the data of NMR spectroscopy, the salts **60** predominate in this mixture. The free enol **62b** was prepared by treatment of the compound **60b** with hydrogen chloride.³⁷



Mor is morpholine; Ar = C₆H₅ (**a**); 4-BrC₆H₄ (**b**).

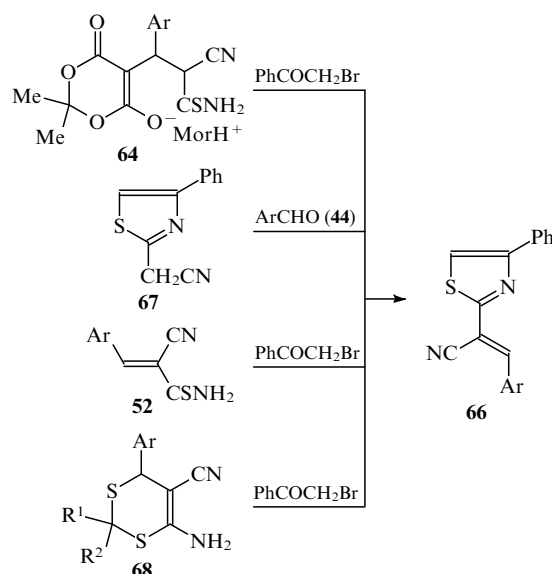
Meldrum's acid (isopropylidene malonate **63**), which is formally a cyclic 1,3-dilactone and a structural analogue of dimedone, is widely used in organic synthesis.³⁸ Being a relatively strong CH acid ($pK_a = 4.97$),³⁹ Meldrum's acid is not enolised in the solid state or in solution.^{40,41} Like dimedone, it reacts with arylidene cyanothioacetamides **52** to give enolates **64**.⁴²





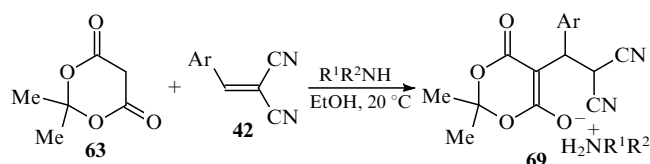
Unlike the salts **55** and **57**, which can be converted into the free enols **56** and **58** by acidification, compounds **64** decompose on treatment with hydrogen chloride in ethanol at 0 °C or on heating in acetic acid to give the initial thioamides **52**. However, in the case of the morpholinium salt **64** (Ar = Ph), free Michael adduct **65** has been prepared.⁴² Heating of the same salt in acetic acid affords thiopyran **54** resulting from dimerisation of benzylidenecyanothioacetamide.³²

The compounds **64** react with phenacyl bromide according to the Hantzsch reaction pattern with elimination of Meldrum's acid and formation of thiazole derivatives **66**. The same compounds have been synthesised by treatment of the thioamides **52** with phenacyl bromide.⁴²



Arylthiazolylcyanoethylenes **66** have previously been obtained by reactions of 2-cyanomethylthiazoles **67** with the aromatic aldehydes **44**,⁴³ or phenacyl bromide with 4-amino-6-aryl-5-cyano-1,3-dithiacyclohexenes **68**.⁴⁴ The latter reaction has served as evidence for the intermediate formation of the thioamides **52** during thermal decomposition of dithiacyclohexenes **68** (see Section VII).^{45, 46}

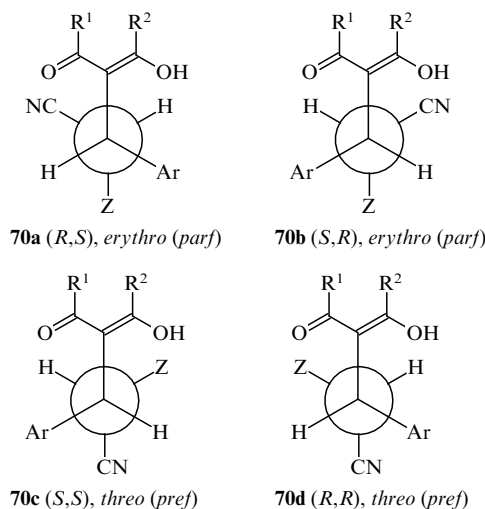
The reaction of Meldrum's acid **63** with arylidenemalononitriles **42** in ethanol in the presence of secondary amines also gives rise to Michael adducts formed as salts **69**.⁴² A similar reaction of dimedone and 4-hydroxycoumarin affords fused 4*H*-pyrans (see Section VI).



When cyclic 1,3-dicarbonyl compounds are made to react with arylidenecyanothioacetamides, the Michael adducts are usually isolated as enol salts of secondary amines. In the case of acyclic 1,3-dicarbonyl compounds, the intermediate adducts cyclise without isolation to the corresponding pyridines (see Section VII).

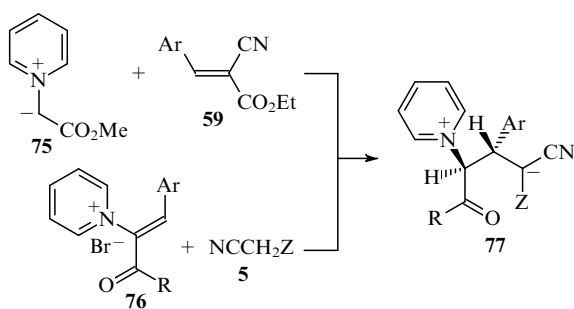
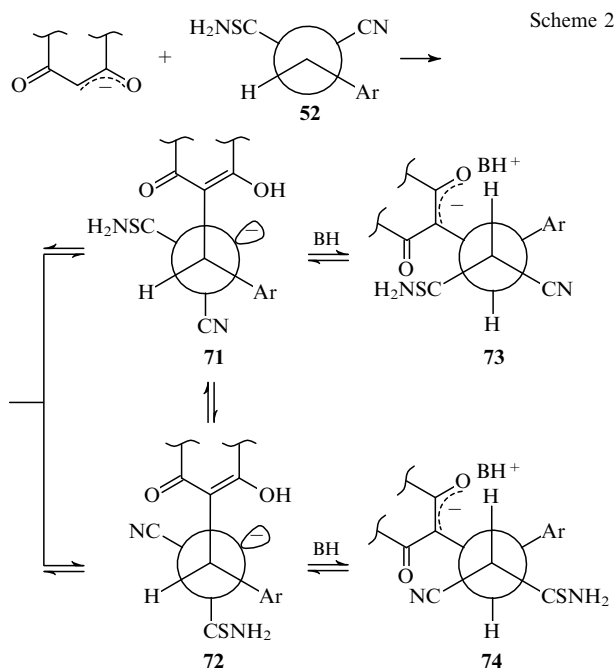
Based on the spin-spin coupling constants, $^3J = 11.5 - 12.5$ Hz, of the methine protons in the compounds **55–58**, **60**, **62**, **64**, **65**, and **69**, it was found that the dihedral angles ϕ between these protons are 158–165°, which corresponds to the antiperiplanar conformation.^{36, 37, 42}

It is known that the selectivity of any reaction is determined by the symmetry of the transition state; therefore, when diastereoisomeric activated complexes are formed, they react at different rates.⁴⁷ The Michael addition of dicarbonyl compounds to unsaturated nitriles of the types **42**, **47**, **52**, or **59** results in the appearance of two asymmetric centres; thus, the reaction system is diastereotopic. Since the attack on the diastereotopic sides of the molecule could give unequal amounts of diastereoisomers, due to the difference between the free energies of the corresponding transition states, this reaction is, in principle, diastereoselective and can afford two pairs of diastereoisomeric adducts, **70a,b** and **70c,d**. The substituent Z is usually represented by ester, amide, thiocarbamoyl, and other similar groups, which, according to the succession rule, are senior with respect to the cyano group. In this case, the stereoisomers **70a** and **70b** constitute an enantiomeric pair of the *erythro*-type (*parf*) diastereoisomers, whereas the isomers **70c** and **70d** belong to the *threo*-type (*pref*).^{48, 49} The predominant formation of one or another stereoisomer depends on the particular conditions.



The addition of a dicarbonyl fragment to the double bond in the compounds **52** existing as *E* isomers^{32, 50} gives intermediate carbanions **71** and **72**. It is known that the inversion of configuration in carbanions occurs relatively easily⁵¹ and that the *E/Z* isomerisation of arylidenecyanoacetates occurs exactly at this stage.⁵² Apparently, the carbanions **71** and **72** are also able to isomerise to each other. The protonation of the carbanions **71** and **72** gives isomers represented by projections **73** and **74**, respectively. Evidently, the course of cyclisation depends not only on thermodynamic factors but also on the spatial structure of the adducts. Therefore, intramolecular cyclisation of *erythro*- and *threo*-diastereoisomers yields different compounds: pyrans or pyridines (see Sections VI and VII, respectively, Scheme 2).

It is known that pyridinium ylides are good reagents for transferring the methylenecarbonyl function to an activated C=C bond.⁵³ When pyridinium ylides **75** react with the unsaturated nitriles **59**, or the nitriles **5** react with unsaturated ketones **76**, Michael adducts **77** are formed.^{53–55}

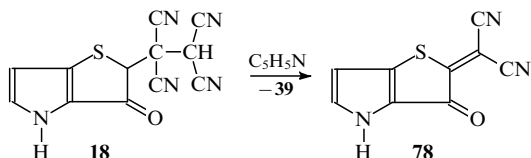


Z = CN, CO₂Et.

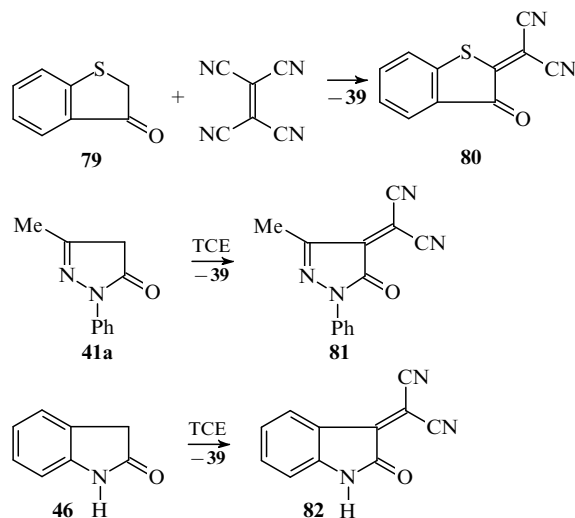
Based on conformational analysis using the magnitudes of the spin-spin coupling constants of methine protons, $^3J = 11.2$ – 11.8 Hz, it was shown that the adducts **77** also exist only in the antiperiplanar conformation. The reactions of unsaturated nitriles with pyridinium ylides have been considered in more detail in a review.⁵⁶

A possible route for subsequent transformations of Michael adducts is decomposition accompanied by elimination of an easily leaving group⁵⁷ [Scheme 1, pathway (a)] and resulting in various rearrangements and exchange of methylene components.^{57–59} The Michael adducts derived from unsaturated nitriles also tend to undergo retro-reactions, and, consequently, the reactions of ylide derivatives of cyanoacetic acids with nucleophiles typically involve dynamic equilibria of the type $1 + 2 \rightleftharpoons 3 \rightleftharpoons 4 \rightleftharpoons 6 + 5$ (see Scheme 1).⁶⁰ These transformations have been considered in detail.⁶¹

The adducts formed from cyclic carbonyl compounds and TCE tend to eliminate malononitrile **39**. Thus on treatment with pyridine, the adduct **18** is cleaved to afford compound **78**.¹⁵

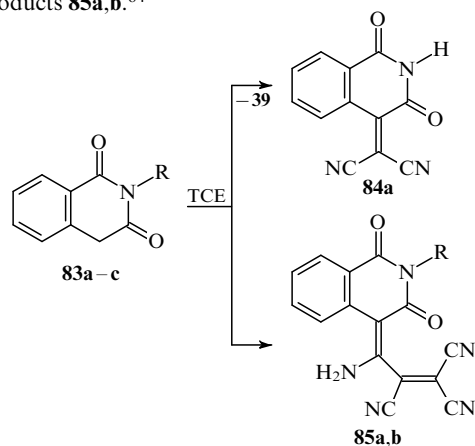


Benzo[*b*]thiophen-3-one **79** reacts with TCE giving rise to unsaturated nitrile **80** without intermediate isolation of the Michael adduct.¹⁵ The reaction of the pyrazolone **41a** with TCE also results in the formation of the corresponding dicyanomethylidene derivative **81**.⁶² 2-Indolinone **46** reacts with TCE in a similar way and gives dicyanomethylideneindolinone **82**.⁶³



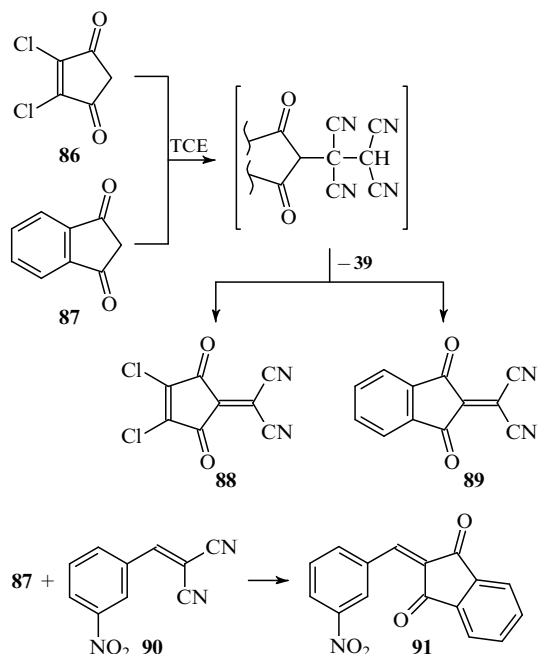
TCE is tetracyanoethylene.

The behaviour of imides **83** in the reaction with TCE depends on the nature of the substituent at the nitrogen atom. For R = H, the reaction occurs according to the Michael pathway followed by elimination of malononitrile **39** to give compound **84a**. However, in the presence of an alkyl substituent, the nucleophilic methylene group in the compound **83** attacks the electrophilic carbon atom of a cyano group in TCE giving rise to the Thorpe reaction products **85a,b**.⁶⁴

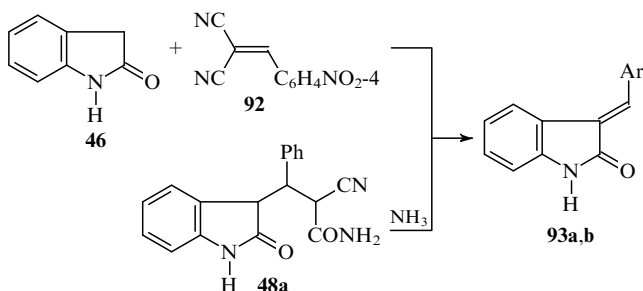


R = H (**83a**), Me (**83b**, **85a**), Et (**83c**, **85b**).

Cyclic diketones such as 4,5-dichlorocyclopent-4-ene-1,3-dione **86**⁶⁵ and 1,3-indanedione **87**⁶⁶ also react with TCE according to the Michael pathway. The products **88** and **89** thus formed contain an electron-deficient double bond. The compound **88** has been used to prepare charge-transfer complexes.⁶⁵ The reaction of indanedione **87** with 3-nitrobenzylidenemalononitrile **90** gives rise to unsaturated diketone **91**.¹¹

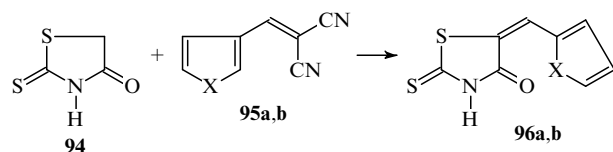


The reaction of 4-nitrobenzylidenemalononitrile **92** with indolinone **46** affords compound **93a**.²⁹ When other arylmethylidenemalononitriles are introduced into this reaction, stable Michael adducts **48** are produced;²⁹ one of them (**48a**) is converted into non-substituted unsaturated ketone **93b** on treatment with ammonia.²⁹



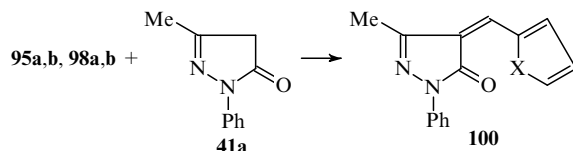
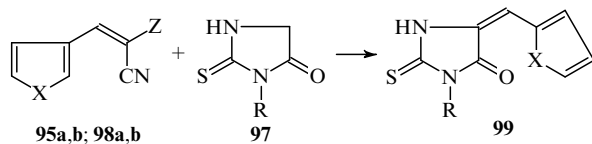
Ar = 4- $\text{NO}_2\text{C}_6\text{H}_4$ (**a**), Ph (**b**).

The reactions of thiazolidine derivative **94** with furylidene- and thienylidene-malononitriles **95a,b** giving unsaturated ketones **96a,b** have been reported.⁶⁷



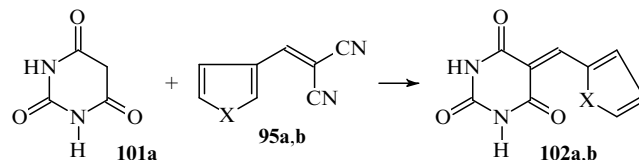
X = O (**a**), S (**b**).

3-R-2-Thiohydanthoins **97** having a similar structure and 3-methyl-1-phenylpyrazolone **41a** react with **95a,b** and **98a,b** to give products **99** and **100**. It has been suggested⁶⁸ that during this reaction, the reactants exchange their methylene components.



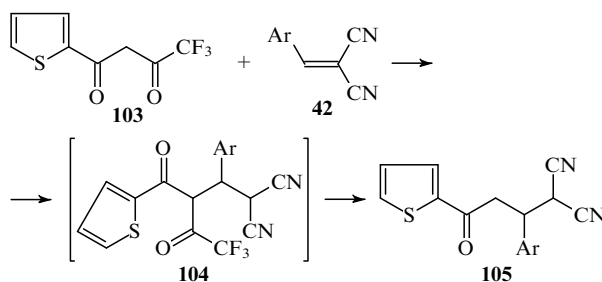
X = O, Z = CN (**95a**); X = S, Z = CN (**95b**);
X = O, Z = CO_2Et (**98a**); X = S, Z = CO_2Et (**98b**).

It has been shown that on refluxing in ethanol with barbituric acid **101a** and triethylamine, substituted furylidene-malononitriles **95a,b** are converted into compounds **102**.⁶⁹ By varying reaction conditions, one can obtain 2-aminopyrano[2,3-*d*]pyrimidines (see Section VI).

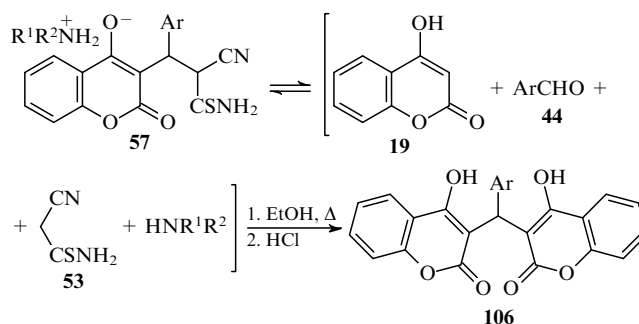


X = O (**a**), S (**b**).

An interesting reaction occurs between arylidenemalononitriles **42** and 1,1,1-trifluoro-3-(2-thenoyl)acetone **103**. The Michael adducts **104** formed intermediately undergo acidic cleavage with elimination of trifluoroacetic acid and are thus converted into substituted dicyanopropanes **105**,^{11,70} which can be used to synthesise substituted pyridines.⁷⁰

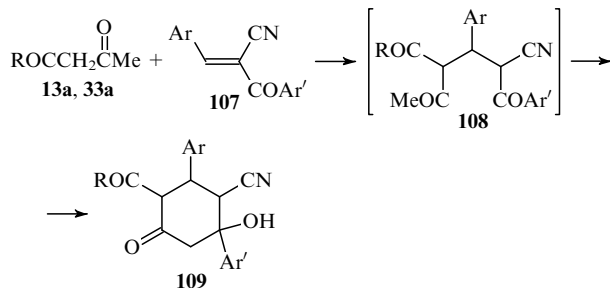


It has been mentioned above that the salts of adducts formed by Meldrum's acid and arylidenecyanothioacetamides **64** enter into a retro-reaction induced by acids and resulting in regeneration of the thioamides **52**. This is in agreement with the known data indicating that Michael adducts are stabilised by bases.⁶⁰ On heating in ethanol, the dimedone and Meldrum's acid derivatives are finally converted into derivatives of hydrogenated pyridine (Section VII). In the case of the salts **57** prepared from 4-hydroxycoumarin the cyclisation is hampered, and, as a result, the retro-reactions prevail. Prolonged refluxing of the salts **57** in ethanol followed by acidification has given aryl-substituted dicoumarins **106**;³⁷ these compounds have also been synthesised by the reaction of 4-hydroxycoumarin **19** with aromatic aldehydes **44**.^{71,72} The chemical properties of the compounds **106** and their analogues have been studied.^{73,74} It was found that they possess a moderate anticoagulant activity and inhibit oxidative phosphorylation in liver mitochondria.⁷⁵ The structure of a dicoumarin **106** (Ar = Ph) has been studied by X-ray diffraction analysis.⁷⁶



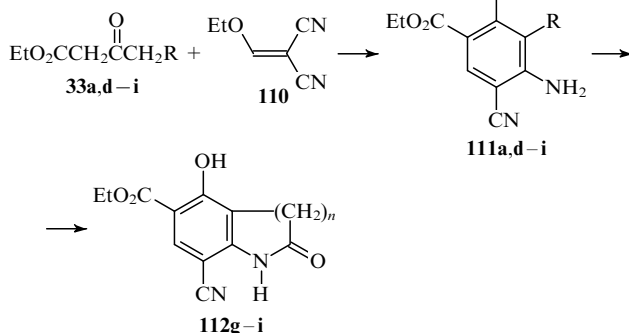
IV. Synthesis of carbocyclic compounds

Carbocyclic compounds are formed in those cases where at the stage of cyclisation of the adducts **7** and **8** (see Scheme 1), the carbon atom of the methyl, methylene, or methine group, activated by electron-withdrawing substituents, acts as the nucleophilic centre, while the carbonyl or nitrile carbon atom acts as the electrophilic centre.⁷ The reactions of 1,3-dicarbonyl compounds **13a** and **33a** with substituted nitriles **107** occur *via* cyclisation of the intermediate Michael adducts **108** at the aryl group and afford compounds **109**.^{23, 77}



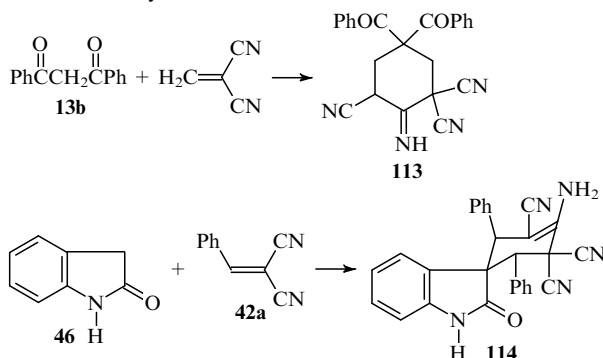
R = Me (**13a**), OEt (**33a**).

The dicarbonyl compounds **33a, d–f** react with ethoxymethylidenemalononitrile **110** to give substituted anilines **111**.^{78–80} When the compounds **33g–i** with R = (CH₂)_nCO₂Et, n = 1, 2, 3, are introduced into this reaction, subsequent condensation is possible, resulting in the formation of fused heterocyclic compounds **112**.⁸⁰

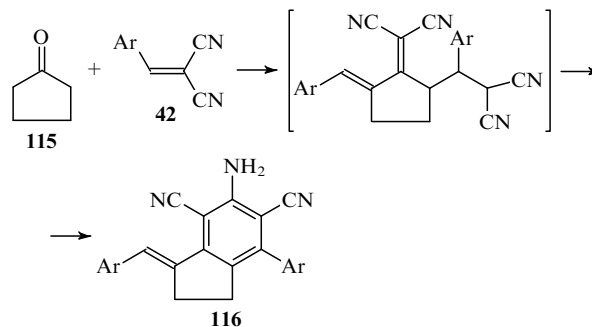


R = H (**a**), Me (**d**), Et (**e**), Ph (**f**), EtO₂CCH₂ (**g**), EtO₂C(CH₂)₂ (**h**), EtO₂C(CH₂)₃ (**i**).

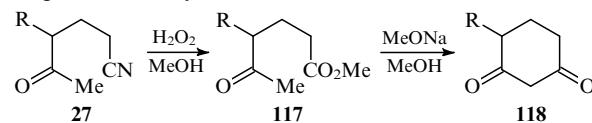
In some cases, the intermediate Michael adducts can add to a second molecule of the starting unsaturated nitrile, and the resulting bis-adduct can undergo Thorpe cyclisation. This route is realised, for example, in reactions of dibenzoylmethane **13b** with 1,1-dicyanoethylene¹ and oxindole **46** with benzylidenemalononitrile **42a**.²⁹ The resulting compounds **113** and **114** contain six-membered carbocycles.



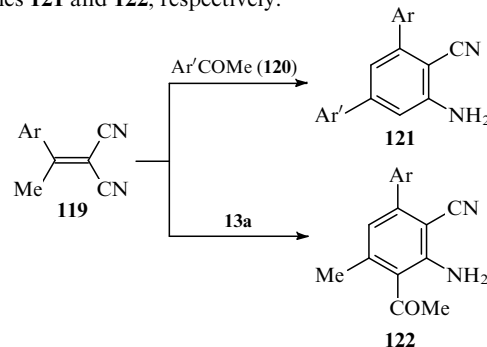
Cyclopentanone **115** also adds two molecules of an unsaturated nitrile giving rise to fused anilines **116**.⁸¹



On treatment with hydrogen peroxide in methanol, the adducts **27** are converted into esters **117**, refluxing of which in the presence of sodium methoxide leads to their cyclisation yielding substituted cyclohexanediones **118**.¹⁷



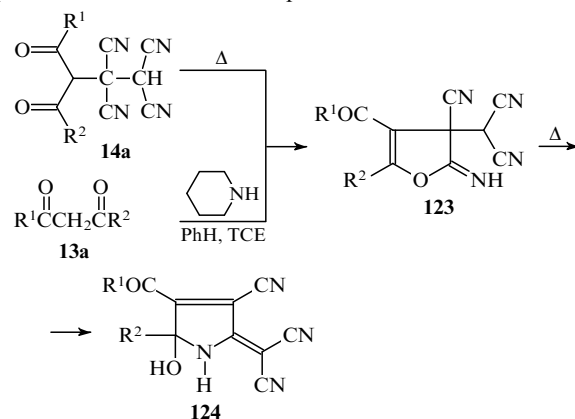
Unsaturated nitriles **119** react with substituted acetophenones **120** or with acetylacetone **13a** to give arylated 2-aminobenzonitriles **121** and **122**, respectively.⁸²

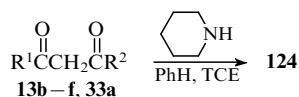


V. Synthesis of five-membered heterocycles

With an appropriate arrangement of the reaction centres, Michael adducts like 1,4-dioxo nitriles cyclise to give five-membered heterocycles, furans and pyrroles. Thus the adduct **14a** is converted into substituted 2-iminofuran **123** even during recrystallisation from a mixture of acetone and petroleum ether. The reaction of acetylacetone **13a** with TCE **9a** in benzene in the presence of pyridine affords immediately the imine **123**.¹⁴

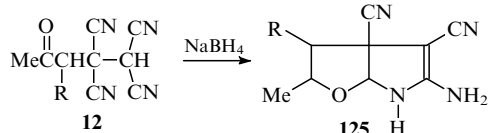
On heating, 2-iminofuran **123** undergoes rearrangement accompanied by migration of the dicyanomethyl group to give dihydropyrroles **124**. The pyrroles **124** are also produced when ethyl acetoacetate **33a** or various acyclic 1,3-diketones **13b–f** (except for acetylacetone) react with TCE in the presence of piperidine. No furans **123** were produced in these reactions.¹⁴



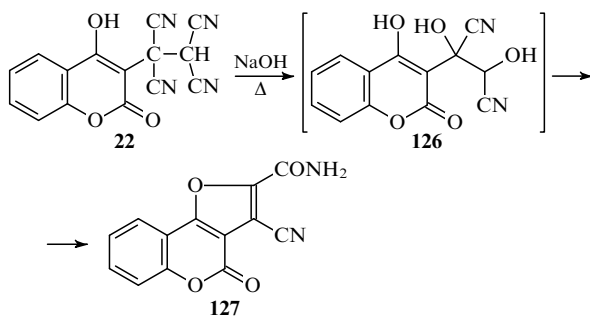


$\text{R}^1 = \text{R}^2 = \text{Me}$ (**13a**, **14a**); $\text{R}^1 = \text{R}^2 = \text{Ph}$ (**13b**);
 $\text{R}^1 = \text{R}^2 = \text{Et}$ (**13c**); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$ (**13d**);
 $\text{R}^1 = \text{CHMe}_2$; $\text{R}^2 = \text{Me}$ (**13e**), CHMe_2 (**13f**); $\text{R}^1 = \text{OEt}$, $\text{R}^2 = \text{Me}$ (**33a**).

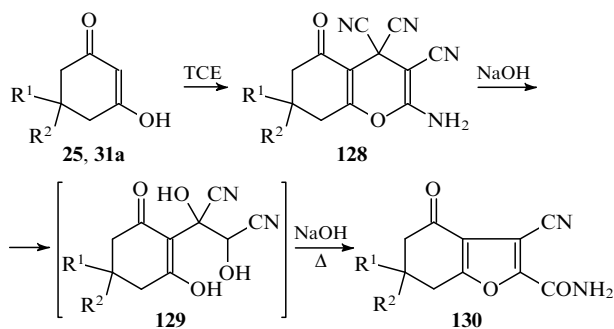
It has been reported⁸³ that during the reduction with sodium tetrahydroborate, acyclic adducts of the type **12** cyclise to substituted tetrahydrofuro[2,3-*b*]pyrroles **125**.



When the adduct **22** is refluxed in an alkaline solution, two cyano groups are substituted to give intermediate **126**, which cyclises with simultaneous hydrolysis of one more cyano group giving rise to furobenzopyranone **127**.¹⁶

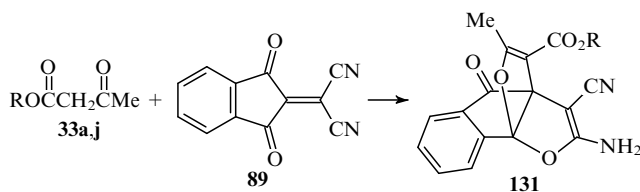


Pyrans **128**, obtained by the interaction of dimedone **25** or cyclohexanedione **31a** with TCE, react with alkali with opening of the pyran ring to give intermediates **129**, which are then converted into fused furans **130** in a similar way.⁸⁴



$\text{R}^1 = \text{R}^2 = \text{Me}$ (**25**), H (**31a**).

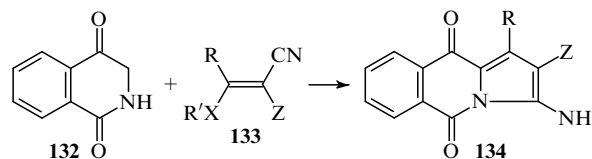
2-(Dicyanomethylidene)-1,3-indanedione **89** reacts with alkyl acetoacetates **33a,j** on refluxing in ethanol. This results in the formation of propellanes **131** in moderate yields.⁸⁵



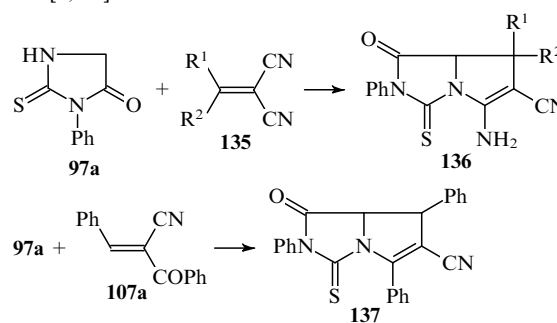
$\text{R} = \text{Et}$ (**33a**), Bu^t (**33j**).

The reactions of isoquinolinedione **132** with unsaturated nitriles **133** containing an easily leaving group R^1X ($\text{X} = \text{O}, \text{S}$) result in the formation of pyrrolo[1,2-*b*]isoquinolinediones **134**.

Cyclisation occurs under mild conditions without isolation of intermediate adducts. The compound **134** was found to possess antiproliferative activity.⁸⁶



3-Phenyl-2-thiohydantoin **97a** reacts with a large number of ylidenemalononitriles **135** giving rise to substituted pyrrolo[1,2-*c*]imidazoles **136**.⁸⁷ However, for unsaturated nitriles containing a benzoyl group, for example, for **107a**, the cyclisation was reported⁸⁷ to involve the CO group instead of CN and to yield pyrrolo[1,2-*c*]imidazole **137**.

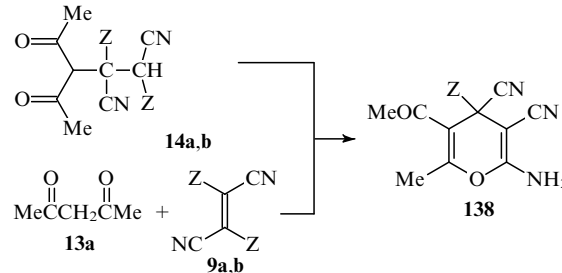


VI. Synthesis of pyrans

Cyclisation of the Michael adducts of the type **7** and **8** (see Scheme 1) giving a pyran ring occurs in those cases where the oxygen atom in δ -hydroxy or δ -oxo nitriles acts as the nucleophilic centre.⁷ As a rule, this affords 4*H*-pyrans. A carbonyl fragment can serve as the electrophilic centre in place of the nitrile group. Depending on the structures of the initial compounds, the formation of pyrans in the reactions under consideration can occur without intermediate Michael reaction between the reactants. The mild conditions needed for these reactions, high yields of products, and also potential biological activities of the resulting 4*H*-pyrans account for the considerable interest aroused by these objects and for the large number of publications on this topic, which have been surveyed in monographs and reviews.^{1,7,88}

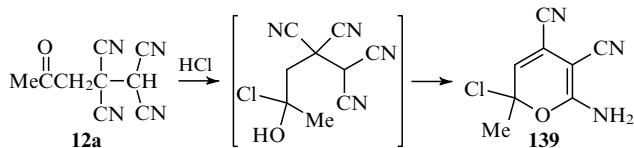
There are two main approaches to the synthesis of the compounds in question, namely, interaction of nitriles with α,β -unsaturated ketones^{23,88} and interaction of carbonyl compounds with α,β -unsaturated nitriles. This section is devoted to the latter approach. However, in each particular case, the most efficient preparative method can be chosen for the synthesis of pyrans, because the above structures can occur in equilibrium ($\text{5} + \text{6} \rightleftharpoons \text{3} \rightleftharpoons \text{1} + \text{2}$ in Scheme 1)^{10,60,61} and these reactions have common intermediates.

The acyclic adducts **14a,b**, prepared by the addition of acetylacetone to TCE or dicyanofumarate, readily cyclise to the corresponding 4*H*-pyrans **138** on refluxing in petroleum ether.¹⁰ The same products are formed when acetylacetone **13a** reacts with nitriles **9a,b** in acetonitrile.

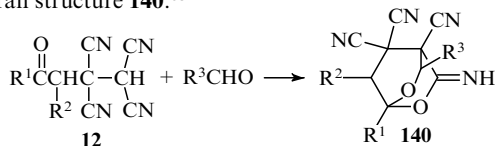


$\text{Z} = \text{CN}$ (**a**), CO_2Et (**b**).

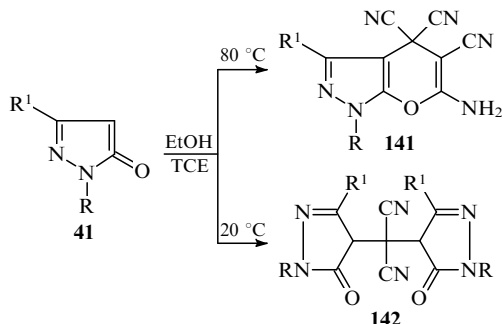
The adduct **12a** synthesised from acetone and TCE cyclises into the 2*H*-pyran **139** under the action of hydrogen chloride.¹³



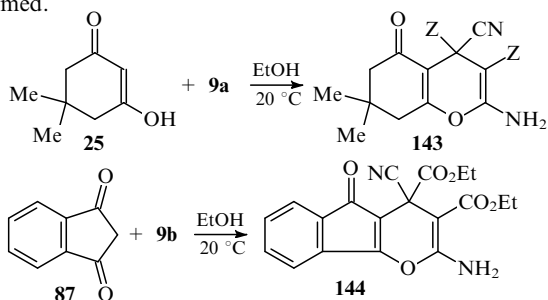
The compounds **12**, which are formed when ketones add to TCE (see Section III), can react with aldehydes at the terminal dicyanomethyl group; this yields bicyclic compounds with the pyran structure **140**.⁸³



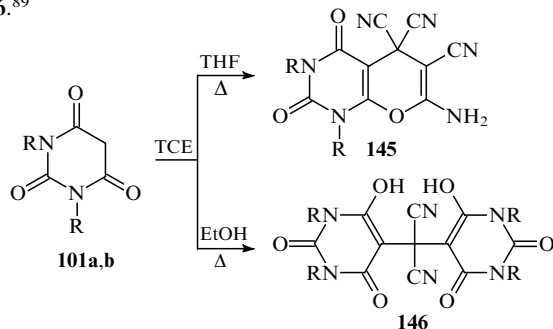
Refluxing of pyrazolones **41** with TCE in ethanol results in the formation of pyrano[2,3-*c*]pyrazoles **141**. This reaction carried out without heating yields bis-adducts **142**.⁸⁹ Apparently, in this case, the rate of elimination of malononitrile from the intermediate Michael adduct is higher than the rate of cyclisation.



When dimedone **25**^{10, 84} reacts with TCE **9a**, or indanedione **87**¹⁰ reacts with dicyanofumarate, fused pyrans **143** and **144** are formed.

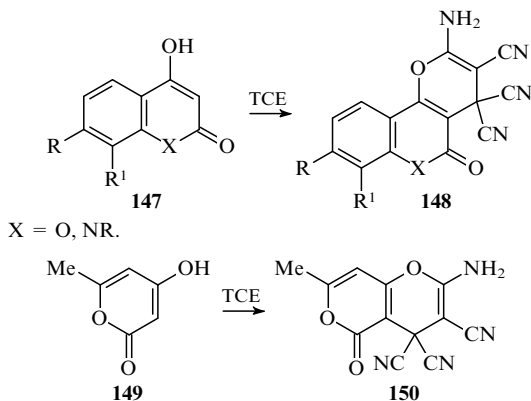


Barbituric acids **101a,b** react with TCE in boiling THF to give fused 4*H*-pyrans **145**.⁸⁹ It is of interest that the same reaction carried out in ethanol results in the formation of bis-adducts **146**.⁸⁹

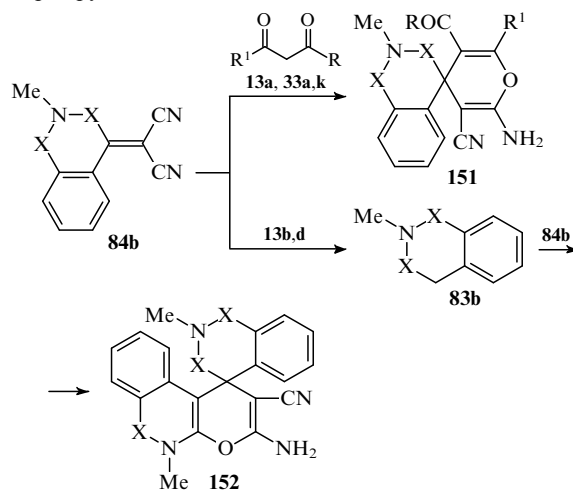


R = H (a), Me (b).

4-Hydroxycoumarin **19** and 4-hydroxy-2-quinolinone **20** can be regarded as completely enolised cyclic 1,3-dicarbonyl compounds. As noted above, they form Michael adducts **22** and **23** upon reactions with TCE.¹⁶ Later, it has been found that the reaction of the substituted coumarins **147** (X = O) and quinolinones **147** (X = NR) with TCE permits the synthesis of fused pyrans **148** in one step without isolation of the adducts of the type **22** and **23**.⁶³ Like 4-hydroxycoumarin, triacetic acid lactone **149** also reacts with TCE giving rise to fused pyran **150**.⁸⁹

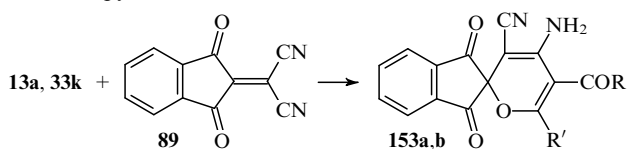


The reactions of carbonyl compounds with dicyanomethylidene derivatives of carbo- and heterocyclic compounds make it possible to synthesise spiro-derivatives of pyrans, which are difficult to obtain by other methods. Thus reactions of 3-dicyanomethylidene-1-methylisoquinoline-2,8-dione **84b** with acetylacetone **13a**, ethyl acetoacetate **33a**, and ethyl benzoylacetate **33k** gave spiropyrans **151**.⁹⁰ When dibenzoylmethane **13b** or benzoylacetone **13d** is used as the dicarbonyl compound, the reaction starts with elimination of malononitrile from the compound **84b** giving homophthalimide **83b**. The latter reacts with excess **84b** to yield spiropyran **152**.⁹⁰



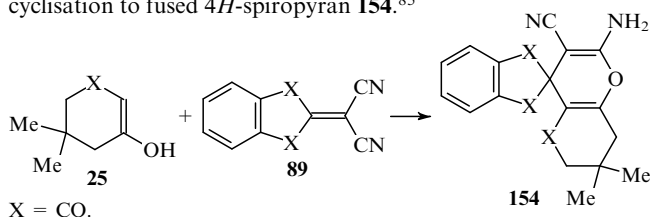
X = CO; R = R¹ = Me; R = OEt; R¹ = Me, Ph.

2-Dicyanomethylidene-1,3-indanethione **89** reacts with acetylacetone **13a** and ethyl benzoylacetate **33k** giving rise to substituted 2*H*-pyrans **153a,b**.⁸⁵

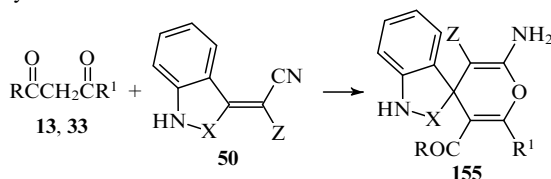


R = R¹ = Me (**13a**, **153a**); R = Et, R¹ = Ph (**33k**, **153b**).

Unlike acyclic dicarbonyl compounds, dimedone adds to the unsaturated nitrile **89** according to Michael; this is followed by cyclisation to fused *4H*-spiropyran **154**.⁸⁵

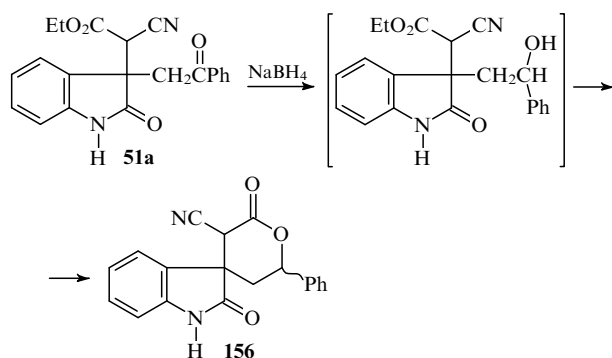


The reactions of 3-cyanomethylidene **50** with a broad range of dicarbonyl compounds of the types **13** and **33** lead to the synthesis of substituted spiropyrans **155** without isolation of intermediate Michael adducts.⁹¹ Similar results have been obtained in another study.⁸⁵

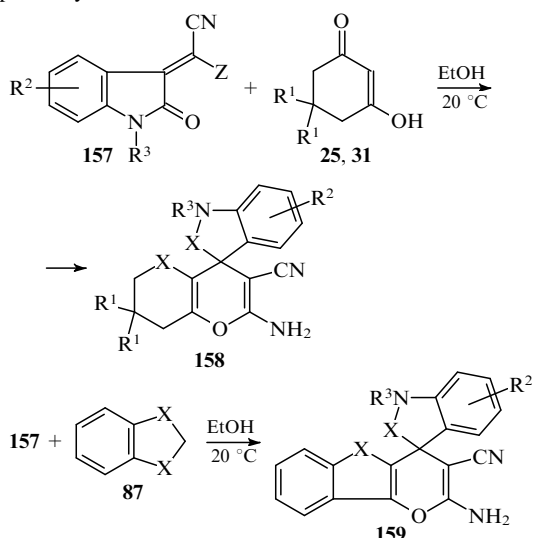


R = Alk, Ar; R¹ = Alk, Ar, OAlk; X = CO; Z = CN, CO₂Et.

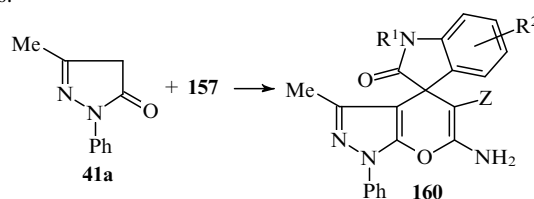
On reduction with sodium tetrahydroborate, the adduct **51a** cyclises giving rise to substituted hydrogenated spiropyran **156**, which has been isolated as a mixture of two diastereoisomers in a ratio of 3 : 1.³⁰



Cyclic 1,3-dicarbonyl compounds — substituted 1,3-cyclohexanediones **25**, **32** and indanedione **87**⁹² — react with 3-cyanomethylidene-2-oxindoles **157** to give spiropyrans **158** and **159**, respectively.

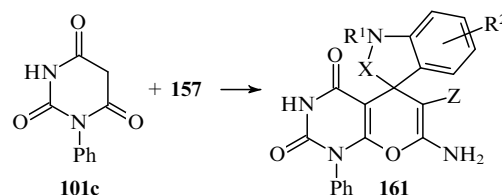


The addition of the pyrazolone **41a** to substituted 3-cyanomethylidene-2-oxindole **157** results in the formation of spiropyrans **160**.^{91,93} Some fluoro-substituted derivatives of **160**, for example, those with R² = 5-F or 4-CF₃, exhibit herbicide properties.⁹³



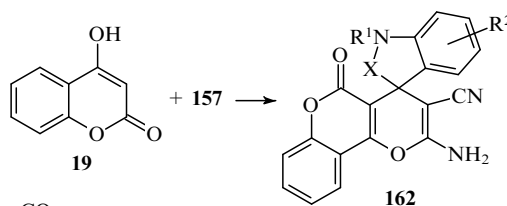
Z = CN, CO₂Et.

Barbituric acids also react with 3-cyanomethylideneindolones **157** to give spiropyrans.^{91,94} In the case of 1-phenylbarbituric acid **101c**, the reaction with fluorine-containing **157** gives rise to spiro compounds **161**.⁹⁵



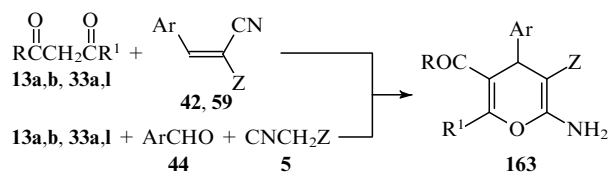
Z = CN, CO₂Et; X = CO.

3-Dicyanomethylidene-2-oxindoles **157** with 4-hydroxycoumarin **19** afford the corresponding spiropyrans **162**.⁹²



X = CO.

Arylidene derivatives of malononitrile and ethyl cyanoacetate smoothly react with 1,3-dicarbonyl compounds containing a highly reactive methylene group yielding 2-amino-4*H*-pyrans. In this case, the intermediate Michael adducts immediately undergo intramolecular cyclisation. The reaction is normally carried out in ethanol at room temperature using catalytic amounts of organic bases. The simplicity and convenience of this route to substituted 2-amino-4-aryl-4*H*-pyrans **163** have been demonstrated in relation to the interaction between ethyl acetoacetate **33a** and the unsaturated nitriles **42**.⁹⁶ Later, ethyl oxaloacetate **33l**⁹⁷ and other acyclic dicarbonyl compounds such as acetylacetone **13a** and dibenzoylmethane **13b**¹¹ were also introduced in the reactions with the unsaturated nitriles **42** and **59**. The aromatic aldehydes **44** and functional derivatives of malonic acid (Z = CN, CO₂Et) can be used instead of the nitriles **42** and **59**; in many cases, this results in simpler preparative procedures.⁹⁶



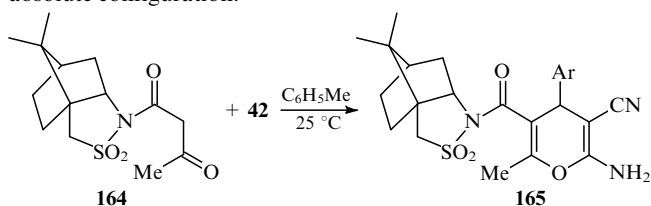
R = R¹ = Me (**13a**); R = R¹ = Ph (**13b**); R = OEt: R¹ = Me (**33a**), R¹ = CO₂Et (**13l**); Z = CN (**42**), CO₂Et (**59**).

This reaction has been extended to hetaryl-substituted derivatives of the unsaturated nitriles **42** and **59**. In particular, 1,3-dicarbonyl compounds have been made to react with thiophene⁹⁸ and pyridine⁹⁹ derivatives and with quaternised pyridines.¹⁰⁰ The structure of the pyrans obtained in this way, namely, 3-(2-amino-

3,5-dicarbethoxy-6-methyl-4(4*H*)-pyranyl-1-methylpyridinium iodide, was studied by X-ray diffraction analysis.¹⁰⁰ It was found that the pyran ring has a boat conformation in which the O and C atoms emerge from the plane of the boat 'bottom'.

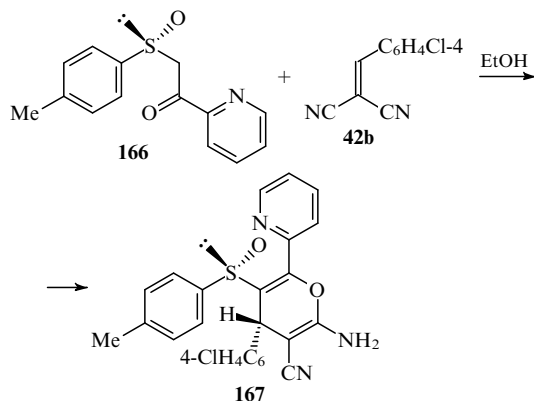
The formation of furyl-substituted pyrans **163** upon interaction of 2-furylidenemalononitriles with ethyl 4-chloro-3-oxobutylate¹⁰¹ or acetylacetone^{102,103} has been reported. In several studies,^{104–108} syntheses of pyrans based on reactions of the unsaturated nitriles **42** and **59** with ethyl acetoacetate or acetylacetone have been reproduced.

The use of optically active esters of acetoacetic acid in the reactions with arylidenemalononitriles was a step forward on the way to the synthesis of chiral 4*H*-pyrans. Thus reaction of esters derived from acetoacetic acid and (1*R*,2*S*,5*R*)-(-)-menthol, (1*S*)-endo-(-)-borneol, or ethyl (*S*)-(-)-lactate with benzylidene- and *m*-nitrobenzylidene-malononitriles **42a** and **90** affords the pyrans **163** containing an optically active substituent. The yields of the mixture of diastereoisomers was 73%–98%;¹⁰⁹ however, the diastereoisomeric excess was no more than 10% and the mixture could not be separated. The reactions of the arylidenemalononitriles **42** with chiral acetoacetylsulfamide **164** are much more stereoselective. Thus pyrans **165** are formed as mixtures of diastereoisomers with a diastereoisomeric excess of 60%–70%. In some cases, this mixture has been separated into individual isomers, and it turned out that all the major isomers are characterised by the same configuration at the newly formed C(4) chiral centre in the pyran fragment. X-Ray diffraction study has shown that in the minor isomer of **165** (Ar = Ph), this atom has the *S*-absolute configuration.



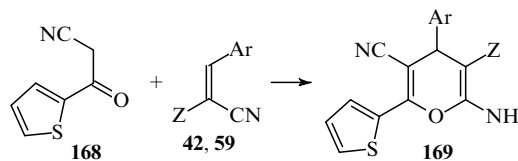
A much higher degree of asymmetric induction has been observed for the reactions of the unsaturated nitriles **42** and **59** with β-oxosulfones and sulfoxides yielding 5-*R*-sulfinyl- and 5-*R*-sulfonyl-substituted pyrans.¹¹⁰ The reaction of the optically active β-oxo sulfoxide **166** with 4-chlorobenzylidenemalononitrile **42b** gives the single enantiomer **167** in 86% yield. According to X-ray diffraction analysis, the C(4) and S atoms in this compound have the (*R,R*) absolute configuration. In 5-sulfinyl-substituted analogues of the pyran **167**, the oxygen atoms and the proton of the RSOC(5)C(4)HAr structural fragment are always *syn*-arranged.

The researchers¹¹⁰ believe that this high degree of asymmetric induction is due to the fact that the electron-withdrawing reaction centre approaches from the side opposite to the *p*-tolylsulfinyl substituent. However, thermodynamic control of the stereoselectivity in this process also cannot be ruled out.



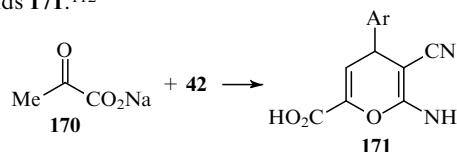
Apart from 1,3-dicarbonyl compounds, α-cyano ketones can also serve as convenient synthons for the synthesis of pyrans. The

reaction of 2-thenoylacetonitrile **168** with the nitriles **42** and **59** giving rise to 5-cyanopyrans **169** provides an example.¹¹¹

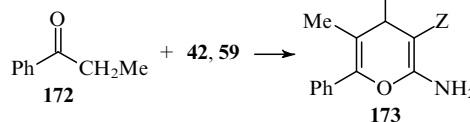


Z = CN (**42**), CO₂Et (**59**).

Sodium pyruvate **170** possesses sufficient CH acidity to be involved in the Michael reaction with the arylidenemalononitriles **42**. Refluxing in ethanol for 3 h in the presence of sodium ethoxide results in the formation of derivatives of 4*H*-pyran-2-carboxylic acids **171**.¹¹²

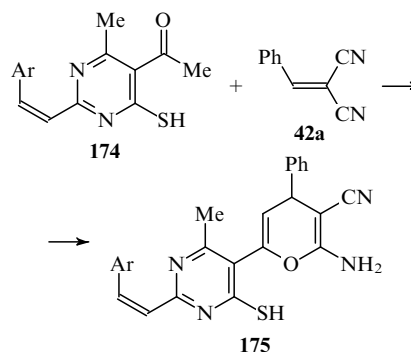


The possibility of synthesising 6-phenyl-substituted 4*H*-pyrans **173** from alkyl aryl ketones has been demonstrated by performing the reaction of the propiophenone **172** with the nitriles **42** and **59**.¹¹³ Some of the compounds **173** have been reported to exhibit antibacterial, including antistaphylococcal, activities.¹¹³

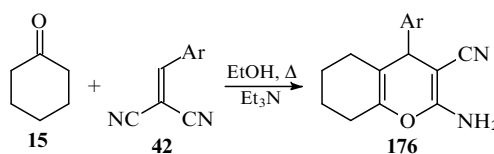


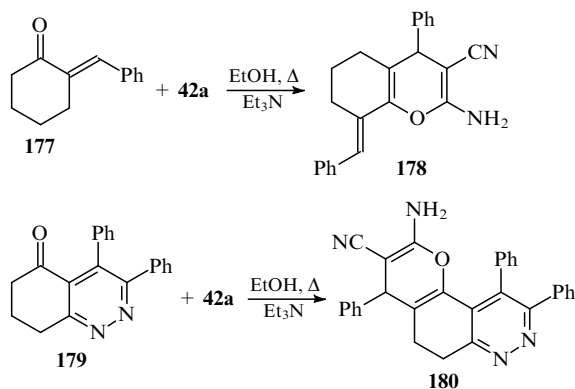
Z = CN (**42**), CO₂Et (**59**).

Acetyl derivatives of heterocyclic compounds can be involved in the Michael reaction as CH acids. A study of the reaction of 5-acetyl-substituted pyrimidines **174** with benzylidenemalononitrile **42a** has shown¹¹⁴ that despite the fact that **174** are polyfunctional compounds, the reaction is highly chemoselective and results in the formation of pyrans **175** in 50%–55% yields.

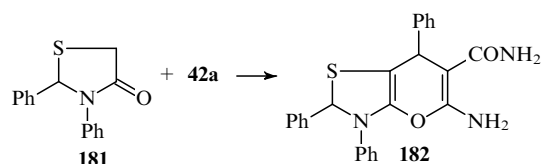


Cyclic ketones serve as the starting compounds for the preparation of fused pyrans. To obtain substituted tetrahydrobenzo[*b*]pyrans **176** from cyclohexanone and the nitriles **42**, it is sufficient to reflux the reactants in ethanol in the presence of triethylamine for 10 min.¹¹⁵ 2-Benzylidenecyclohexanone **177** enters into this reaction under similar conditions to give pyrans **178**.¹¹² When substituted tetrahydrocinnolin-5-one **179** is made to react with benzylidenemalononitrile **42a**, polyfused pyran **180** is produced.¹¹⁶

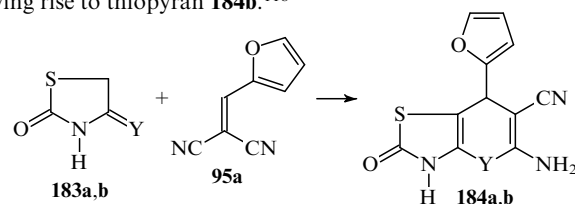




Five-membered heterocyclic carbonyl compounds also react with unsaturated nitriles giving rise to fused 4*H*-pyrans. Thus thiazolone **181** reacts with benzylidenemalononitrile **42a** upon refluxing in ethanol for 6 h in the presence of triethylamine. It has been noted¹¹⁷ that this reaction is accompanied by hydrolysis of the cyano group and affords 3-carbamoyl-substituted pyran **182**.

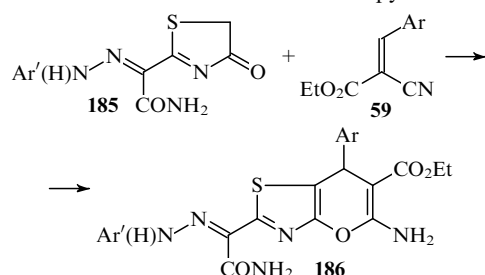


The reaction of compound **183a** with furylidenemalononitrile **95a** affords pyran **184a**.¹¹⁸ Compound **183b** reacts in a similar way giving rise to thiopyran **184b**.¹¹⁸



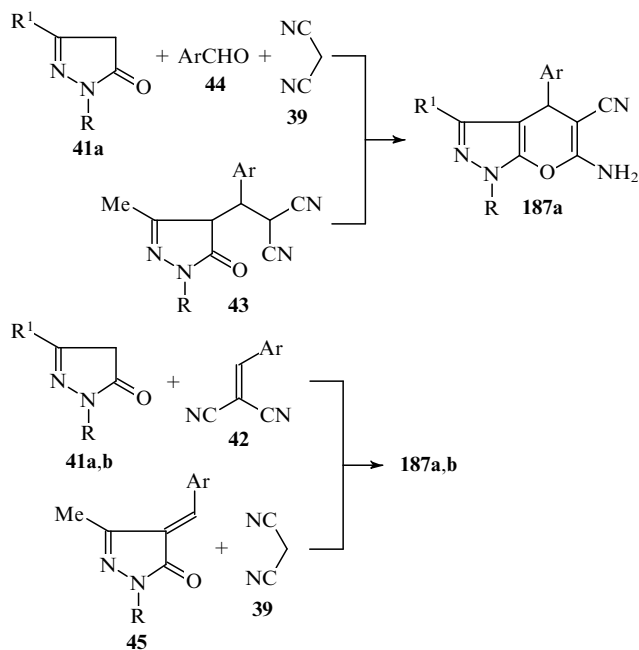
Y = O (a), S (b).

Thiazolone derivatives **185** react with ethyl arylidenecyanoacetates **59** with the formation of 2-aminopyrans **186**.^{119, 120}



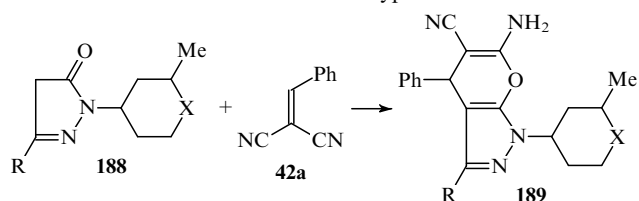
Among the reactions of carbonyl compounds with unsaturated nitriles, the transformation of 3-methylpyrazol-5-ones **41** yielding pyranopyrazoles **187** deserves special attention. The simplicity of the experiment and the high yields and the potential biological activity of the reaction products^{28, 121} account for the large number of publications dealing with this topic. The synthetic capacity of the reactions of the pyrazolones **41** with arylidenemalononitrile **42** giving stable Michael adducts **43** was considered in Section III. On treatment with bases, the resulting adducts cyclise to pyrans **187**. The latter have also been isolated when the compounds **41** have been heated with **42** in the presence of morpholine.^{11, 24–27} The aromatic aldehydes **44** and unsaturated ketones **45** react with malononitrile **39** or with the pyrazolones **41** under conditions described by the researchers cited above^{24, 27} to give aminopyrans **187**. 3-Trifluoromethylpyrazol-5-ones react with the nitriles **42** in a similar way; on boiling in ethanol with

piperidine, they are converted into 5-trifluoromethyl-substituted pyrans **187b**.¹²²



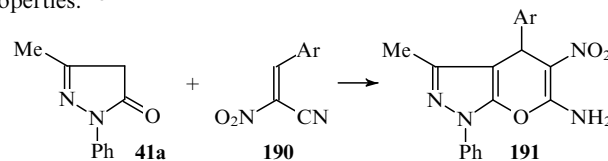
R¹ = Me (a), CF₃ (b).

The use of 1-heteryl-substituted pyrazolones **188** in the reaction with benzylidenemalononitrile **42a** permits the synthesis of 1-heterylpyrano[2,3-*c*]pyrazoles **189**, which exhibit antimutagenic activity.²⁸ In the absence of bases, it is possible to isolate intermediate Michael adducts of the type **43**.

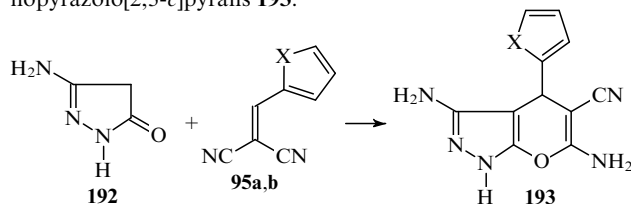


R = Me, Ph; X = O, S.

The reaction of arylidenenitroacetone nitriles **190** with the pyrazolone **41a** results in the formation of difficultly accessible 4-aryl(hetaryl)-3-nitro[2,3-*c*]pyrazoles **191** exhibiting antiallergic properties.¹²³

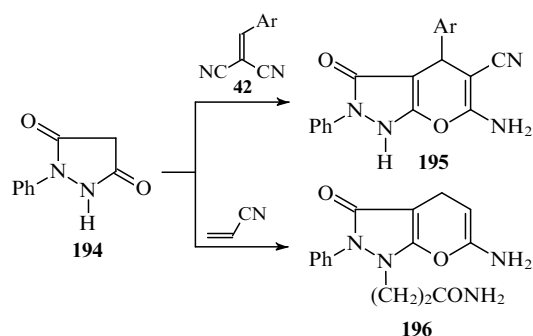


It has been reported⁶⁸ that 3-aminopyrazolone **192** reacts with 2-furyl- and 2-thienyl-substituted derivatives **95a,b** to give 5-aminopyrazolo[2,3-*c*]pyrans **193**.

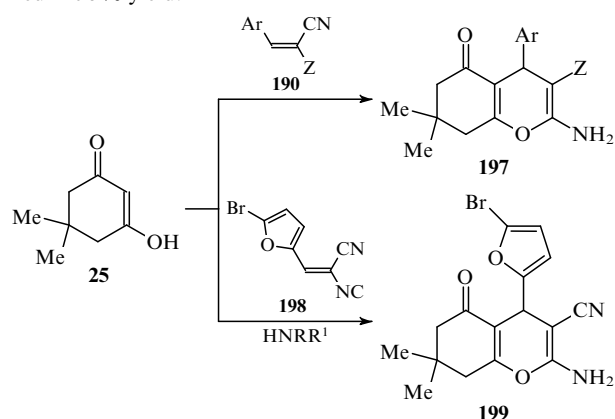


Y = O (a), S (b).

Pyrazoline-3,5-dione **194** reacts with aryl-substituted unsaturated nitriles **42** similarly to the pyrazolone **41** to yield fused 2-amino-4*H*-pyrans **195**.^{68, 124} Acrylonitrile forms bis-adduct **196**.¹²⁴

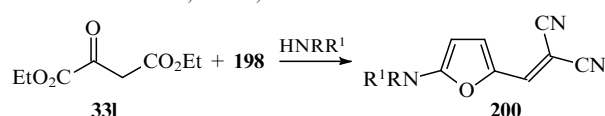


Cyclic 1,3-diketones are strong CH acids and are substantially enolised.¹²⁵ Enolisation is important for the formation of the pyran ring,⁷ and cyclic 1,3-dicarbonyl compounds are widely known as convenient reagents for the synthesis of fused 4*H*-pyrans. Thus a number of fused 4*H*-pyrans **197** containing a nitro group have been obtained by reactions of dimedone **25** with aryl (or hetaryl) derivatives of nitroacetonitrile **190**.^{123, 126–128} Some of them were found to exhibit antiallergic properties.¹²³ When dimedone **25** reacts with 5-bromofurfurylidene malononitrile **198** in the presence of secondary amines, substituted pyran **199** is formed in 95% yield.⁹⁷

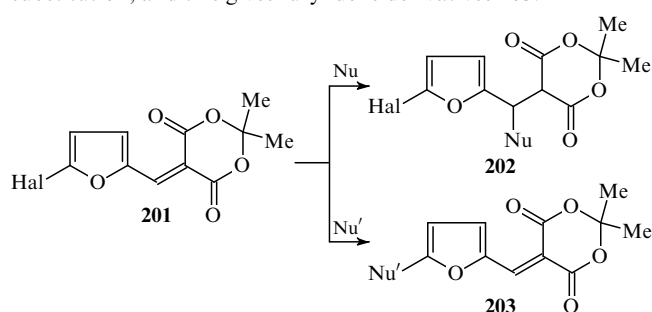


Z = NO₂.

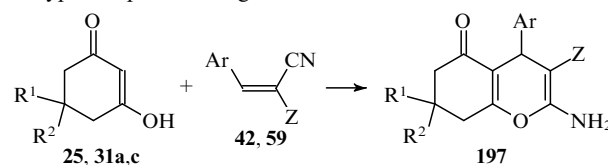
Oxalacetate **331** does not react with the nitrile **198** under these conditions; in this case, only the bromine atom is substituted by a secondary amine residue. The rate of nucleophilic substitution in the furan nucleus in this system proves to be higher than the rate of Michael addition and, hence, the nitriles **200** are formed.



These findings are consistent with the available data on nucleophilic reactions in the series of furylidene derivatives **201**.¹²⁹ It was shown that hard nucleophiles (Nu) enter into the addition reaction to give adducts **202**. In the case of soft nucleophiles (Nu'), the halogen in the furan ring undergoes nucleophilic substitution, and this gives furylidene derivatives **203**.

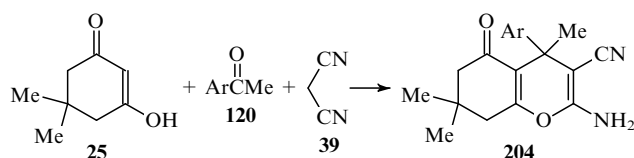


Numerous representatives of substituted tetrahydro-4*H*-benzo[*b*]pyrans **197**^{11, 26, 130–132} have been prepared by interaction of 1,3-cyclohexanediones with the aryl(or hetaryl)-substituted α,β -unsaturated nitriles **42** and **59**. It was found that some compounds of the type **197** possess fungicidal activities.¹³⁰

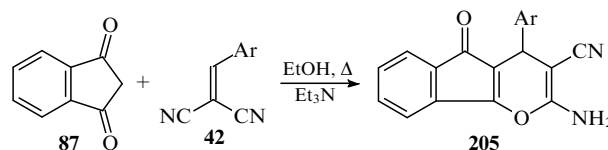


R¹ = R² = Me (**25**); R¹ = R² = H (**31a**); R¹ = Ph, R² = H (**31c**); Z = CN (**42**), CO₂Et (**59**).

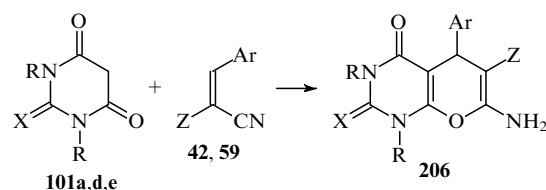
Fused pyrans of the type **197** can also be obtained by the reaction of dimedone with aromatic aldehydes and malononitrile.¹³³ The reaction of dimedone with the substituted acetophenones **120** and malononitrile affords 4-methyl-substituted pyrans **204**.¹³³



1,3-Indanedione **87** reacts with arylidenemalononitriles **42** to give fused pyrans **205**. The reaction requires a 20-min heating in ethanol in the presence of triethylamine.¹¹²



It has been mentioned above that the reaction between barbituric acid and arylidenemalononitriles in boiling ethanol affords the compounds **102** resulting from elimination of malononitrile. However, at room temperature in dioxane, barbituric acid **101a** reacts with the nitriles **42** or **59** giving rise to substituted 2-aminopyrano[2,3-*d*]pyrimidines **206**.^{134, 135} The compounds **206** are also formed in the reaction with 2-thiobarbituric acid **101d**¹¹⁹ and 1,3-diphenyl-2-thiobarbituric acid **101e**.¹³⁶

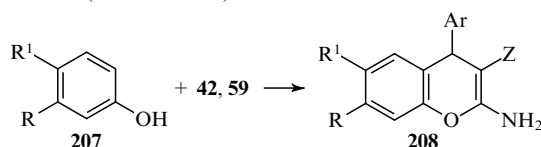


R = H: X = O (**a**), S (**d**); R = Ph, X = S (**e**); Z = CN (**42**), CO₂Et (**59**).

In this Section, we also present numerous examples of reactions of unsaturated nitriles with phenols, which can be regarded as completely enolised ketones.¹²⁵

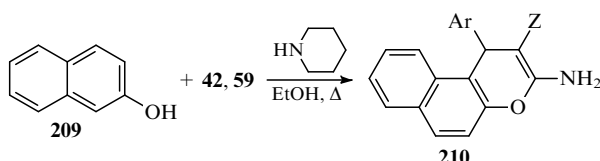
It is known that interaction of activated phenols (resorcinol, *m*-aminophenol, phloroglucinol) with α,β -unsaturated nitriles under the conditions of the Hoesch reaction¹³⁷ does not involve the cyano group. The phenols add to the double bond giving β -arylpropionitriles or products of their subsequent cyclisation ('anomalous Hoesch reaction'¹³⁸). Thus in the presence of acid catalysts, cyanoethylation of substituted resorcinol derivatives results in the formation of 3,4-dihydrocoumarins.^{138–141} Arylidene derivatives of malononitrile **42** and the cyanoacetate **59** react with phenols **207** under conditions of basic catalysis on short-term heating in ethanol. This affords substituted 4*H*-benzo[*b*]pyrans

208 in 65%–90% yields.^{142, 143} On refluxing in ethanol for 15 min in the presence of piperidine, non-substituted phenol also gives pyrans **208** ($R = R' = H$).¹⁴⁴



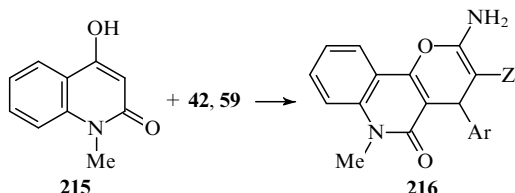
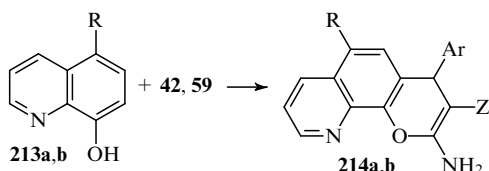
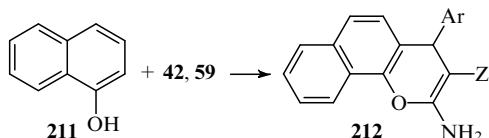
$R = OH, NH_2$; $R' = H, Alk$; $Z = CN$ (**42**), CO_2Et (**59**).

Under similar conditions, 2-naphthol **209** reacts with the nitriles **42** and **59** to give substituted 4*H*-naphtho[2,1-*b*]pyrans **210**.^{143, 145} In this case, the arylidenemalononitriles **42** can be replaced by a mixture of the corresponding aromatic aldehydes and malononitrile.¹⁴⁶



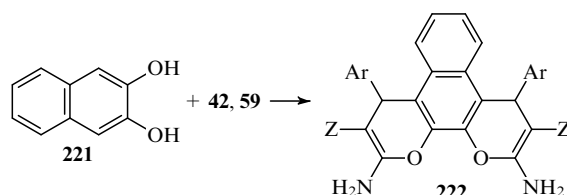
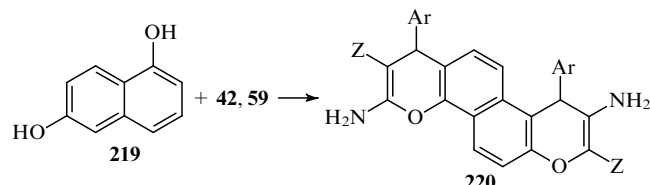
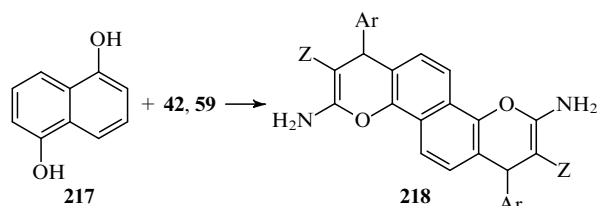
$Z = CN$ (**42**), CO_2Et (**59**).

1-Naphthol **211** reacts with the nitriles **42** and **59** on a short-term heating in ethanol in the presence of a base giving rise to the corresponding fused pyrans **212** in 65%–85% yields.^{144, 147, 148} 8-Hydroxyquinoline **213** behaves in a similar way and upon the reaction with **42**, it is converted into pyrans **214** in yields of up to 80%.¹⁴⁴ When 2-aminosulfo-derivatives of 8-hydroxyquinoline **213b** are made to react with the nitriles **42** and **59**, the corresponding aminosulfonyl-derivatives **214b** are produced.¹⁴⁹ Under similar conditions, 4-hydroxy-1-methyl-2-quinolinone **215** reacts with the nitriles **42** and **59** affording fused pyrans **216**, their yields ranging from 80% ($Z = CO_2Et$) to 90% ($Z = CN$).¹⁴⁴



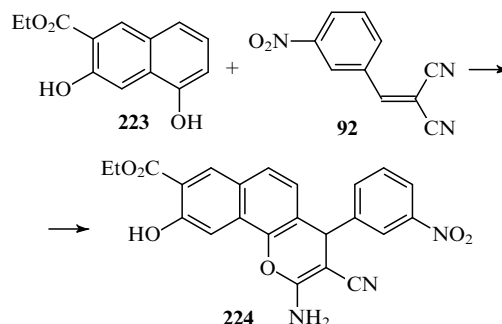
$R = H$ (**a**), R_2NSO_2 (**b**); $Z = CN$ (**42**), CO_2Et (**59**).

Dihydroxynaphthalenes are capable of condensing with two molecules of **42** or **59** to give naphthodipyran. Thus 1,5-dihydroxynaphthalene **217** was converted into naphtho[1,2-*b*:5,6-*b'*]dipyran **218**,^{147, 150} 1,6-dihydroxynaphthalene **219** into naphtho[1,2-*b*:6,5-*b'*]dipyran **220**,¹⁵⁰ while 2,3-dihydroxynaphthalene **221** and the nitriles **42** and **59** form naphtho[1,2-*b*:3,4-*b'*]dipyran **222**.^{150, 151}



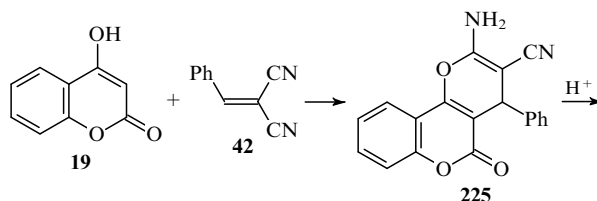
$Z = CN$ (**42**), CO_2Et (**59**).

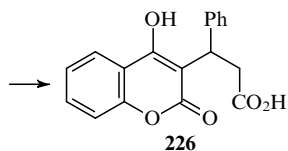
The reaction of ethyl 3,5-dihydroxynaphthalene-2-carboxylate **223** with 3-nitrophenylmethylidenemalononitrile **92** occurs selectively giving rise to naphtho[1,2-*b*]pyran **224**.¹⁵²



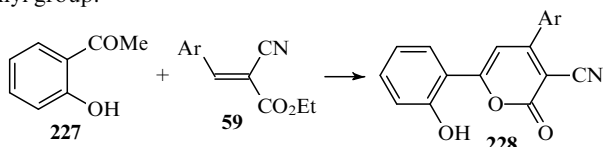
Among fused pyrans — derivatives of 2-naphthol, dihydroxynaphthalenes, hydroxyquinolines, and hydroxyisoquinolines, — compounds with high antiproliferative activities have been found.¹⁵³ Some of them have been recommended for treatment of immune disorders and also for a number of diseases such as rheumatoid arthritis, atherosclerosis, cirrhosis, cancer, *etc.*^{152, 153}

On refluxing with benzylidenemalononitrile **42a** in pyridine¹⁵⁴ or water,¹⁵⁵ 4-hydroxycoumarin **19** is converted into 4*H*-pyran **225**, which undergoes acid hydrolysis being thus converted into compound **226** serving as the intermediate in the synthesis of a rodent poison, warfarin. The pyran **225** is also formed when benzylidenemalononitrile **42a** is made to react with 4-hydroxycoumarin **19** in ethanol at room temperature in the presence of an equimolar amount of a base; Michael adducts were not isolated in this reaction.³⁷

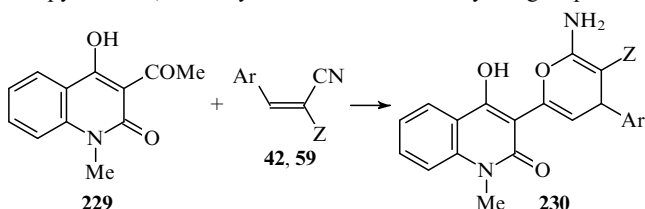




The reactions of *C*-acetyl-derivatives of phenols with unsaturated nitriles involve the methyl group of the acetyl fragment. For example, 2-hydroxyacetophenone **227** reacts with the nitriles **59** giving 2*H*-pyran-2-ones **228**, which result from intramolecular cyclisation of the intermediate Michael adduct at the ethoxycarbonyl group.



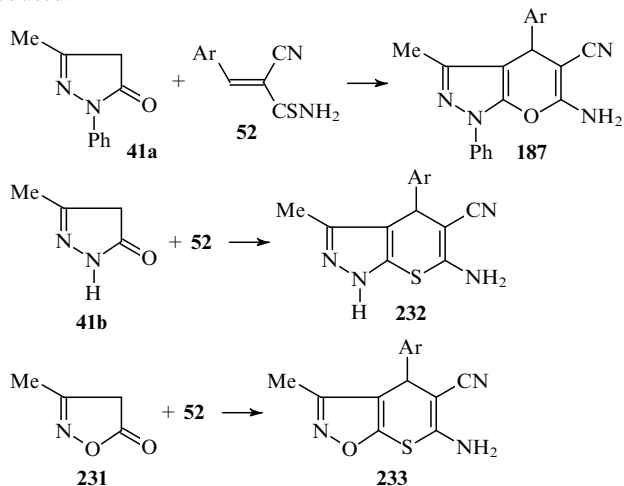
To the contrary, the reaction of 3-acetyl-4-hydroxy-1-methyl-2-quinolinone **229** with the nitriles **42** and **59** yields only 2-amino-4*H*-pyrans **230**,¹⁴⁹ i.e. cyclisation involves the cyano group.



Z = CN (**42**), CO₂Et (**59**).

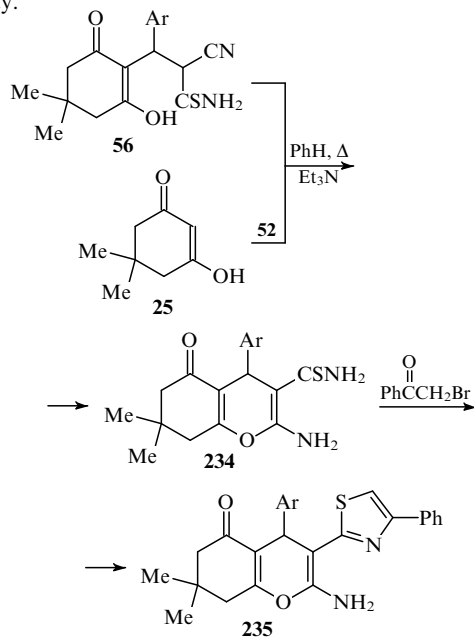
The formation of the pyrans **61a,b** upon the reaction of 4-hydroxycoumarin with arylidenecyanoacetates **59** has been considered previously (see Section III).

Arylidenecyanothioacetamides **52** can also serve as convenient intermediates in the synthesis of 4*H*-pyrans and their derivatives. It has been reported¹⁵⁶ that the reaction of the phenyl-substituted pyrazolone **41a** with thioacetamides **52**, like the reaction with the nitriles **42**, affords the pyrans **187**. However, when the thioamides **52** are made to react with the pyrazolone **41b** or with isoxazolone **231**, thiapyrans **232** and **233**, respectively, are produced.



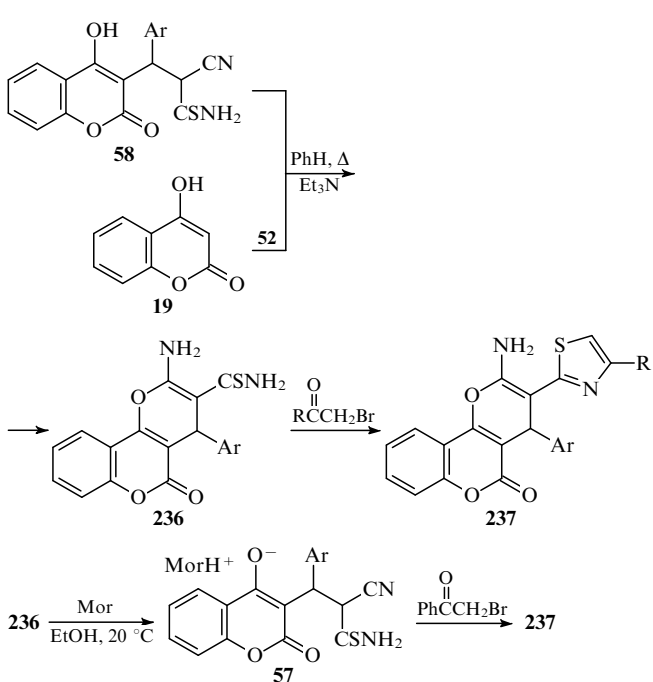
As has been noted in Section III, the interaction of cyclic 1,3-dicarbonyl compounds (dimedone, 4-hydroxycoumarin, and Meldrum's acid) with arylidenecyanothioacetamides results in the formation of Michael adducts, which can cyclise according to various pathways depending on the reaction conditions. Thus on refluxing in benzene with a catalytic quantity of triethylamine, the adducts are converted into fused 3-thiocarbamoyl-4*H*-pyrans **234**. However, reaction of the arylidenecyanothioacetamides **52** with dimedone **25** under the same conditions is a more convenient

route to the pyrans **234**.^{36,157} The thiocarbamoyl group in the pyrans **234** can be modified according to the Hantzsch reaction pattern on treatment with phenacyl bromide in DMF. Substituted 3-(4-phenylthiazol-2-yl)-4*H*-pyrans **235** were synthesised in this way.



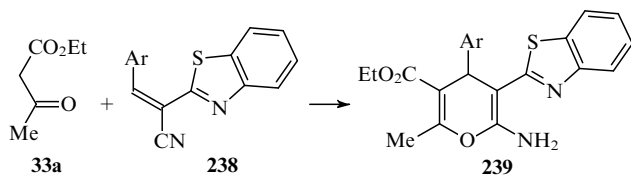
Evidently, a necessary condition for the intramolecular cyclisation to occur is close arrangement of the reaction centres, the OH and CN groups. Consideration of the projections presented in Section III (**71–74**) shows that conditions favourable for the cyclisation to pyrans are realised in the conformation **74**. Since the yields of the pyrans **234** in this reaction reach 90%,³⁶ it is assumed that under these conditions, the conformers **73** undergo the reverse reaction with regeneration of the initial compounds **25** and **52**.

The adducts **58** prepared from 4-hydroxycoumarin cyclise to fused 2-amino-3-thiocarbamoyl-4*H*-pyrans **236** on boiling in benzene with triethylamine. Higher yields of the pyrans **236** (up to 73%) can be attained when the reactants **19** and **52** react directly with each other.³⁷

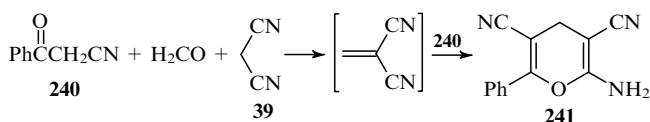


Treatment of the pyrans **236** with α -haloketones resulted in the synthesis of the corresponding 3-(4-phenylthiazol-2-yl)-4*H*-pyrans **237**.³⁷ The pyran ring in the compounds **236** can be cleaved by secondary amines; this gives the acyclic salts **57**, which are converted into the pyrans **237** on treatment with phenacyl bromide.³⁷

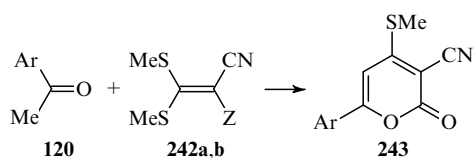
Reactions of arylbenzothiazolylcyanoethylenes **238** with ethyl acetoacetate **33a** afford benzothiazolyl-substituted pyrans **239**.¹⁵⁸



The synthesis of pyrans based on alkylidene derivatives of malonic acids has not been adequately elaborated yet. A three-component reaction between benzoylacetonitrile **240**, formaldehyde, and malononitrile **39** in ethanol in the presence of triethylamine should be mentioned.¹⁵⁹ Apparently, this reaction involves intermediate formation of 1,1-dicyanoethylene, which then reacts with the ketone **240** to give pyran **241** having no substituent at the 4-position.¹⁵⁹

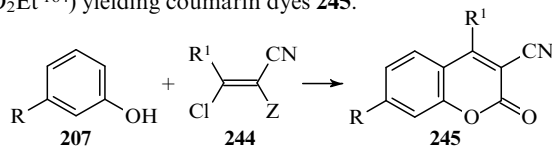


In some cases, unsaturated nitriles contain easily leaving groups such as methylthio, halo, or trichloromethyl groups. As has been noted in Section II, the products of addition of carbonyl compounds to these nitriles can eliminate a readily leaving fragment and then cyclise. Several syntheses of pyrans based on this approach have been reported. Thus the 2,2-di(methyl-thio)methylidene derivatives of malononitrile or cyanoacetate **242a,b** react with the acetophenones **120** with elimination of the methylthio group to give pyran-2-ones **243**.^{160–162}



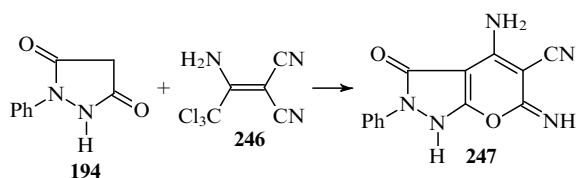
Z = CN (a), CO₂Et (b).

Substituted *m*-aminophenols (or resorcinol) **207** react with β -chloro-substituted unsaturated nitriles **244** (Z = CN¹⁶³ or CO₂Et¹⁶⁴) yielding coumarin dyes **245**.

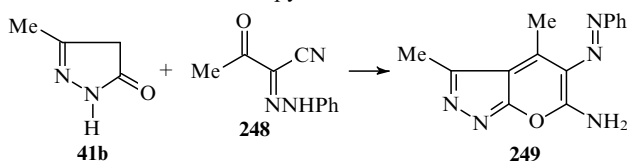


R = OH, Me₂N, Et₂N; Z = CN, CO₂Et.

The reaction of pyrazoline-3,5-dione **194** with trichloro-substituted nitrile **246** is accompanied by elimination of chloroform and gives rise to substituted 6-iminotetrahydropyrano-[2,3-*c*]pyrazole **247**.¹²⁴



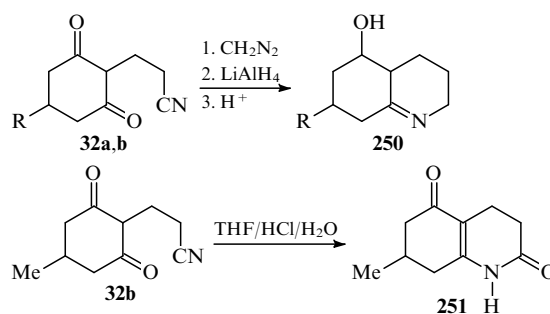
Although the phenyl-substituted acetylacetonitrile **248** is formally also an α,β -unsaturated nitrile, it does not enter into the Michael reaction with carbonyl compounds. The addition of the pyrazolone **41b** involves the carbonyl group of **248** and results in the formation of fused 2*H*-pyrans **249**.¹⁶⁵



VII. Synthesis of pyridines

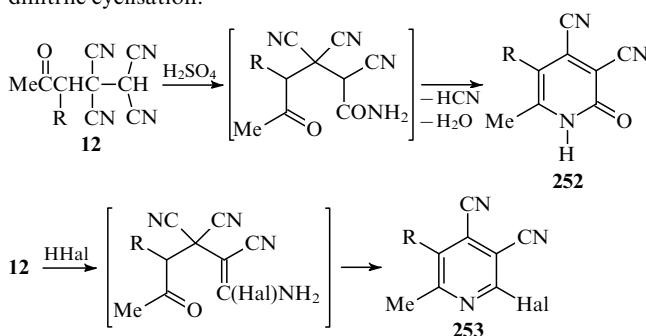
The reactions of carbonyl compounds with α,β -unsaturated nitriles opens the way to the synthesis of pyridine derivatives that are difficult to obtain by other methods. It is clear that pyridines can be formed if the intermediate adducts undergo cyclisation involving a nucleophilic nitrogen atom, in particular, the nitrogen of the nitrile group. A more widely used variant is incorporation of the nitrogen atom from ammonium acetate or enamine. The method for the synthesis of pyridones and pyridine-thiones with participation of amides and thioamides seems promising. The reactions resulting in the synthesis of 2-aminopyridines have been considered in detail and systematised in a monograph.⁸ Published data on the synthesis of 3-cyano-2(1*H*)-pyridones, -pyridine-thiones, and -pyridineselenones have been surveyed in a review.¹⁶⁶ In this Section, we consider the characteristic features of the preparation of pyridines based on reactions of carbonyl compounds with unsaturated nitriles.

The reduction of the nitrile group in the adducts **32** by lithium aluminium hydride results in the generation of an amine and, as a consequence, in the formation of hydrogenated quinolines **250**.¹⁹ The cyano group in the adduct **32b** is hydrolysed with subsequent cyclisation giving rise to hydrogenated quinoline **251**, which has been used as the starting compound in a 14-stage synthesis of 12-epilycopodine.²⁰

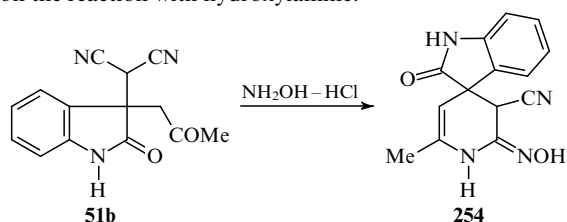


R = H (a), Me (b).

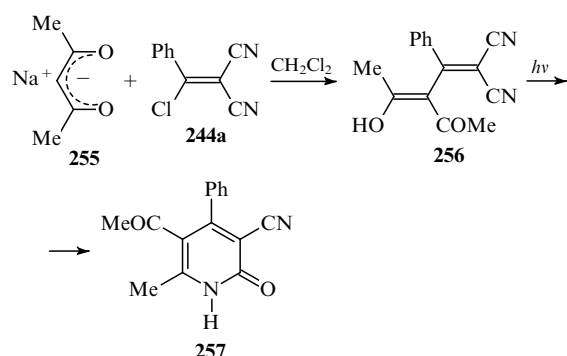
On treatment with acids, the adducts **12** cyclise to substituted 3,4-dicyano-2(1*H*)-pyridones **252**. The reaction includes hydrolysis of the cyano group followed by cyclisation of the resulting amide.¹³ Treatment of the compounds **12** with hydrogen halides affords 2-halopyridines **253** according to the known mechanism of dinitrile cyclisation.^{13, 83}



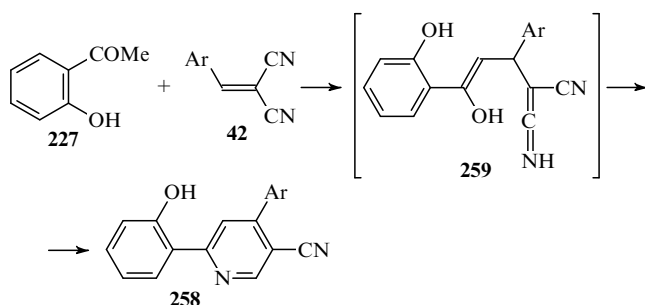
The adduct **51b** has been converted into spiro-compound **254** upon the reaction with hydroxylamine.³⁰



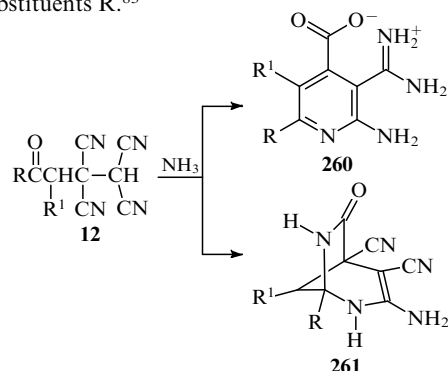
Sodium acetylacetonate **255** reacts with the chloro-substituted derivative of malononitrile **244a** giving rise to the *cis*-isomer of the substitution product **256**, which transforms into the *trans*-isomer on exposure to UV radiation in methanol; the latter cyclises *in situ* to 3-cyano-2(1*H*)-pyridone **257**.¹⁶⁷



The formation of pyridines **258** upon cyclisation of intermediates **259** resulting from interaction of 2-hydroxyacetophenone **227** with the nitriles **42** has been reported.¹⁴⁹

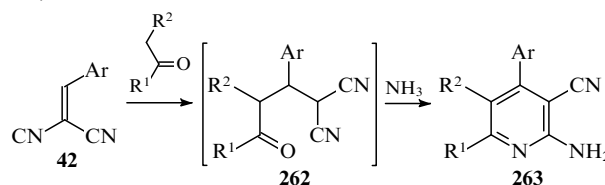


Ammonia can also be used as the source of nitrogen needed to close a pyridine ring. Thus treatment of the adducts **12** with ammonia yields either 2-aminopyridines in the betaine form **260** or bicyclic pyridine derivatives **261**, depending on the nature of the substituents *R*.⁸³

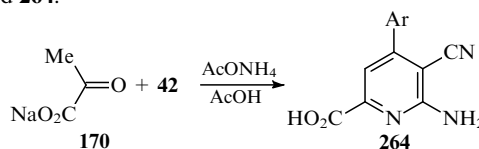


Among the numerous methods for the synthesis of 2-aminopyridines,⁸ we would like to mention interaction of the unsaturated nitriles **42** with carbonyl compounds in the presence of ammonium acetate. The aromatic aldehydes **44** and malononitrile

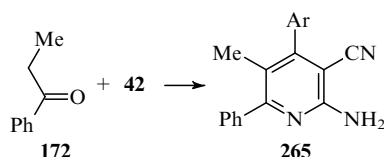
39 can be used instead of **42**.¹⁶⁸ It has been reported¹⁶⁹ that the interaction between these compounds yields the nitrile **42**, to which carbonyl compounds then add. Treatment of Michael adducts **262** with ammonia induces their cyclisation to pyridines **263**. Among this series of reactions, the synthesis of alkyl-substituted pyridines **263** ($\text{R}^1, \text{R}^2 = \text{H}, \text{Alk}$) from the nitriles **42** and aliphatic ketones has been studied.¹⁷⁰ Substituted acetophenones ($\text{R}^1 = \text{Ar}'$, $\text{R}^2 = \text{H}$) have also been used;¹⁶⁹ in this case, the reactions were conducted with heterocyclic derivatives of malononitrile such as 5-methoxy-2,3-diphenylbenzo[*b*]furan-6-ylidenemalononitrile¹⁷¹ and 5-nitrobenzo[*b*]thiophen-2-ylidenemalononitrile.¹⁷² The compounds **263** containing a bipyridine fragment ($\text{Ar} = \text{pyridyl}$) and possessing cardiotonic properties have been prepared from pyridinecarbaldehyde, the appropriate ketone, and ammonium acetate.¹⁷³



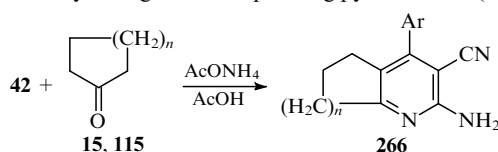
Refluxing of sodium pyruvate **170** with the nitriles **42** and ammonium acetate in acetic acid affords derivatives of α -picolinic acid **264**.¹¹²



It has been shown for propiophenone **172** that alkyl aryl ketones react with the nitriles **42** forming either the pyrans **173** (Section VI) or 2-aminopyridines **265**. The latter are formed when the reactants are refluxed in acetic acid with ammonium acetate.¹¹³

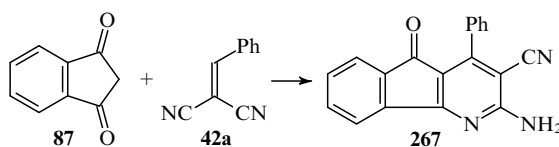


Cyclopentanone **115** and cyclohexanone **15** react with the nitriles **42** yielding the corresponding pyridines **266** ($n = 1, 2$).¹⁶⁹



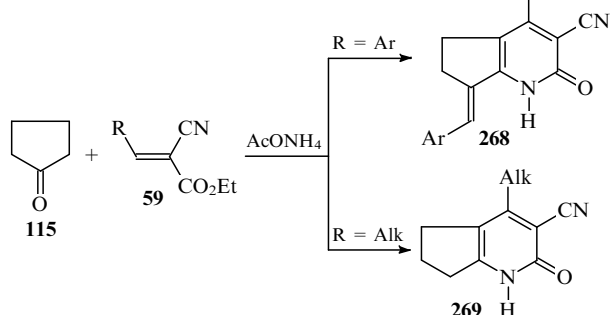
$n = 1$ (**115**), 2 (**15**).

When 1,3-indanedione **87** is refluxed with benzyldenemalononitrile **42a** and ammonium acetate in acetic acid, fused 2-aminopyridines **267** are produced.¹¹²

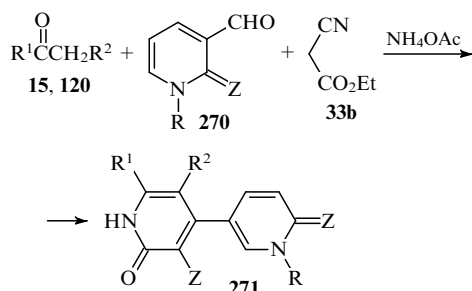


The introduction of aryl(alkyl)idene derivatives of ethyl cyanoacetate into reactions with carbonyl compounds and ammonium acetate makes it possible to synthesise substituted 3-cyano-2(1*H*)-pyridones. When cyclopentanone **115** reacts with

arylidene derivatives of the cyanoacetate **59** in the presence of ammonium acetate, 7-arylidene-2-pyridones **268** are formed. Evidently, in this case, a second molecule of the cyanoacetate is cleaved under the reaction conditions,⁶⁰ and the aromatic aldehyde formed *in situ* enters into the condensation. The alkyl-derivatives **59** do not undergo this cleavage and form pyridones **269**.¹⁷⁴

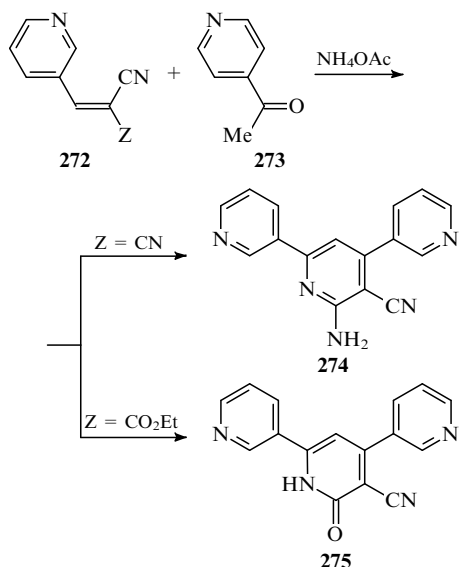


The condensation of the cyanoacetate **33b** and compounds **270** — 3-formyl-2(1*H*)-pyridones ($Z = \text{O}$), -pyridinethiones ($Z = \text{S}$), and -pyridinoselenones ($Z = \text{Se}$) — with cyclohexanone **15** and the substituted acetophenones **120** in the presence of ammonium acetate gives rise to bipyridine derivatives **271**.¹⁷⁵ Substituted 2-chloro-3-formylquinolines have also been used as the aldehyde constituent for the preparation of hetarylpyridines of the type **271**.¹⁷⁶



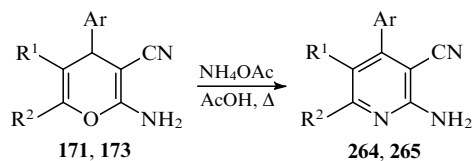
$\text{R}^1 - \text{R}^2 = (\text{CH}_2)_4$ (**15**); $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{H}$ (**120**); $Z = \text{O}$, S , Se .

Refluxing 3-pyridyldienemalononitrile **272** ($Z = \text{CN}$) or ethyl 3-pyridyldienecyanoacetate ($Z = \text{CO}_2\text{Et}$) with 3-acetylpyridine **273** and ammonium acetate affords derivatives of the alkaloid nicotelline **274** or **275**, respectively.¹⁷⁷



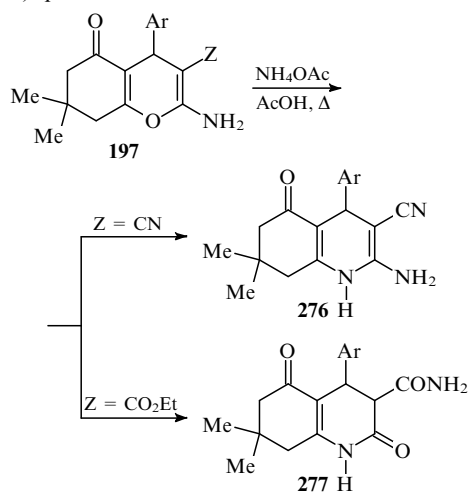
The formation of a pyran ring upon intramolecular interaction of hydroxy and cyano groups is reversible.⁷ Therefore, under

certain conditions, for example, under the action of nucleophiles, the pyran ring can be cleaved. Thus 2-aminopyridines **264**¹¹² and **265**¹¹³ are formed when the pyrans **171** and **173** are treated with ammonium acetate in boiling acetic acid.

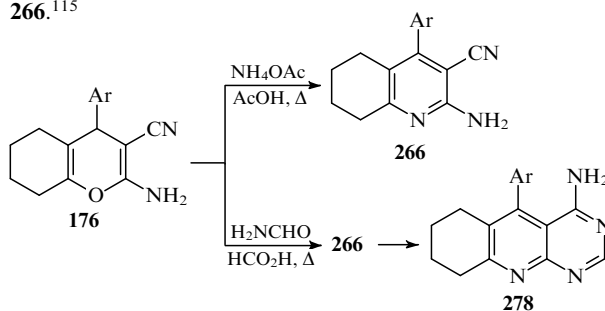


$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{CO}_2\text{H}$ (**171**, **264**); $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Ph}$ (**173**, **265**).

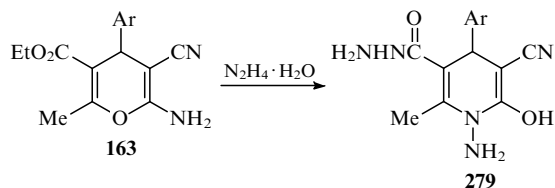
It has been reported¹³² that the fused pyrans **197** ($Z = \text{CN}$), prepared from dimedone and arylidenemalononitriles, recyclise in a similar way giving rise to 2-amino-3-cyano-6-hydroquinolines **276**. 3-Ethoxycarbonyl-substituted pyrans **197** ($Z = \text{CO}_2\text{Et}$) are converted under these conditions into 3-carbamoyl-6-hydroquinoline-2(1*H*)-quinolinone derivatives **277**.¹³²



The fused pyrans **176** recyclise on treatment with ammonium acetate to give tetrahydroquinolines **266**. Formamide can also act as a nucleophile in this reaction. When **176** are heated in formamide in the presence of formic acid, pyrido[2,3-*d*]pyrimidine derivatives **278** are produced *via* the intermediate quinolines **266**.¹¹⁵

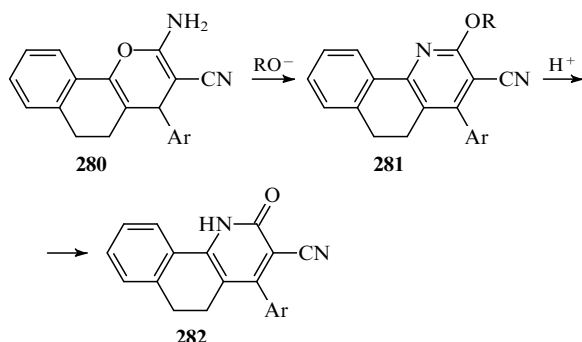


It has been noted¹¹⁰ that treatment of the 5-ethoxycarbonyl-pyran derivatives **163** with hydrazine hydrate results in their recyclisation to 1-amino-1,4-dihydropyridines **279**.

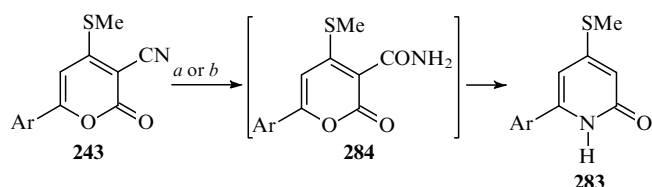


Treatment of 2-aminopyrans with nucleophilic reagents, for example, alkoxides, may lead to opening of the pyran ring followed by cyclisation to pyridine with participation of the

amino-group nitrogen. This provides a route from fused pyrans **280** to pyridine derivatives **281**,¹⁷⁸ which are converted into pyridones **282** in acid media.¹⁷⁹

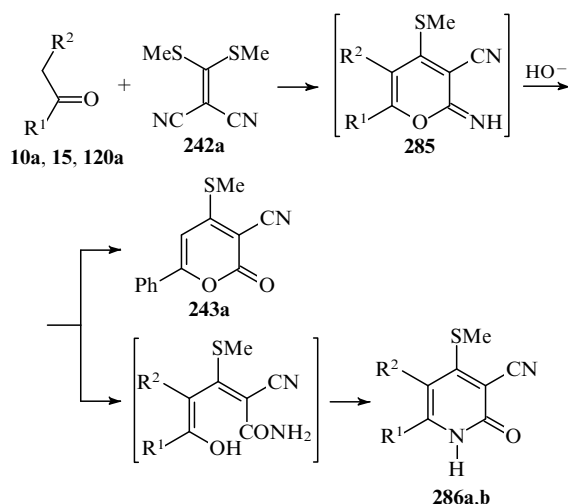


The pyrans **243** are capable of recycling to pyridones **283** in the $\text{CH}_3\text{COOH}-\text{HBr}$ system [pathway (a)]. Apparently, this process begins with the hydrolysis of the cyano group to an amide group with the intermediate formation of pyran **284**. The yields of the pyridones **283** are 24%–32%. It should be noted that the yields of the pyridones **283** in the alkaline recycling of compounds **284** obtained preliminarily by treating the nitrile **243** with polyphosphoric acid (PPA) [pathway (b)] are considerably higher (66%–81%).¹⁶⁰



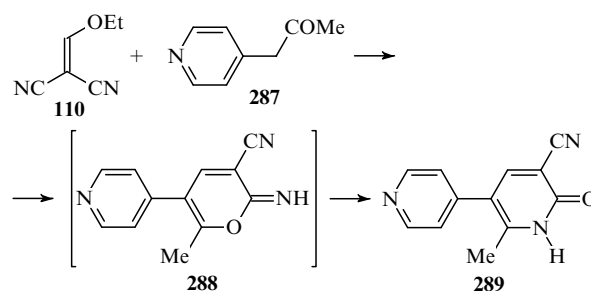
(a) $\text{CH}_3\text{CO}_2\text{H}/\text{HBr}$; (b) 1. PPA, 2. NaOH.

The reactions of acetone, cyclohexanone, or acetophenone with the dithioacetal **242a** involve intermediate formation of pyrans **285**.¹⁶⁰ However, whereas in the case of acetophenone, the imino group in the intermediate is hydrolysed, and this yields the pyran **243a**, in the case of acetone and cyclohexanone, the iminopyrans **285** undergo nucleophilic opening of the ring followed by transformation into the pyridones **286a,b**.

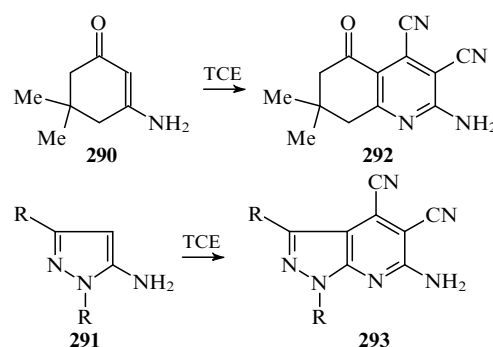


$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$ (**10a**, **286a**); $\text{R}^1 = \text{R}^2 = (\text{CH}_2)_4$ (**15**, **286b**);
 $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$ (**120a**, **243a**).

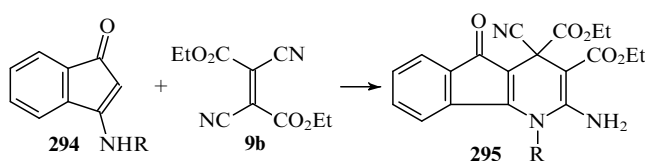
The reaction between the compounds **287** and **110** occurs in a similar way and involves the formation and recyclisation of the pyran **288**. This procedure is used to prepare the cardiotonic preparation milrinone **289**.¹⁸⁰



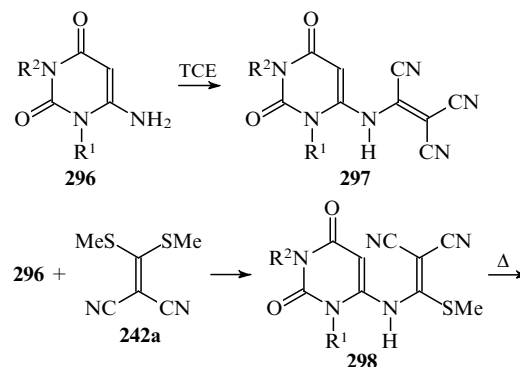
The nucleophilic nitrogen atom needed to close a pyridine ring can also be provided by enamines, prepared from mono- and dicarbonyl compounds. It is known that enamines add to an activated double bond more readily than the corresponding ketones.¹⁸¹ The interaction of enamines **290** and **291** with TCE **9a** occurs as substitution of the cyano group and subsequent cyclisation of the intermediate products to fused pyridines **292**⁸⁴ and **293**.⁸⁹

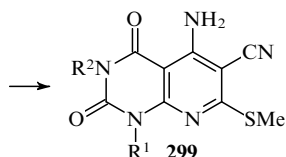


The dicyanofumarate **9b** reacts regioselectively with enamines **294**, prepared from indanethione, giving rise to *N*-substituted fused 1,4-dihydropyridines **295**.¹⁸²

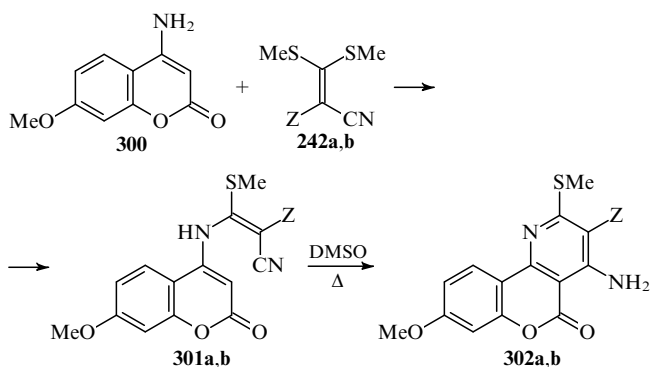


The reactions of some cyclic enamines with unsaturated nitriles containing a nucleofugal group follow a different pathway. In these cases, the activated $\text{C}=\text{C}$ bond of the nitrile undergoes nucleophilic attack by the enamine nitrogen atom. In some cases, acyclic substitution products have been isolated. Subsequently they can cyclise forming fused pyridines. Thus aminouracils **296** react with TCE or the nitriles **242a** to give the corresponding substitution products **297**⁸⁹ and **298**.¹⁸³ On heating in diphenyl ether, the latter cyclise to pyridopyrimidines **299**.¹⁸³

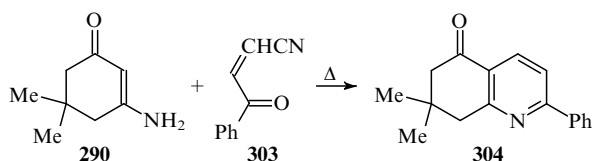




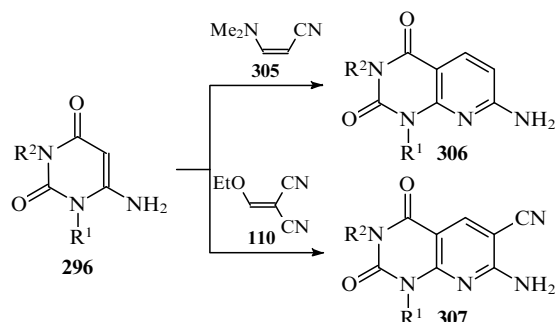
The reaction of 4-aminocoumarin **300** with the nitriles **242a,b** occurs in a similar way.¹⁸⁴ The cyclisation of the substitution products **301a,b** to fused compounds **302a,b** occurs upon heating in DMSO. The enamine **290** prepared from dimedone reacts with isomeric benzoylacrylonitrile **303** to give tetrahydroquinoline **304**.¹⁸⁵ In the case of *trans*-**303**, the reaction is conducted by refluxing in toluene, whereas for the *cis*-isomer, it is carried out in acetic acid.



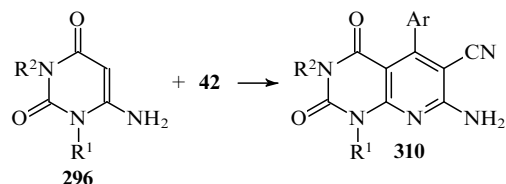
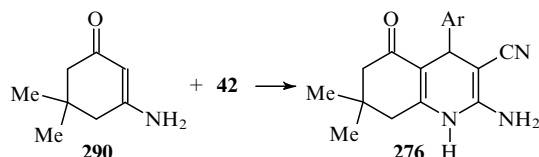
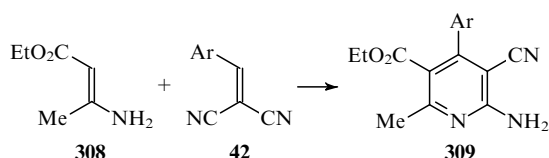
Z = CN (a), CO₂Et (b).



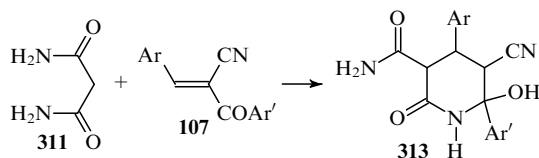
The unsaturated nitriles **305** and **110** contain groups that can be easily replaced by nucleophiles. The reaction of these compounds with the substituted 6-aminouracil derivatives **296** occurs as the substitution of the dimethylamino or ethoxy group by the heterocycle followed by cyclisation to fused pyridines **306**¹⁸⁶ and **307**,¹⁸⁷ respectively. Compounds of the type **306** are of interest as potential dihydrofolate reductase inhibitors.¹⁸⁶



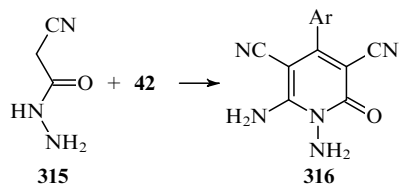
The arylidenemalononitriles **42** undergo Michael reactions with the enamines **308** and **290** derived from acetoacetate and dimedone, and also with the compounds **296**; the reaction is followed by cyclisation to pyridines **309**,¹⁸⁸ 1,4,5,6,7,8-hexahydroquinolines **276**,¹³² and substituted pyrido[2,3-*d*]pyrimidines **310**.¹⁸⁹



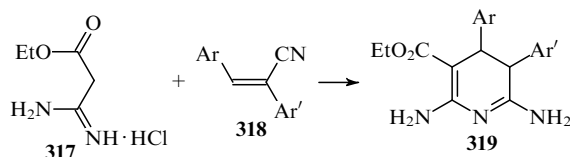
Methods for the synthesis of pyridines based on amines are widely used. In this case, the nitrogen atom of the amide group of one of the reactants participates in the formation of a pyridine ring. This method permits the synthesis of 2(1*H*)-pyridone derivatives. An amide group can be contained both in the carbonyl and the nitrile component. The former type of reaction is represented by the addition of malonodiamide **311** or acetoacetanilide **312** to the unsaturated nitriles **107** and **42**. The intramolecular cyclisation of the intermediate adducts affords hydrogenated pyridones **313**¹⁹⁰ and **314**.¹⁹¹



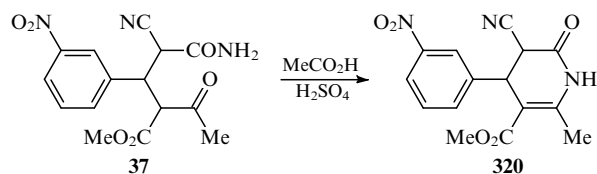
It has been shown¹⁹² that the reaction of cyanoacetylhydrazine **315** with the arylidenemalononitriles **42** gives rise to 1-amino-2(1*H*)-pyridones **316**.



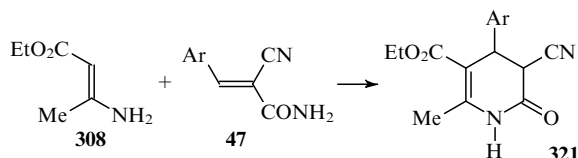
Amidine **317** reacts with nitriles **318** similarly to amides, giving rise to hydrogenated 2,6-diaminopyridines **319**, which possess diuretic and cardiotonic activities.¹⁹³



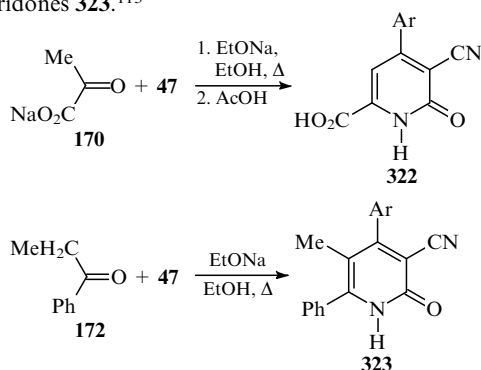
The second type of reactions proceeds in the case of unsaturated nitriles containing an amide group. It was mentioned in Section III that the addition of methyl acetoacetate **35** or oxindole **46** to arylidenecyanoacetamides yields stable Michael adducts. In some cases, they can be subsequently cyclised. Thus the adduct **37** was converted into 3,4-dihydro-2(1*H*)-pyridone **320** in 95% yield by treatment with sulfuric acid in acetic acid.²²



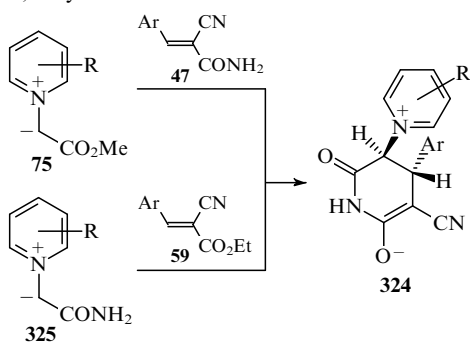
Similar *cis*-3,4-dihydro-2-pyridones **321** were synthesised by the reaction of the amides **47** with the enamine **308**.¹⁸⁹



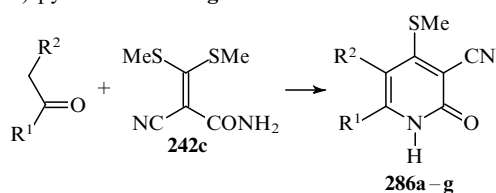
Arylideneacyanoacetamides **47** are transformed into acids **322** upon interaction with sodium pyruvate **170**. This reaction is completed when the reactants have been refluxed in ethanol in the presence of sodium ethoxide for 3 h.¹¹² The reaction of the amides **47** with propiophenone **172** under similar conditions affords the corresponding 5-methyl-6-phenyl-substituted 2(1*H*)-pyridones **323**.¹¹³



The pyridinium ylides **75** react with arylidenecyanoacetamides **47** yielding the betaine pyridiniumolates **324**.¹⁹⁴ The same products are formed when the arylidenecyanoacetates **59** are made to react with ylides **325** containing an amide group.^{194–196} In all cases, only *trans*-isomers of the betaines **324** were isolated.



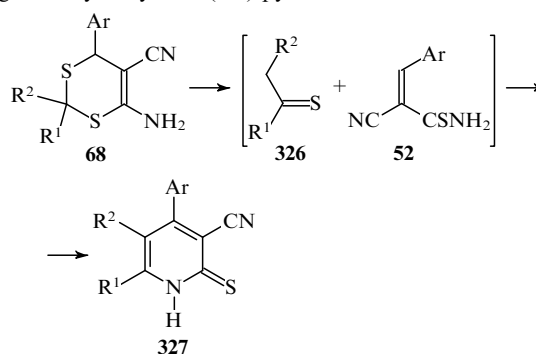
The amidonitriles **242c** react with a broad range of carbonyl and 1,3-dicarbonyl compounds in the DMSO–KOH system at room temperature. The reaction occurs as the nucleophilic vinylic substitution of the methylthio group followed by cyclisation to 2(1*H*)-pyridones **286a–g**.¹⁶⁰



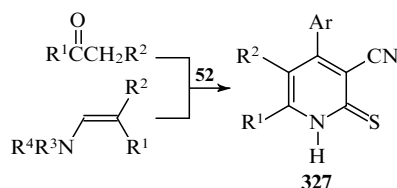
$\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$ (a); $\text{R}^1 - \text{R}^2 = (\text{CH}_2)_4$ (b); $\text{R}^1 = \text{Ar}$, $\text{R}^2 = \text{H}$ (c); $\text{R}^1 = \text{Ph}$; $\text{R}^2 = \text{Me}$ (d), CO_2Et (e); $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Ac}$ (f), CO_2Et (g).

The reactions of arylidenecyanothioacetamides with carbonyl compounds afford the corresponding pyridine-2(1*H*)-thiones, methods for the synthesis of which (as well as their oxygen and selenium analogues) have been described in a review.¹⁶⁶ Here we consider the characteristic features of this reaction in more detail. The interest in this reaction was aroused after the discovery of recyclisation of 2,2-dialkyl-4-amino-6-aryl-5-cyano-1,3-dithiacyclohex-4-enes **68** to 4-aryl-3-cyano-2(1*H*)-pyridine-thiones.^{45, 197, 198}

Previously, it was known that 1,3-dithianes, analogous to the compounds **68**, undergo thermal decomposition giving rise to thioketones and ylidene derivatives of cyanothioacetamides.¹⁹⁹ In the molecules of the dithianes **68**, there occurs intramolecular conformationally rigid conjugation, as has been established by X-ray diffraction analysis for the compound with $\text{Ar} = \text{Ph}$, $\text{R}^1 - \text{R}^2 = (\text{CH}_2)_5$.²⁰⁰ Therefore, heat treatment of **68** induces cleavage of the ring at the weakest C–S bonds. The products **52** and **326** thus formed undergo the Michael reaction followed by cyclisation to give 4-aryl-3-cyano-2(1*H*)-pyridinethiones **327**.



Study of the regularities of recyclisation made it possible to offer a convenient method for the synthesis of substituted pyridinethiones **327**.^{46, 200, 201} This method consists in interaction of arylidenecyanothioacetamides **52** with a broad range of carbonyl compounds such as aliphatic ketones,^{35, 46, 201, 202} substituted acetophenones,^{202, 203} and cyclic ketones,^{35, 46, 200, 201} and also enamines. Due to the high reactivity of enamines, it is better to use them in this reaction.

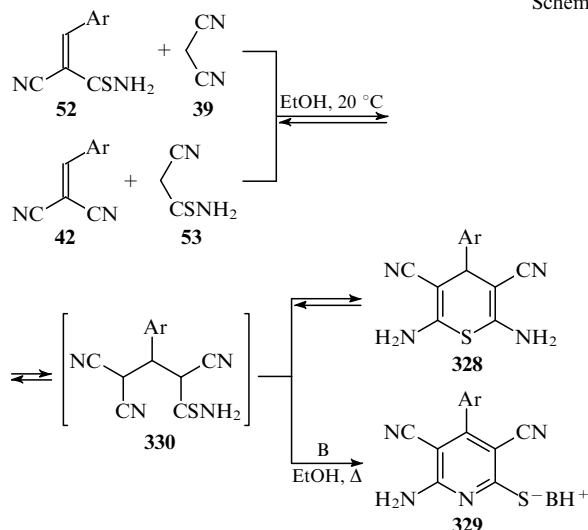


Later, the pyridinethiones **327** were also obtained by the reaction of the arylidene derivatives **52** with acetone and acetophenone on refluxing in ethanol.²⁰⁴ The fused pyridinethiones **327** in which $\text{R}^1 - \text{R}^2$ are polymethylene chains were prepared by the reaction of arylmethylenecyanothioacetamides **52** with cyclic ketones in boiling dioxane.^{205–207} In addition, the interaction of the 2-thienyl- and 2-furyl-derivatives **52** with cyclic ketones resulted in the synthesis of 4-hetaryl-substituted fused pyridine-thiones of the type **327**.²⁰⁸

Arylideneacyanothioacetamides **52** react with malononitrile **39** to give 6-amino-4-aryl-3,5-dicyano-4*H*-thiopyrans **328** (Scheme 3). The same compounds can be prepared by coupling of arylidenemalononitriles **42** with cyanothioacetamide **53**.²⁰⁹ This reaction is reversible, the thiopyrans **328** being formed at room temperature.

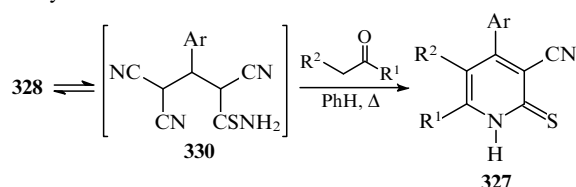
When the compounds **328** are refluxed in ethanol in the presence of bases, they recyclise to give pyridinethiolates **329**.^{209, 210} The same products **329** are also formed when the initial reactants **42** and **53** or **52** and **39** are refluxed in ethanol in the presence of bases. Presumably the intermediate Michael

Scheme 3



adduct **330** cyclises under mild conditions to the thiopyran **328**, while in the presence of bases, intermolecular interaction of thioamide and nitrile groups occurs, resulting in irreversible formation of pyridinethiolates **329** (see Scheme 3). A similar recyclisation has been found for selenium analogues of **328** and **329**.^{211–213}

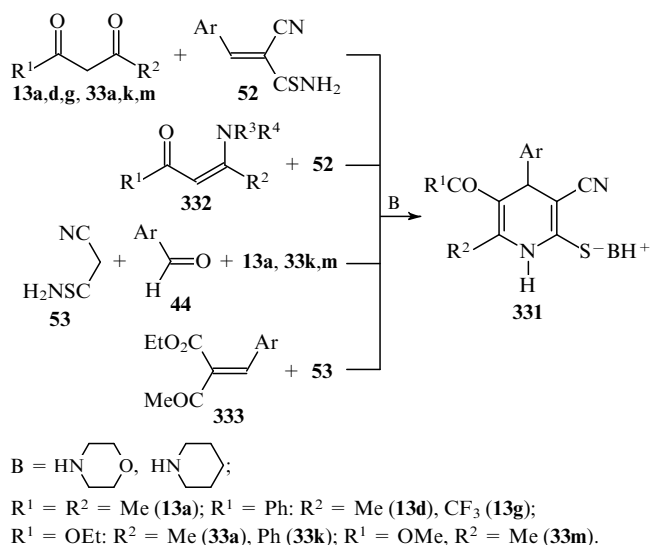
Refluxing the thiopyrans **328** in benzene with various ketones (acetone, acetophenone, cyclohexanone, cyclopentanone) affords the pyridinethiones **327** in 64%–85% yields.²¹⁴ Apparently, since both the thiopyrans **328** and the intermediate Michael adducts **330** are thermodynamically unstable, under the reaction conditions, the ring in the thiopyrans **328** is cleaved and the adduct **330** undergoes reversible decomposition to give the initial compounds **52** and **39**. When a carbonyl compound is added, its addition to the nitrile **52** becomes the predominant process, because it results in the irreversible formation of the pyridinethione **327**, which is assumed²¹⁴ to be thermodynamically the most stable compound in this system.



The overall process can be represented as exchange by the methylene components with elimination of malononitrile and incorporation of the ketone carbon skeleton in its place.²¹⁴ Thus, the interaction of ketones with the thiopyrans **328** occurs similarly to their interaction with arylidenecyanothioacetamides **52**.

The reaction of arylidenecyanothioacetamides **52** with acyclic 1,3-dicarbonyl compounds such as acetylacetone **13a**^{202, 215, 216} or ethyl acetoacetate **33a**^{202, 217, 218} follows a somewhat different pathway. The electron-withdrawing carbonyl group at the 5-position stabilises the intermediate dihydropyridine owing to conjugation with the π -system of the pyridine ring.²¹⁹ In the presence of organic bases, such as piperidine, morpholine, *etc.*, substituted 3-cyano-1,4-dihydropyridine-2-thiolates **331** have been obtained. The same products are formed when the corresponding enamines **332** are introduced in the reactions with the nitriles **52**^{202, 215, 217, 220} and also in the multicomponent condensation of the aromatic aldehydes **44**, cyanothioacetamide **53**, and a dicarbonyl compound in the presence of excess piperidine (Scheme 4).^{221–223}

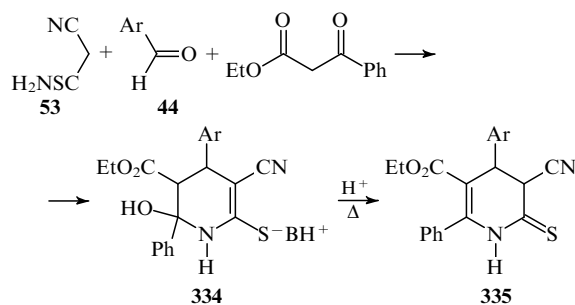
Scheme 4



The pyridinethiolates **331** have also been obtained by reactions of unsaturated dicarbonyl compounds **333** and cyanothioacetamide **53**.^{217, 224}

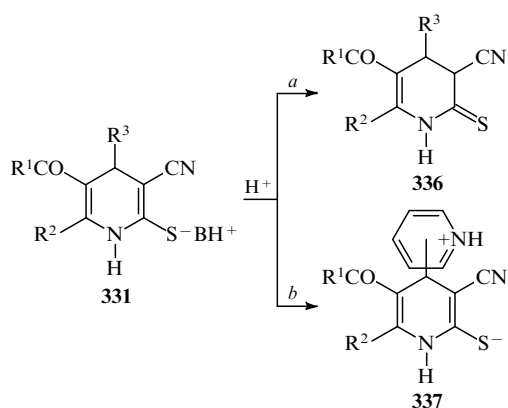
In the case of non-symmetrical dicarbonyl compounds such as benzoylacetone **13d** or 3-benzoyl-1,1,1-trifluoroacetone **13g**, the reaction occurs regioselectively and gives benzoylated pyridinethiolates **331** ($R^1 = \text{Ph}$).²¹⁸ The enamines **332** derived from non-symmetrical diketones **13d**, **g** react in a similar way.²¹⁸ 2-Furylidene-²¹⁸ and 3- and 4-pyridylidenecyanothioacetamides^{35, 218, 225} as well as mixtures of the corresponding aldehydes **44** and the thioamide **53**^{35, 218} also react with the dicarbonyl compounds **13a** and **33k**, **m** to give the corresponding derivatives of 4-hetaryl-1,4-dihydropyridine-2-thiolates **331** (see Scheme 4).

When the aryl substituent contains an electron-withdrawing substituent²²² or when the reaction is carried out with ethyl benzoylacetate,²²³ it is possible to isolate 6-hydroxy-substituted pyridinethiolates **334**, which are dehydrated on heating in an acid medium giving rise to compounds **335**.^{222, 223}



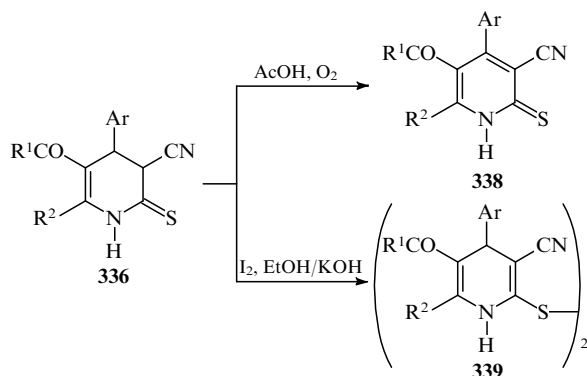
The structure of the pyridinethiolates **331** was studied by X-ray diffraction analysis.²²⁶ The dihydropyridine ring in morpholinium 5-acetyl-3-cyano-6-methyl-4-(2-nitrophenyl)-1,4-dihydro-2-pyridinethiolate was found to exist in a flattened-boat conformation. The negative charge is mostly localised on the sulfur atom. The latter accounts for the high regioselectivity of alkylation reactions of the thiolates **331**. They react with haloalkanes or dimethyl sulfate exclusively at the sulfur atom yielding the corresponding 2-alkylthio-derivatives.^{35, 202, 218, 223, 225, 227, 228}

Protonation of 4-aryl(furyl)-substituted derivatives **331** affords 3,4-dihydro-2(1*H*)-pyridinethiones **336**.^{202, 215–218, 220–223, 228} Upon acidification, the 4-(3- and 4-pyridyl)pyridine-thiolates **331** are converted into the corresponding betaines **337**.^{35, 218, 225, 227}

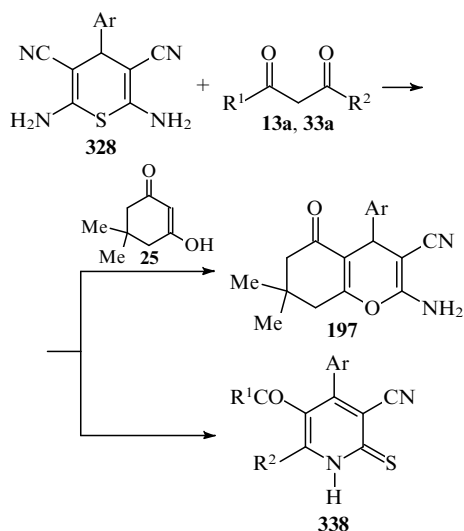


(a) $R^3 = \text{Ar}, \text{O-C}_6\text{H}_4$; (b) $R^2 = \text{N-C}_6\text{H}_4$.

Since 3,4-dihydropyridines are markedly less stable than their 1,4-dihydro-analogues,²¹⁹ it should be expected that they would be readily dehydrogenated. In fact, on storing at room temperature or on heating in ethanol or acetic acid, the thiones **336** are dehydrogenated to give pyridinethiones **338**, disulfides of 1,4-dihydropyridine-2-thiols **339**, or mixtures of these products, depending on the reaction conditions and the structures of the initial compounds.^{35, 202, 215, 217, 218, 223}

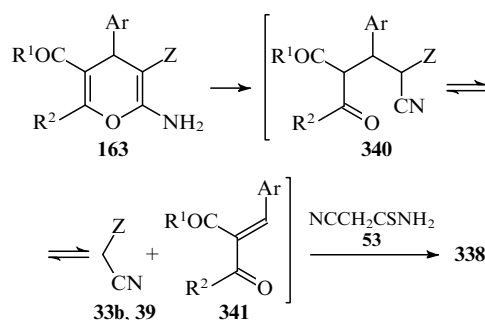


The pyridinethiones **338** were synthesised by interaction of the thiopyrans **328** with the acyclic dicarbonyl compounds **13a** and **33a**.²¹⁴ The addition of dimedone **25** to the system causes exchange by methylene components accompanied by elimination of cyanothioacetamide, which results in the formation of the fused pyrans **197**.²¹⁴



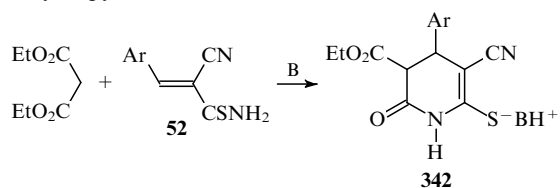
$R^1 = R^2 = \text{Me}$ (**13a**); $R^1 = \text{OEt}$, $R^2 = \text{Me}$ (**33a**);
 $Z = \text{CN}$ (**39**), CO_2Et (**33b**).

The non-fused 4-hetaryl-substituted pyrans **163** recyclise on treatment with cyanothioacetamide to give the pyridines **338**.⁹⁹ The formation of a pyran ring is reversible; this ring can open on treatment with nucleophiles. The acyclic intermediate **340** thus formed undergoes retro-decomposition^{10, 60} to the initial components **33b** (or **39**) and **341**. The addition of cyanothioacetamide **53**, introduced in the reaction medium, to unsaturated ketone **341** shifts the equilibrium towards the stable thione **338**. Synthesis of the pyridines **338** by direct interaction of arylidenecyanothioacetamides **52** with the dicarbonyl compounds **13a** and **33a** has been reported.²²⁹ The reaction requires refluxing in ethanol for 3 h in the presence of a catalytic amount of piperidine.



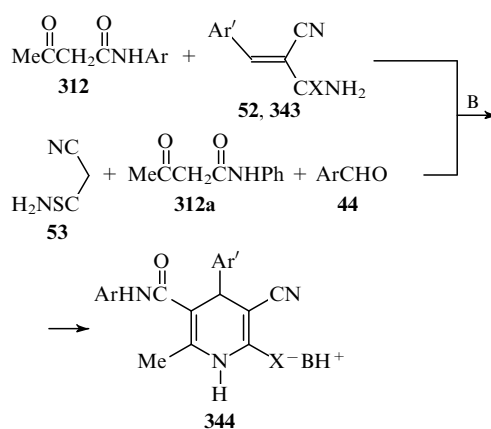
$R^1 = R^2 = \text{Me}$ (**13a**); $R^1 = \text{OEt}$, $R^2 = \text{Me}$ (**33a**);
 $Z = \text{CN}$ (**39**), CO_2Et (**33b**).

The reaction of ethyl malonate with *ortho*-substituted arylidenecyanothioacetamides results in the corresponding 2(1*H*)-oxo-3,4-dihydropyridine-6-thiolates **342**.²³⁰



$\text{Ar} = 2\text{-ClC}_6\text{H}_4$, $2\text{-IC}_6\text{H}_4$, $2\text{-NO}_2\text{C}_6\text{H}_4$; $\text{B} = \text{O-C}_6\text{H}_4\text{-N-Me}$.

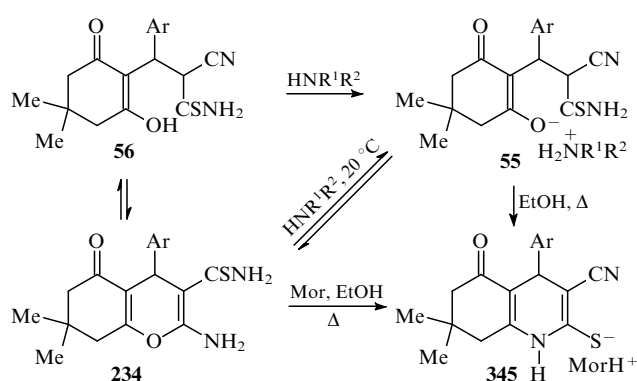
Acetoacetanilides **312** react with the aryl(hetaryl)idenecyanothioacetamides **52** or with arylidenecyanoselenoacetamides **343**, synthesised recently, to give the corresponding 1,4-dihydropyridine-2-thiolates and -selenolates **344**.²³¹ A method for preparing the thiolates **344** ($\text{X} = \text{S}$) from the aldehydes **44**, cyanothioacetamide **53**, and *N*-acetoacetylaniline **312a** has been developed.²³²



$\text{X} = \text{S}$ (**52**), Se (**343**).

The Michael adducts **56**, derived from dimedone and arylidenecyanothioacetamides, or their salts can cyclise to either the pyran derivatives **234** (see Section III) or substituted quinolines

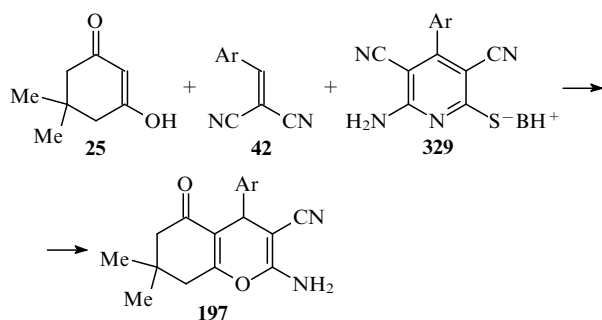
Scheme 5



345, depending on the reaction conditions.^{36, 158} The interconversion of the adducts **56**, the salts **55**, and the pyran derivatives **234** are presented in Scheme 5. The Michael adduct salt **55**, produced from arylidenethioacetamides and cyclic 1,3-dicarbonyl compounds in ethanol at room temperature, cyclise on heating giving rise to quinolinethiolates **345**. Refluxing of the adducts **56** in benzene gives rise to the 3-thiocarbamoyl-4*H*-pyrans **234**, which are also converted into the quinolinethiolates **345** on treatment with morpholine followed by refluxing of the reaction mixture. However, if the pyrans **234** are treated with secondary amines at room temperature, it is possible to isolate the intermediates **55**.^{36, 157, 158} Thus, recyclisation of the pyrans **234** to quinoline-2-thiolates **345** occurs *via* a stage of formation of the acyclic salts **55**, the formation of the pyrans **234** from the compounds **56** being a reversible process.

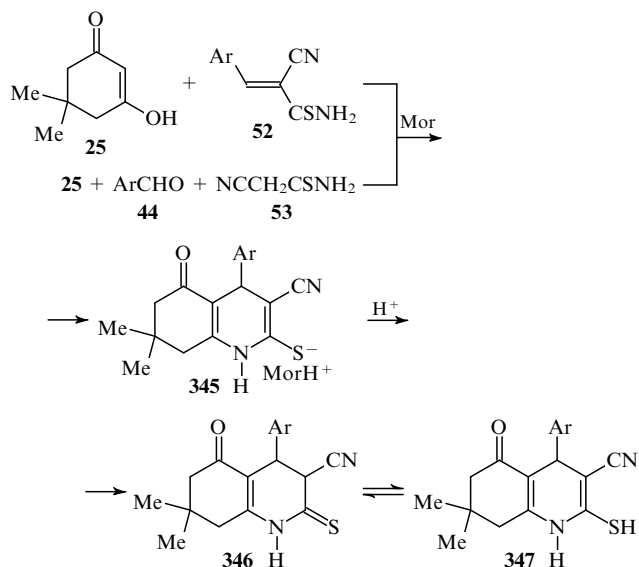
The interaction of the compounds **56** with morpholine in ethanol followed by refluxing of the salts **55** formed *in situ* was also found to yield quinolinethiolates **345**.^{34, 36, 158} The cyclisation to the quinolines **345** should be realised for the *threo*-isomers of the intermediates **55** represented by the projection **73** (Section III).

Yet another recyclisation route of 3-thiocarbamoyl-4*H*-pyrans **234** is their transformation into 3-cyano-4*H*-pyrans **197** on refluxing in benzene in the presence of malononitrile and triethylamine.¹⁵⁸ The compounds **197** are also formed when dimedone **25** reacts with arylidenemalononitriles **42**¹³¹ or the thiopyrans **329**.²¹⁴



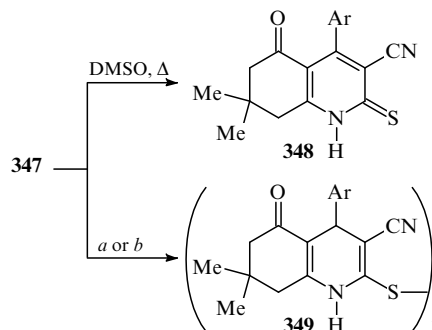
As was shown in Section VI, opening of the 4*H*-pyran ring under the action of secondary amines is also typical of analogous 4-hydroxycoumarin derivatives **236** and thus, it is a common feature of 3-thiocarbamoyl-derivatives of pyrans.

Convenient preparative methods for the synthesis of the quinolinethiolates **345** have been developed consisting of the interaction of dimedone **25** with arylidenethioacetamides **52** or directly with the aromatic aldehydes **44** and cyanothioacetamide **53**.²³³ On treatment with acids, the thiolates **345** are converted into compounds existing as thiones **346** in the solid state and entirely passing into the tautomeric thiol form **347** in solution (DMSO, trifluoroacetic acid, or acetone).^{36, 233}



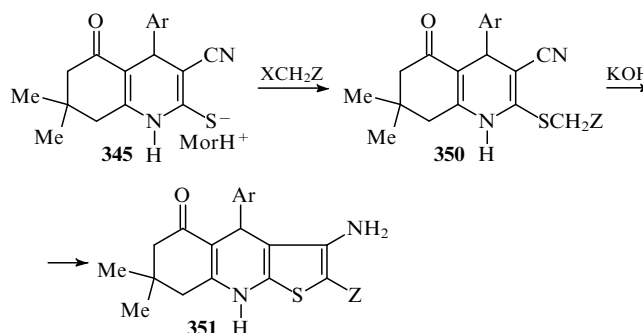
It should be noted that all the thiols **347** formed exist as mixtures of two stereoisomers, although the initial thiolates **345** contain only one isomer.

The quinolinethiones **346** are more stable to dehydrogenation than their non-fused analogues **335**. The regioselective dehydrogenation of the compounds **346** and **347** to give 3,4-dehydroderivatives **348** was accomplished by heating them in DMSO at 80–100 °C.²³³ Oxidation of **346** and **347** by atmospheric oxygen or by nitrobenzene results in the formation of a mixture of dehydrogenated quinolinethiones **348** and disulfides **349**. The latter have been obtained in preparative yields by treating the compounds **347** by iodine in an alkaline alcoholic solution.²³³



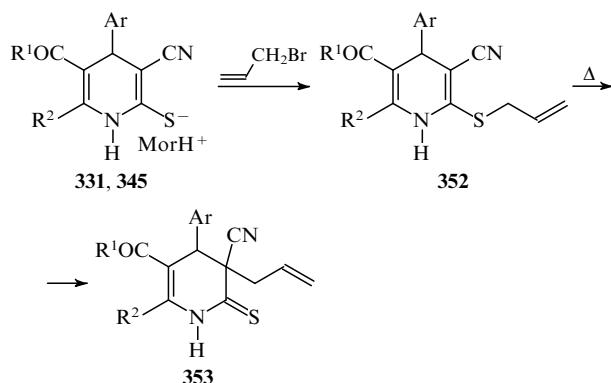
(a) I₂, KOH, EtOH; (b) O₂, PhNO₂.

The interaction of quinolinethiolates **345** with alkyl halides occurs regioselectively giving 2-alkylthio-derivatives of quinolines **350**; when these products contain electron-withdrawing substituents, they cyclise in the presence of excess base to 4,5,6,7,8,9-hexahydrothieno[2,3-*b*]quinolines **351**.^{34, 35, 158, 234}



X = Cl, Br; Z = C₆H₅, CN, CO₂Et.

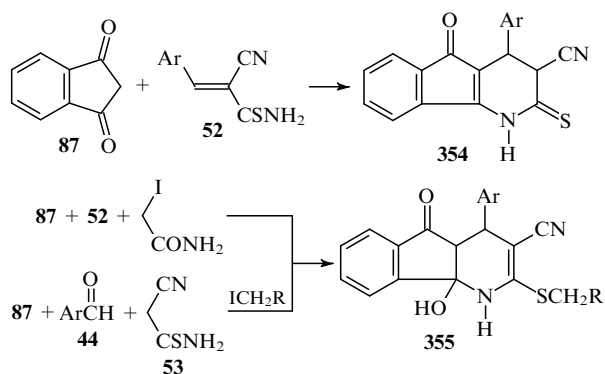
The reactions of 1,4-dihydropyridine-2-thiolates **331** and hexahydroquinolinethiolates **345** with allyl bromide involve the sulfur atom, like reactions with other alkyl halides. However, the 2-allylthio-1,4-dihydropyridine derivatives **352** thus formed undergo regioselective [3 + 3]-sigmatropic rearrangement on heating without a solvent or in a DMSO or ethanol solution giving rise to substituted 3-allyl-3-cyano-1,2,3,4-tetrahydropyridine-2-thiones **353** in high yields.²³⁵



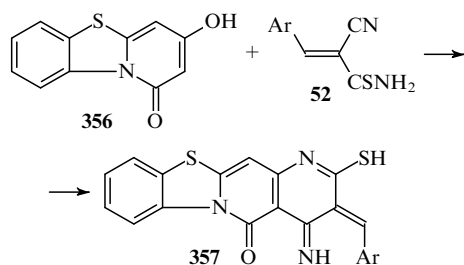
$R^1 = \text{Me, EtO}$; $R^2 = \text{Me}$ (**337**); $R^1 - R^2 = \text{CH}_2\text{C}(\text{Me})_2\text{CH}_2$ (**345**).

The structures of the initial compounds and the products were studied and proved by IR and ^1H and ^{13}C NMR spectroscopy^{236, 237} and also by X-ray diffraction analysis.²³⁸ A thermal rearrangement of this type is also typical of substituted 2-allylseleno-3-cyano-1,4-dihydropyridines;^{237, 238} apparently this is a common property of compounds of the 2-allylthio(seleno)-1,4-dihydropyridine series.

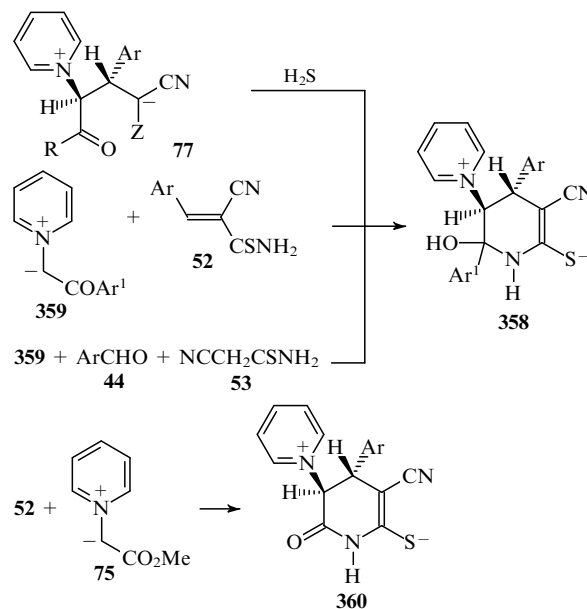
The reactions of arylidenecyanothioacetamides **52** with cyclic 1,3-dicarbonyl compounds have also been studied in relation to indane-1,3-dione **87**. It was found that this reaction affords fused 3,4-dihydropyridine-2-thiones **354**.²³⁹ Three-component condensation of cyanothioacetamide **53**, the aldehydes **44**, and the indanedione **87** and the subsequent treatment with iodoalkanes give rise to fused 2-alkylthio-9*b*-hydroxy-1,4-dihydroindano-[1,2-*b*]pyridines **355**.^{239, 240} Similar products are formed from the compounds **52** and **87** in the presence of iodoacetamide.²³⁹



Pyridobenzothiazole **356** reacts with the arylidenecyanothioacetamides **52** on refluxing in ethanol or pyridine. The structure **357** has been assigned to the reaction product.²⁴¹

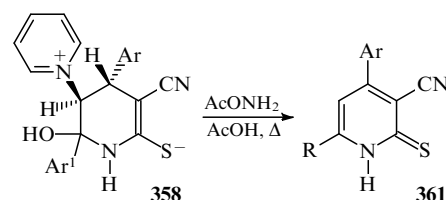


As has been mentioned in Section III, pyridinium ylides react with unsaturated nitriles giving the betaines **77**, which cyclise on treatment with hydrogen sulfide to the corresponding pyridine-thiolates **358** with retention of the *trans*-pseudoaxial arrangement of the C(3)H and C(4)H protons.⁵⁴ The same thiolates have been obtained by reaction of pyridinium ylides **359** with arylidenecyanothioacetamides **52** or by a three-component reaction of the ylides **359** with the aldehydes **44** and the thioamide **53**.^{54, 242} The ylide **75** and the compounds **52** form betaines **360**.^{194, 196}



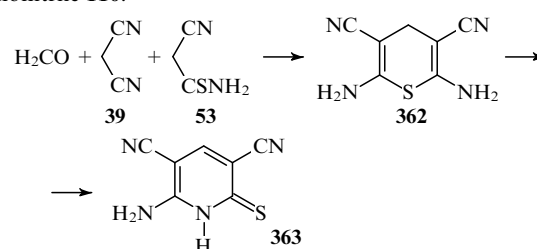
Some stereochemical aspects of the synthesis of pyridine betaines have been surveyed in a review;⁹ the atropo- and the stereo-selectivity of formation of these compounds have been discussed.²⁴³ Nucleophilic reactions of pyridinium ylides have been considered in greater detail in another review.⁵⁶

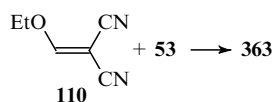
On heating in acetic acid with ammonium acetate, all the hydrogenated pyridinethiolates **358** eliminate pyridine yielding the corresponding pyridinethiones **361**.^{54, 242, 244, 245}



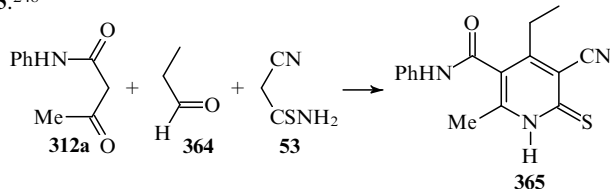
Based on the interaction of the pyridinium ylide **359** ($\text{Ar}' = 3\text{-pyridyl}$) with 3-pyridylmethylenecyanothioacetamide, a method for the synthesis of the tobacco alkaloid nicotine and its analogues has been developed.²⁴⁶

Pyridinethiones having no substituents at the 4-position can be synthesised using reactions with formaldehyde. Thus three-component condensation of formaldehyde, malononitrile **39**, and cyanothioacetamide **53** gives ¹⁵⁹ 2(1*H*)-pyridinethione **363**, which is produced *via* a stage of recyclisation of 4*H*-thiopyran **362**. The compound **363** has been obtained previously as the product of interaction of cyanothioacetamide **53** with ethoxymethylenemalononitrile **110**.²⁴⁷

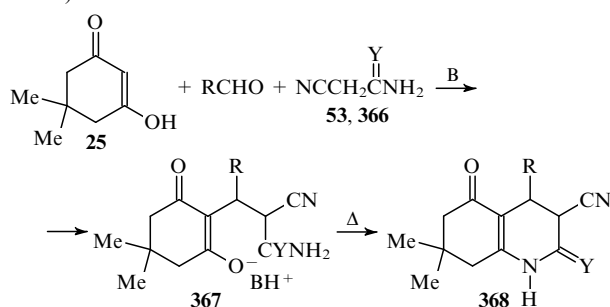




Three-component condensation of aliphatic aldehydes with carbonyl compounds and cyanothio(seleno)acetamides opened up way to 4-alkyl-substituted 2(1*H*)-pyridinethions and -selenones, which had been difficult to synthesise before. The reaction of the anilide of acetoacetic acid **312a** with propionaldehyde **364** and cyanothioacetamide **53** yields 4-ethyl-substituted pyridine **365**.²⁴⁸

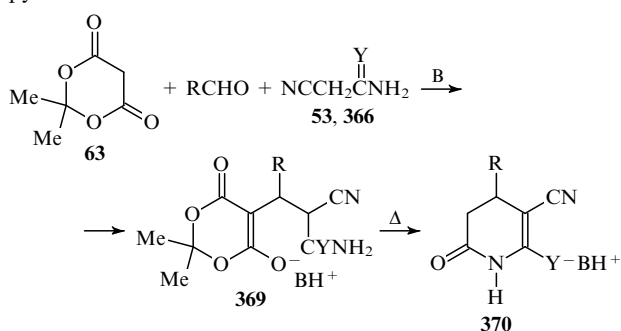


Dimedone **25** reacts with aliphatic aldehydes and the cyanoamides **53** or **366** to give compounds **367** similar to the aryl derivatives **55** described previously. The compounds **367** can be regarded as adducts of dimedone and alkylidenecyanothio(seleno)acetamides, which are apparently formed *in situ* in this reaction. When the temperature is increased, the compounds **367** cyclise to 4-alkyl-substituted hexahydro-2(1*H*)-quinolinethiones(-selenones) **368**.²⁴⁹



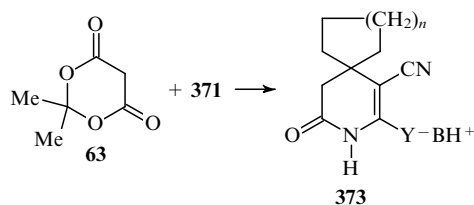
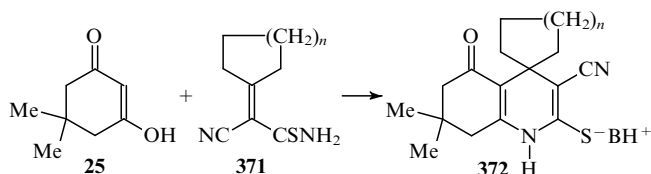
Y = S (**53**), Se (**366**).

Under these conditions, Meldrum's acid **63** forms analogous salts **369**; at higher temperatures, they cyclise with destruction of the 1,3-dioxane ring, being thus converted into hydrogenated pyridones **370**.²⁴⁹



Y = S (**53**), Se (**366**).

The use of compounds **371**, resulting from condensation of cyclic ketones with cyanothioacetamide, in the reactions with the dicarbonyl compounds **25** and **63** permitted the synthesis of spiroderivatives of hydrogenated quinolines **372** and pyridones **373**, which are of interest from the stereochemical viewpoint.²⁴⁹



Analysis of the published data indicates that reactions of carbonyl compounds with α,β -unsaturated nitriles is a quite promising field of research. Studies along this line make it possible to synthesise a large number of diverse organic compounds possessing useful practical properties and also make a substantial contribution to the development of theoretical problems of organic chemistry.

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Reactions of thiocyanogen and thiocyanogen halides with unsaturated compounds

E V Skorobogatova, V R Kartashov

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Abstract. Data on the reactions of thiocyanogen and thiocyanogen halides with unsaturated compounds are systematised. The kinetic, stereo-, and regiochemical regularities of these reactions are analysed. The bibliography includes 81 references.

I. Introduction

Reactions of thiocyanogen and thiocyanogen halides with alkenes belong to the important methods used for the preparation of organic isothiocyanates and thiocyanates. The presence of several reaction centres in these compounds^{1,2} opens up wide prospects for their application in the synthesis of diverse heterocyclic compounds.^{3–14} Organic isothio- and thiocyanates and compounds based on them possess fungicidal and bactericidal activity,^{15–17} manifest properties of optically active crystals¹⁸ and organic superconductors.¹⁹

The ability of thiocyanogen to add to a double bond served as a basis for the development of a method for the quantitative determination of the degree of unsaturation of individual organic compounds, fats, and oil²⁰ (the thiocyanogen value).

Despite the practical importance of alkene thiocyanation, its mechanism remained poorly studied for a long time. It was stated that the chemical properties of thiocyanogen, (SCN)₂, and thiocyanogen halides are similar to those of halogens; in view of this, they are often called pseudo-halogens.²¹ In the middle of the 1960s, the first studies on the stereochemistry and mechanism of reactions of thiocyanogen and thiocyanogen halides with alkenes appeared. To date, a large body of experimental data have been obtained; they require systematisation and reviewing.

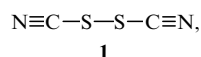
We have made an attempt to generalise the data available on the reactions of thiocyanogen and thiocyanogen halides with unsaturated compounds both under conditions of electrophilic addition and under UV irradiation.

II. Reactions of thiocyanogen and thiocyanogen halides with alkenes under heterolytic conditions

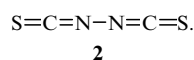
Thiocyanogen was first isolated in an analytically pure form in 1919.²² It is a very unstable compound with m.p. –2 °C, but its

solutions in organic solvents are stable for rather long periods of time.^{22–24}

IR Spectra of thiocyanogen in carbon disulfide and pentachloroethane²⁵ are in favour of its disulfide structure (structure 1)



However, the main absorption band in the IR spectra recorded in ether is somewhat shifted towards lower frequencies, whence a conclusion was made²⁵ that the isothiocyanate form (structure 2) of thiocyanogen in ether is preferred



This assignment is doubtful. For example, a similar shift of the absorption band in the IR spectra of thiocyanogen iodide was explained²⁶ by the formation of a charge-transfer complex of thiocyanogen iodide with ether as a low-basic solvent.

The coincidence of the heat of formation of thiocyanogen found experimentally with the theoretical value calculated assuming the disulfide structure^{27–29} is in favour of structure 1. It was confirmed by UV spectroscopic data for thiocyanogen in the gas phase and by theoretical calculations.³⁰

Thiocyanogen chloride can be obtained quantitatively by the reaction of chlorine with (SCN)₂²⁵ or with AgSCN³¹ in the gas phase or in organic solvents. However, it decomposes rapidly in solutions.^{25,32} Mass spectrometric studies showed that the potential for formation of the SCN⁺ particle from thiocyanogen chloride is lower than the potential for its formation from (SCN)₂.²⁹

According to the data of IR,^{25,33} microwave,³⁴ and photoelectron spectroscopy,³⁵ structure 3 is preferable for thiocyanogen chloride to structure 4.



The data available to date indicate that the S–Cl bond in the thiocyanogen chloride molecule is polarised under heterolytic reaction conditions.

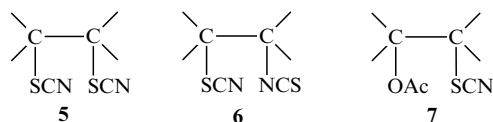
1. Main pathways of the reaction of thiocyanogen and thiocyanogen chloride with alkenes

Benzene, chloroform, and other non-nucleophilic solvents, as well as acetic acid, are the most common solvents used in reactions of alkenes with thiocyanogen. As a rule, these reactions result in a mixture of adducts, *i.e.*, dithiocyanates 5 and isothiocyanatodithiocyanates 6; in solutions in acetic acid, solvato-adducts 7 are also formed.

E V Skorobogatova, V R Kartashov Nizhnii Novgorod State Technical University, ul Minina 24, 603600 Nizhnii Novgorod, Russian Federation. Fax (7-831) 236 23 11. Tel. (7-831) 236 93 57

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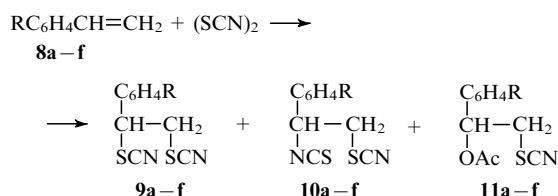
Uspekhi Khimii 67 (5) 474–485 (1998); translated by S S Veselyi



It was shown^{36,37} that the reaction rate increases with an increase in the solvent polarity and in the electron-donating properties of the substituent at the double bond of the alkene.

It was found in a study of the reaction of styrenes with thiocyanogen in AcOH that the second-order reaction constants correlate with the Brown–Okamoto constants (σ^+) of substituents. The reaction constant ρ^+ is -5.3 .³⁸ These data indicate the electrophilic character of the reaction and a considerable polarity of the transition state.³⁸

The products of the reaction of styrenes **8a–f** with thiocyanogen in acetic acid include 1-(aryl)ethane-1,2-diylthiocyanates **9a–f**, 2-(aryl)-2-isothiocyanatoethyl thiocyanates **10a–f**, and products of the conjugate addition of acetic acid, *i.e.* 2-(aryl)-2-acetoxyethyl thiocyanates **11a–f**. The yields of the latter depend on the electron-donating properties of the aryl substituent (Table 1).^{38,39} Thus, the introduction of electron-withdrawing substituents into the benzene ring of styrene increases the yields of thiocyanates **11a–f**, whereas electron-donating substituents decrease the yields.



The adducts **10** and solvato-adducts **11** are formed regioselectively. Similar regiochemistry of the formation of compounds **10** is observed in the reaction of $(\text{SCN})_2$ with styrene **8c** in benzene (Table 1).⁴⁰

The high polarity of the transition state (the limiting step of the reaction of thiocyanogen with alkenes) is evident from the greater effect of LiClO_4 on the overall reaction rate in comparison with the effect of this salt on the sulfonylhalogenation of alkenes.³⁹ In reactions with styrene³⁹ and cyclohexene,⁴¹ the second-order reaction constants depend linearly on the LiClO_4 concentration according to Eqn (1)

$$k_{\text{exp}} = k_0 (1 + b[\text{LiClO}_4]), \quad (1)$$

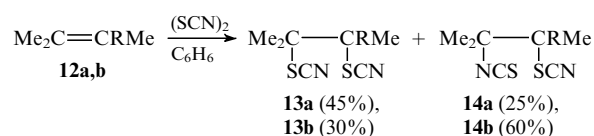
where k_{exp} and k_0 are the observed reaction rate constants in the presence and in the absence of the salt, respectively. The b parameter varies from 17 to 38 depending on the reaction temperature and the alkene structure,³⁹ whereas for sulfonylhalogenation, it varies from 4.5 to 8.^{39,42–44}

The formation of adducts **6** with isothiocyanate groups is undoubtedly related to the ambidentate properties of the thio-

cyanate anion. The table below lists the charge distributions in the SCN^- anion calculated by MO LCBO (method A)⁴⁵ and by MO LCAO in the Wolfberg–Helmholtz (method B)⁴⁶ and Hückel approximations (method C).⁴⁷

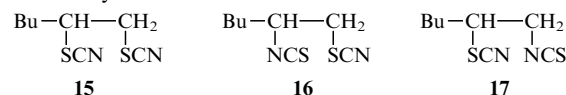
Method	Charge distribution on atoms		
	S	C	N
A	-0.7108	$+0.1934$	-0.4826
B	-0.24	$+1.00$	-1.76
C	-0.31	$+0.09$	-0.79

It was shown⁴⁰ that increasing the number of substituents at the alkene double bond increases the fraction of the adduct of type **6** containing the isothiocyanate group. For example, a comparison of the results of reactions of $(\text{SCN})_2$ with 2-methylbut-2-ene **12a** and 2,3-dimethylbut-2-ene **12b** in benzene shows that the yield of isothiocyanate **14b** is considerably higher than that of thiocyanate **14a**.



R = H(a), Me (b).

Under similar conditions, hex-1-ene gives hexane-1,2-diyl dithiocyanate **15** in 42% yield as well as 2-isothiocyanatohexyl thiocyanate **16** and 1-isothiocyanatohexane-2-yl thiocyanate **17** in 27% overall yield.



The observed ratio of the reaction products **15**:(**16**+**17**) is explained⁴⁰ by the effect of steric and electronic factors of the substrate and the thiocyanate anion in the step of the formation of reaction products.

It was found⁴⁸ that the reaction of *trans*- and *cis*-hex-3-enes with $(\text{SCN})_2$ gives *erythro*- and *threo*-4-isothiocyanatohexane-3-yl thiocyanates **18** and hexane-3,4-diyl dithiocyanates **19**, respectively, as the main reaction products. The ratio of products **18**:**19** depends substantially on the properties of the solvent. In aprotic solvents, this ratio decreases with an increase in the polarity of the solvent, *e.g.*, it is 2.15 in benzene and 0.46 in acetonitrile.



The product ratio of this reaction in low-polar solvents is affected substantially by the addition of iron powder. For example, the ratio of isomers **18**:**19** changes to 0.03 in benzene. The observed ratio of the reaction products was explained⁴⁸ in terms of the HSAB concept.⁴⁹ In the opinion of Maxwell *et al.*,⁴⁸ the ambident thiocyanate anion in non-polar solvents is mostly solvated at the soft sulfur atom (interaction involving charge transfer). This results in charge-controlled attack of the intermediate carbocation by the nitrogen atom. As the dielectric constant of the solvent increases, the direction of the reaction of the SCN^- anion with the intermediate changes from charge-controlled to frontally-controlled with attack by the sulfur atom. A decrease in the fraction of product **18** in acetonitrile can also be explained by an association of the thiocyanate anion with the solvent similar to dipole-dipole interaction.



Table 1. Yields of the products of the reaction of styrenes **8a–f** with thiocyanogen in acetic acid.

Compound	R	Product yields (%)		
		9	10	11
a	4-OMe	78	—	—
b	4-Me	59	~20	21
c	H	36 (44) ^a	~20 (22) ^a	42
d	4-Cl	36	~20	44
e	3-Cl	—	—	85–90
f	3-F	—	—	85–90

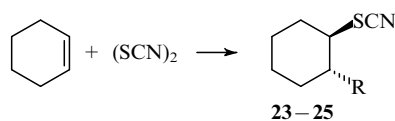
^a The numbers in parentheses indicate the yields of the products in benzene.

The preferential (84%) formation of dithiocyanate **19** in acetic acid is explained⁴⁸ by the coordination of the solvent with the thiocyanate anion with the formation of hydrogen bonds mainly with the nitrogen atom.

Reactions of alkenes with thiocyanogen chloride in acetic acid generally result in products of addition of ClSCN to the alkene double bond and solvato-adducts of the type **7**. For example, the reaction of ethylene with thiocyanogen chloride gives 2-chloroethyl thiocyanate and 2-acetoxyethyl thiocyanate in 64% and 6% yields, respectively.⁵⁰ The addition of thiocyanogen chloride to asymmetric aliphatic alkenes occurs both according to and against the Markovnikov rule, whereas solvato-addition always occurs according to the Markovnikov rule. For instance, the reaction of propene with ClSCN in AcOH gives a mixture of adducts: 2-chloropropyl thiocyanate **20** (54%), 1-chloropropane-2-yl thiocyanate **21** (27%), and 2-acetoxypropyl thiocyanate **22** (18%).⁵¹ The ratio of thiocyanates **20**:**21** is the same if the reaction is carried out in chloroform.⁵² The reaction of hex-1-ene with ClSCN in AcOH occurs similarly to give 2-chlorohexyl thiocyanate (49%), 1-chlorohexane-2-yl thiocyanate (28%), and 2-acetohexyl thiocyanate (15%).⁵¹ The addition of ClSCN to styrene **8c** obeys the Markovnikov rule to give 2-chloro-2-phenylethyl thiocyanate and 2-acetoxy-2-phenylethyl thiocyanate in 41% and 50% yields, respectively.⁵¹

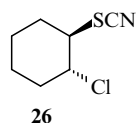
2. Stereochemistry of alkene thiocyanation

The reaction of (SCN)₂ and ClSCN with cyclohexene occurs stereoselectively. The reaction of (SCN)₂ with cyclohexene in benzene gives *trans*-isomers of cyclohexane-1,2-diyl dithiocyanate **23** and 2-isothiocyantocyclohexyl thiocyanate **24**. The reaction in acetic acid gives *trans*-2-acetoxycyclohexyl thiocyanate **25** in addition to the above products **23** and **24**.⁴⁰



Compound	R	Yield (%)	
		in C ₆ H ₆	in AcOH
23	SCN	32	48
24	NCS	16	22
25	OAc	—	24

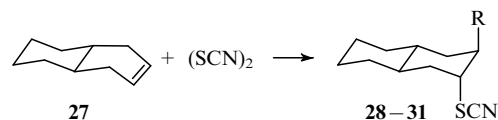
The reaction of cyclohexene with ClSCN in acetic acid results in *trans*-2-chlorocyclohexyl thiocyanate **26** (77%) and a solvato-adduct **25** (15%).⁵⁰



Similar results were also obtained in the reaction of (SCN)₂ and ClSCN with 4-methylcyclohexene.^{40,50} The reaction with (SCN)₂ gave *trans*-isomers of 4-methylcyclohexane-1,2-diyl dithiocyanate, 5-methyl-2-isothiocyantocyclohexyl thiocyanate, and 4-methyl-2-isothiocyantocyclohexyl thiocyanate.⁴⁰ The reaction with thiocyanogen chloride gave a mixture of regioisomeric *trans*-adducts (2-chloro-4-methylcyclohexyl thiocyanate and 2-chloro-5-methylcyclohexyl thiocyanate) and *trans*-solvato-adducts (2-acetoxy-4-methylcyclohexyl thiocyanate and 2-acetoxy-5-methylcyclohexyl thiocyanate).⁵¹

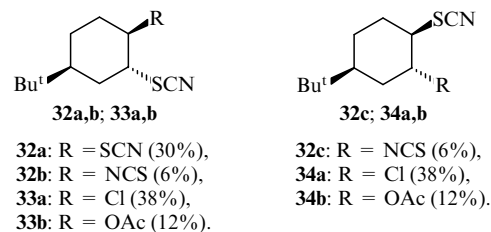
Reactions with conformationally rigid and conformationally fixed alkenes give products in which the functional groups formed upon the addition of the reagent occupy the *trans*-diaxial positions. For example, the reaction of ClSCN with 5 α -2-cholestene in acetic acid results in 2 β -chloro- and 2 β -acetoxy-3 α -thiocyanato-5 α -cholestanes in 82% and 11% yields, respectively.⁵¹

The reaction of thiocyanogen with *trans*- Δ^2 -octalin **27** in benzene affords *trans*-decalin-2a,3a-dithiocyanate **28** (yield 10%) and *trans*-3a-isothiocyantodecalin-2a-thiocyanate **29** (yield 5%). If the reaction is carried out in acetic acid, *trans*-3a-acetoxycyclohexyl-2a-thiocyanate **30** is formed in addition to the adducts **28** and **29**. The yields of decalins **28**–**30** are 40%, 18%, and 21%, respectively.⁴⁰ Solvato-adduct **30** and *trans*-3a-chlorodecalin-2a-thiocyanate **31** were isolated in 25% and 69% yields, respectively, from the reaction mixture of octalin **27** with thiocyanogen chloride.⁵⁰



R = SCN (**28**), NCS (**29**), OAc (**30**), Cl (**31**).

The reaction of 4-*tert*-butylcyclohexene with thiocyanogen in acetic acid gives products **32a**–**c**,⁴⁰ while the reaction with thiocyanogen chloride gives compounds **33a,b** and **34a,b**.⁵¹ The functional groups in compounds **32a**–**c**, **33a,b**, and **34a,b** have a *trans*-diaxial configuration.



The rule of *trans*-addition of thiocyanate-containing reagents also holds for such highly strained alkenes as cyclopropenes.^{52,53} The reactions of 3,3-dimethylcyclopropene with thiocyanogen chloride and thiocyanogen in CHCl₃ and AcOH afford adducts with *trans*-configuration, namely, *trans*-2-chloro-3,3-dimethylcyclopropyl thiocyanate (80%) and *trans*-3,3-dimethylcyclopropyl-1,2-diyl dithiocyanate (20%), respectively.⁵²

The reaction of (SCN)₂ and ClSCN with stereoisomeric acyclic alkenes is *trans*-stereospecific.⁵⁰ Thus, the reaction of thiocyanogen chloride with *cis*-but-2-ene gives 3-chlorobutane-2-yl thiocyanate (81%) and 3-acetoxybutane-2-yl thiocyanate (15%) with *threo*-configurations. The same compounds but with *erythro*-configurations are formed in the reaction with *trans*-but-2-ene. They were isolated in 89% and 8% yields, respectively.

Similar results were obtained in the reaction of thiocyanogen with *cis*- and *trans*-2,5-dimethylhex-3-enes in benzene.⁵⁰ In this case, ($\pm$)- and *meso*-2,5-dimethylhexane-3,4-diyl dithiocyanates, as well as *threo*- and *erythro*-2,5-dimethyl-4-isothiocyantohexane-3-yl thiocyanates, respectively, are formed.

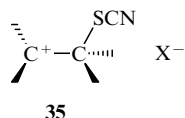
The observed stereochemical features agree with the stepwise reaction scheme and the cyclic structure of the intermediate.^{54–56}

The stereoselectivity of addition is violated in reactions with alkenes containing aryl substituents at the double bond. For example, the reactions of *cis*- and *trans*-stilbenes with ClSCN afford a mixture of *threo*- and *erythro*-2-chloro-1,2-diphenylethyl thiocyanates and *threo*- and *erythro*-2-acetoxy-1,2-diphenylethyl thiocyanates. The yield of the adducts was ~50% with predominant formation of the *trans*-isomer. The solvato-adducts are also predominantly of the *trans*-type (the *trans*- and *cis*-isomer ratio was 9:1; the total yield was ~40%). A mixture of adducts with *threo*- and *erythro*-configuration is formed in dichloromethane, chloroform, and benzene.⁵⁷ The reaction of *trans*-1-phenylpropene with (SCN)₂ in benzene is also non-stereospecific.⁴⁰ However, in this case the total yield of the reaction products does not exceed 20%.

The stereochemistry of the addition of thiocyanate-containing reagents to aryl-substituted alkenes is close to the stereochemistry

observed in reactions of the latter with bromine and its analogues,⁵⁸ but differs substantially from the stereochemistry of the addition of sulfonyl halides where high *trans*-stereoselectivity is a typical feature.^{54–56}

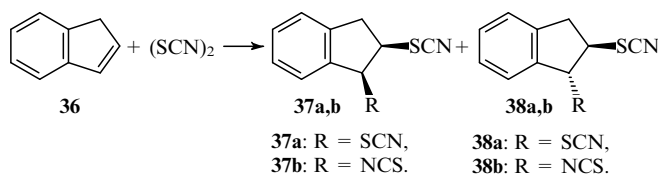
It was assumed^{40,57} that the intermediate **35** with an open structure is formed in the rate-limiting step of the reaction of (SCN)₂ and ClSCN with aryl-substituted alkenes.



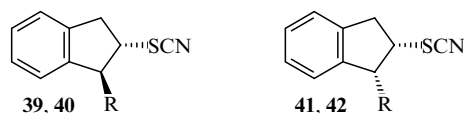
X = SCN, Cl.

This assumption agrees well with kinetic data obtained for the reaction of styrenes with thiocyanogen in AcOH.³⁸

The reactions of thiocyanogen and thiocyanogen chloride with indene and acenaphthylene are not stereoselective, either. Indene **36** reacts with (SCN)₂ in benzene to give *cis*- **37a** and *trans*-indane-2,3-diyl dithiocyanates **38a** as well as *cis*- **37b** and *trans*-3-isothiocyanatindane-2-yl thiocyanates **38b**.⁴⁰



The reaction with thiocyanogen chloride in acetic acid gives 22% of a mixture of *trans*- **39** and *cis*-3-chloroindane-2-yl thiocyanates **41** (in the 15:7 ratio) and 70% of *trans*- **40** and *cis*-3-acetoxyindane-2-yl thiocyanates **42** in which the *trans*-isomer predominates.⁵¹

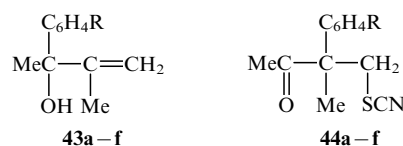


R = Cl (**39**, **41**), OAc (**40**, **42**).

Acenaphthylene reacts with thiocyanogen chloride in AcOH to give a mixture of *cis*- and *trans*-2-chloroacenaphthenyl thiocyanates in 21:79 ratio (total yield 61%) and a mixture of *cis*- and *trans*-2-acetoxyacenaphthenyl thiocyanates in 12:88 ratio and in 35% total yield.⁵⁷

3. Molecular rearrangements and proton elimination in reactions of thiocyanogen and thiocyanogen chloride with alkenes

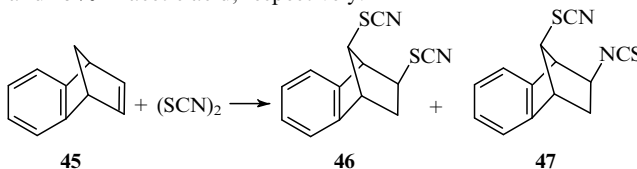
Reactions of thiocyanogen and thiocyanogen chloride with alkenes commonly involve skeletal rearrangements. This was first discovered in a study of a reaction of 2-aryl-3-methylbut-3-en-2-ols **43a–f** with thiocyanogen in a mixture of AcOH with Ac₂O.⁵⁹ The main reaction products are thiocyanatoketones **44a–f** formed due to the aryl group migration. The yield of 3-aryl-3-methyl-4-thiocyanatobutan-2-ones **44a–c** is close to quantitative. The yields of ketones **44d–f** were 72%, 60%, and 46%, respectively. The reactions of alkenes **43d–f** give the adducts, namely, 3-aryl-3-hydroxy-2-methylbutane-1,2-diyl dithiocyanates, in addition to thiocyanatoketones **44d–f**.



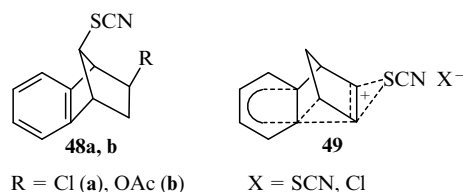
R = 4-OMe (**a**), 4-Me (**b**), 3-Me (**c**), H (**d**), 4-Cl (**e**), 3-Cl (**f**).

The second-order reaction rate constants (first-order with respect to each reagent) correlate with the Hammett constants of substituents. The reaction constant is negative, $\rho = -2.35$.⁵⁹

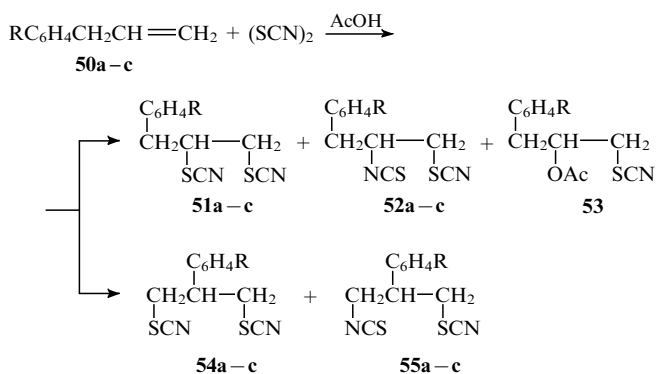
The addition of thiocyanogen to benzonorbornadiene **45** in chloroform and acetic acid gives exclusively products of the Wagner–Meerwein rearrangement:⁶⁰ 2-*exo*-7-*anti*-dithiocyanato-5,6-benzobicyclo[2.2.1]hept-5-ene **46** and 2-*exo*-isothiocyanato-7-*anti*-thiocyanatobenzobicyclo[2.2.1]hept-5-ene **47**. The total yield of the products is 90%. The relative content of compounds **46** and **47** is 51% and 49% in chloroform and 75% and 25% in acetic acid, respectively.



Rearrangement is the only direction of the reaction of benzonorbornadiene with ClSCN. When the reaction was carried out in chloroform, compound **48a** was isolated in 95% yield. In acetic acid, 2-*exo*-chloro- **48a** and 2-*exo*-acetoxy-7-*anti*-thiocyanato-5,6-benzobicyclo[2.2.1]hept-5-ene **48b** are formed in 83:17 ratio in 80% overall yield.⁶⁰ It is assumed that an ion pair **49** is formed as an intermediate without substantial manifestation of a dative bond.⁶⁰



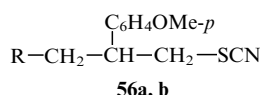
Rearrangement is also possible in the thiocyanation of allylbenzenes **50**. It was found^{42,61} that, in addition to the usual 1,2-addition products **51–53**, these reactions give rearrangement products **54, 55**.



R = 4-OMe (**a**), 4-Me (**b**), H (**c**).

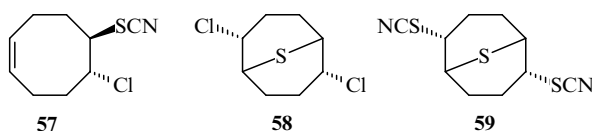
The reaction of thiocyanogen with alkene **50a** in a mixture of anhydrous AcOH with acetic anhydride (4:1, v/v) gives a product of 1,2-migration of the aryl group, viz., 2-(4-methoxyphenyl)propane-1,3-diyl dithiocyanate **54a** in 70% yield.⁶¹ The fraction of rearrangement products decreases abruptly with a decrease in the electron-donating properties of the aryl substituent.^{42,61}

The proportion of rearrangement products formed in the reaction of alkenes **50** with ClSCN is much larger than in the reaction with (SCN)₂. For example, the reaction of alkene **50a** with ClSCN in AcOH results only in products of 1,2-shift of the aryl group, i.e. 2-(4-methoxyphenyl)-3-chloropropyl thiocyanate (**56a**) and the solvato-adduct **56b**, in the 9:1 ratio.⁴²



R = Cl (**a**), OAc (**b**).

In addition to the main addition product **57**, the reaction of thiocyanogen chloride with (*Z,Z*)-cycloocta-1,5-diene in AcOH also gave products of a *trans*-annular reaction, *i.e.* bicycles **58** and **59**.²¹ Conversely, the reaction of the same diene with thiocyanogen gives only an adduct, namely, cyclooct-5-ene-1,2-diyl dithiocyanate.²¹



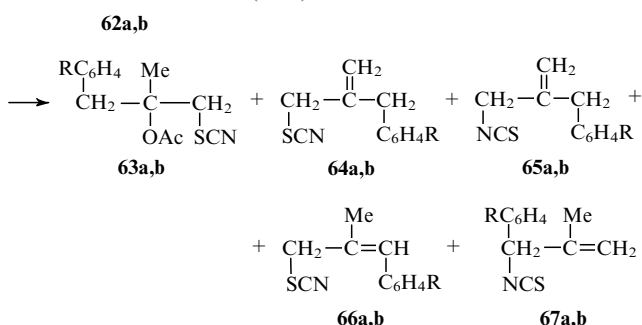
The reactions of (SCN)₂ and ClSCN with 1-methylcyclopropane in chloroform and acetic acid have been studied.^{52, 62, 63} The reactions occur in several directions to give a mixture of products. In addition to the corresponding adducts and solvato-adducts, addition products with cyclopropane ring opening were isolated.

The reaction of (SCN)₂ and ClSCN with *gem*-disubstituted alkenes occurs with considerable peculiarities. For example, isobutene reacts with (SCN)₂ in acetic acid to give an addition product, methallyl isothiocyanate **60a**, and a solvato-adduct, 2-acetoxy-2-methylpropyl thiocyanate **61**, in a 1:4 ratio in 60%–70% total yield instead of adducts. It is believed⁶⁴ that the formation of isothiocyanate **60a** is the result of allyl rearrangement of the thiocyanate **60b** formed initially.



R = NCS (**a**), SCN (**b**).

Thiocyanation of 3-aryl-2-methylprop-1-enes **62a, b** afforded solvato-adducts (2-acetoxy-3-aryl-2-methylpropyl thiocyanates **63a, b**), addition products (**64a, b** and **64a, b** as a mixture), and products **66a, b** and **67a, b**. The ratio of the sum of unsaturated products **64a–67a** to the acetate **63a** is 1:1, and the ratio of compounds **64b–67b** to compound **63b** is 1:2.⁶⁴



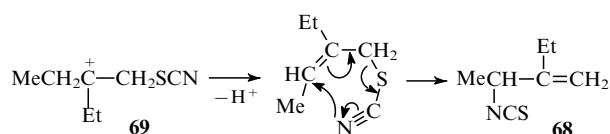
R = H (**a**), 4-Cl (**b**).

Unsaturated compounds are also formed in the reaction of thiocyanogen with 2-methylbut-2-ene in acetic acid.⁶⁴

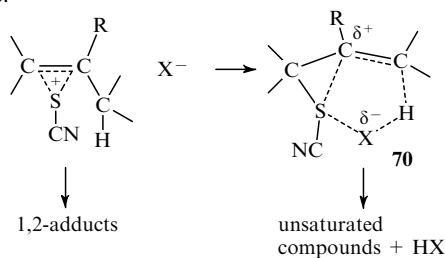
Similarly, the reaction of isobutene⁶⁴ and 2-ethylbut-1-ene⁵¹ with ClSCN in AcOH affords the corresponding unsaturated compounds **60a** and 3-ethylbut-3-en-2-yl isothiocyanate **68** in addition to the adducts and solvato-adducts.

The reactions studied show again that (SCN)₂ resembles halogens and interhalogen electrophilic reagents.⁵⁸

It was assumed⁵¹ that unsaturated compounds are formed due to the elimination of a proton from intermediate **69**.



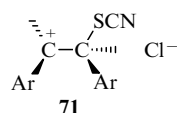
However, an alternative scheme may be suggested for these reactions according to which unsaturated compounds may be formed from a cyclic intermediate through a highly polar intermediate **70**. The stabilising effect of substituents at the β-carbon atom in the carbocationic centre on the intermediate state probably favours such a transformation of the cyclic intermediate.⁶⁵



X = SCN, Cl.

Unsaturated compounds are also formed in reactions of ClSCN with phenyl-substituted alkenes. The reaction with 1,1-diphenylethylene afforded a product of the β-proton elimination, *viz.*, 2,2-diphenylvinyl thiocyanate, in 10% yield. 1,1-Diphenyl-2-thiocyanatoethanol was also isolated from the reaction mixture. It is believed⁵¹ that this compound is formed as a result of hydrolysis of the adduct formed initially, 2-chloro-2,2-diphenylethyl thiocyanate. The reaction of ClSCN with triphenylethylene gave a β-proton elimination product, 1,2,2-triphenylvinylthiocyanate, in 75% yield.⁵¹

This reaction is assumed⁵¹ to occur through the formation of the intermediate **71**.



Finally, let us consider the data that allow one to deduce the structure of the intermediate formed in the thiocyanation of alkenes. According to some data,⁶⁶ the intermediate may have a structure of a π-complex **72** with two electron-deficient S–C bonds without noticeable overlapping of the 3*p*-orbital of the sulfur atom with the π-antibonding orbital of the alkene (dative bond) or of a three-membered cyanosulfonium ion **73** with two ordinary two-electron S–C bonds.



X = SCN, Cl.

Intermediates of the type **73** are assumed to be formed in the sulfonylhalogenation of alkenes.^{54, 67, 68} From the formal structural point of view, ClSCN and (SCN)₂ can be regarded as sulfonyl chlorides (ClSR) and sulfonyl thiocyanates (NCSSR) in which the hydrocarbon group is replaced by the cyano group. In this case, one should expect a similarity in the chemical behaviour of these two types of electrophilic reagents and formation of intermediates with similar structures.

However, as can be seen from the above data, despite the formal similarity, the thiocyanation of alkenes differs substantially in many respects from the reaction of alkenes with sulfonyl

halides. The formation of rearrangement products and unsaturated compounds, as well as transannular cyclisation and the cyclopropene ring opening, are in better agreement with the assumption that the intermediate in the thiocyanation of alkenes has the structure **72**. In the absence of the dative bond or if it manifests itself insignificantly, the carbon skeleton of π -complex **72** can be largely deficient in electron density. This stimulates the processes described above.

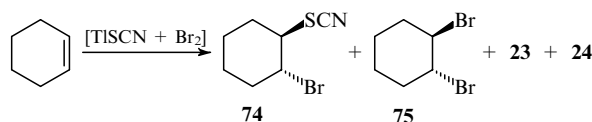
It follows from stereochemical data that in reactions of $(\text{SCN})_2$ and ClSCN with aryl-substituted alkenes, the intermediate **35** with an open structure is more stable than the cyclic one. The sulfonylation of such alkenes occurs *trans*-selectively.^{54–56} The difference between thiocyanation and sulfonylation can be explained by the smaller bond strength in the cyclic intermediate **72** than in the episulfonium ion due to the absence of overlapping of *p*- and π^* -orbitals. Therefore, the reaction occurs through a non-cyclic intermediate in the presence of substituents capable of noticeable conjugation with the electron-deficient carbon atom.

Taking into consideration the properties of the media in which these reactions are usually carried out (aprotic and protic solvents with low dielectric constants), one can assume that, irrespective of the exact structure of its cation, the intermediate exists as a tight ion pair, which is possibly in equilibrium with a solvate-separated ion pair.^{42, 50, 53, 57, 59, 69} It was assumed^{38, 39} that the interaction between the sulfur atom of the cation and the counter-ion exists.

4. Addition of thiocyanogen bromide and thiocyanogen iodide to alkenes

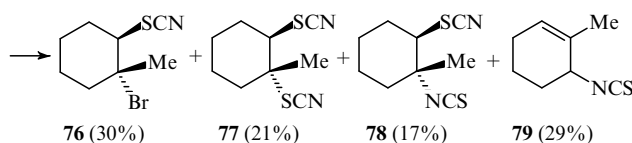
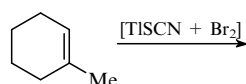
Thiocyanogen bromide has been obtained both in solution^{25, 70} and in gas phase.³⁵ Like ClSCN , it is an unstable compound. The reaction of BrSCN with alkenes has been little studied. The procedure for the preparation of the reagent affects considerably the result of the reaction. In one study,⁷¹ it was prepared by the reaction of bromine with lead thiocyanate in CCl_4 . Its subsequent reaction with oct-1-ene resulted in a mixture of 1,2-dibromooctane and 2-bromooctyl thiocyanate. The reaction products were not separated. The conclusion on their structures was done on the basis of GLC and elemental analysis data. It was also assumed that a small amount of 1-bromooctane-2-yl thiocyanate was present in the reaction mixture.

Several procedures were attempted⁷² with the aim of obtaining vicinal bromothiocyanates. It was found that the optimum conditions are those where an alkene is treated with an equimolar amounts of bromine and thallium thiocyanate in moist CCl_4 or CHCl_3 . The reaction of these reagents with cyclohexene gave *trans*-2-bromocyclohexyl thiocyanate **74** as the main product (50%) and small amounts (3%–5%) of *trans*-1,2-dibromocyclohexane **75** and thiocyanates **23** and **24**.

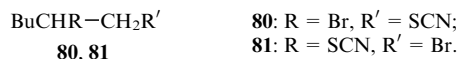


When lead thiocyanate was used, the yield of thiocyanate **74** decreased to 20%.

The reaction of 1-methylcyclohexene with the same reagents gave similar *trans*-addition products **76**–**78** and an unsaturated compound, 2-methylcyclohex-2-enyl isothiocyanate **79**. The structure of *trans*-2-bromo-*cis*-2-methylcyclohexyl thiocyanate **76** indicates that the sulfur atom is the electrophilic centre in the BrSCN molecule.

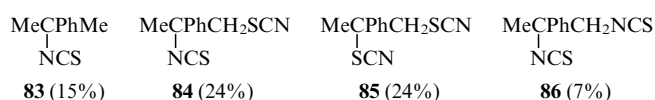


The reaction with hex-1-ene is less regioselective. Isomeric products are formed in this case, namely, 2-bromohexyl thiocyanate **80** (44%), 1-bromohexane-2-yl thiocyanate **81** (9%) and compounds **15**–**17** (total yield 18%).

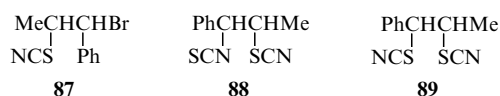


Styrene **8c** reacts under the conditions specified above to give 2-bromo-2-phenylethyl thiocyanate **82** (44%) and compounds **9c** (18%) and **10c** (12%). The yield of adduct **82** increases to 77% upon the addition of KBr to the reagent.

Unlike in the reactions mentioned above, the reaction of the system bromine–thallium thiocyanate with 2-phenylpropene does not give a vicinal bromothiocyanate. In this case, 2-phenylpropane-2-yl isothiocyanate **83**, 2-phenyl-2-isothiocyanatopropyl thiocyanate **84**, 2-phenylpropane-1,2-diyl dithiocyanate **85**, and 2-phenylpropane-1,2-diyl diisothiocyanate **86** were obtained.



Under the same conditions, the reactions of *trans*- β -methylstyrene result in *threo*- and *erythro*-1-bromo-1-phenylpropane-2-yl thiocyanates **87** in 11% and 8% yields, respectively, *threo*-1-isothiocyanato-1-phenylpropane-2-yl thiocyanate **88** (11%), and a mixture of *threo*- and *erythro*-1-phenylpropane-1,2-diyl dithiocyanates **89** (total yield 20%).⁷²



It is assumed⁷² that, depending on the alkene structure, either *S*-cyanosulfonium ion of the type **73** ($\text{X} = \text{Br}$) or a cation with an open structure (for aryl-substituted alkenes) are formed as intermediates.

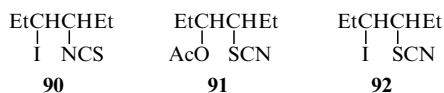
Reactions of alkenes with thiocyanogen iodide are of considerable interest as a method for the synthesis of vicinal iodothio- and iodoisothio-cyanates that can be used efficiently in the synthesis of heterocyclic compounds.^{6, 11–14} It is a problem to establish a procedure for the preparation of the reagent that would ensure the selective synthesis of these adducts.

By analogy with thiocyanogen chloride and bromide, ISCN was obtained using the reaction of iodine with thiocyanogen. It should be noted that there is no common viewpoint regarding the position of equilibrium in this system. For example, it was reported²⁶ that thiocyanogen iodide was formed in a solution in CCl_4 ; conversely, the formation of a substantial amount of thiocyanogen iodide was considered unlikely in other papers.^{35, 73} Nevertheless, although the data presented above are controversial, the use of a solution of iodine and thiocyanogen leads rather smoothly to the formation of iodothio- and iodoisothio-cyanates in many reactions with alkenes.

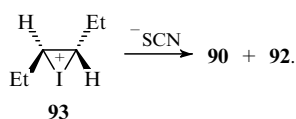
In another method, a system consisting of iodine or iodine-containing electrophiles and salts with the thiocyanate anion were used as the source of ISCN . The advantage of this method is the possibility of varying the reaction conditions over a wide range by changing the properties of the medium and the nature of the salt.

The reaction of *cis*- and *trans*-hex-3-enes with the $\text{I}_2-(\text{SCN})_2$ system has been studied.⁷⁴ It was found that in benzene, *threo*- and *erythro*-4-iodohexane-3-yl isothiocyanates **90**, respectively, are

formed along with a small amount of the addition product **18**. The same reaction in AcOH results in compounds **18**, **19**, and **91**. It was concluded on this basis⁷⁴ that ISCN was not formed in acetic acid. However, a study of the reactivity of the $I_2-(SCN)_2$ system with *trans*-hex-3-ene⁶ showed that the *erythro*-adduct **90** and *erythro*-4-iodohexane-3-yl thiocyanate **92** are the main products in benzene, dichloromethane, chloroform, and acetic acid. The ratio of compounds **90**:**92** in AcOH is ~2:1 and the total yield is ~60%. In other solvents studied, their ratio changes from 3.5 to 6.0 and the total yield varies from 70% to 80%. Compounds **18**, **19**, and **91** are formed in small amounts.



It was assumed⁶ that in all solvents ISCN is the actual electrophile, and, according to the expected polarisation of the reagent, the reaction involves the intermediate **93**.



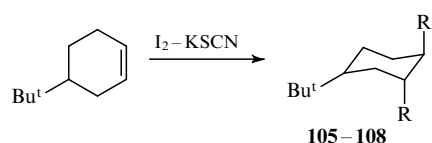
For comparison, the reaction of *trans*-hex-3-ene with the KSCN– I_2 system was studied. In chloroform, the ratio of products **92**:**90** is 4:1, which differs markedly from that (1:6) obtained in the reaction described above. It is believed⁶ that the reaction pathways are different.

The $I_2-(SCN)_2$ system reacts with unsymmetrical aliphatic alkenes to give regioisomeric iodothio- and iodoisothiocyanates. The main reaction products with 4-methylpent-1-ene in benzene are 2-iodo-4-methylpentyl thiocyanate **94**, 1-iodo-4-methylpentane-2-yl thiocyanate **95**, 2-iodo-4-methylpentyl isothiocyanate **96**, and 1-iodo-4-methylpentane-2-yl isothiocyanate **97**.⁷³ The total yield and ratio of the reaction products depend on experimental conditions, in particular on the quality of lead thiocyanate used for the preparation of thiocyanogen solutions. The highest yield of the reaction products (72%) and satisfactory selectivity are observed when the process is carried out in the dark in oxygen-free nitrogen. Iodothiocyanates **94** and **95** were isolated in 17% yield (ratio 3:1) and the yield of iodoisothiocyanates **96** and **97** was 51% (ratio 1:2).

Similar results were obtained in the reaction with oct-1-ene and 3,3-dimethylbut-1-ene. The reaction with oct-1-ene gives a mixture of 2-iodooctyl thiocyanate **98** and 1-iodooctane-2-yl thiocyanate **99** in 18% total yield (ratio 1.5:1) and a mixture of 2-iodooctyl isothiocyanate **100** and 1-iodooctane-2-yl isothiocyanate **101** in 55% total yield (ratio 1:2). The reaction with 3,3-dimethylbut-1-ene affords 3,3-dimethyl-2-iodobutyl thiocyanate **102** (10%), 3,3-dimethyl-2-iodobutyl isothiocyanate **103** (40%), and 3,3-dimethyl-2-iodobutane-2-yl isothiocyanate **104** (2%).

In this case, the formation of a iodonium ion of the type **93**, which is attacked by a nucleophile from the less sterically hindered side, is also assumed.⁷³

It is noteworthy that with an $I_2-(SCN)_2$ system as the reagent, the proportion of vicinal iodoisothiocyanates in the reaction products exceeds significantly that of iodothiocyanates. It was noted⁶ that the fraction of iodothiocyanates formed is substantially larger when the I_2 –KSCN system is used. This tendency is also confirmed by the results of the reaction with 4-*tert*-butylcyclohexene in chloroform. Iodothiocyanates **105** and **106** in the 5:4 ratio were obtained as the main products (total yield 65%), and the yield of iodoisothiocyanates **107** and **108** was only 12% (ratio 5:4).⁶



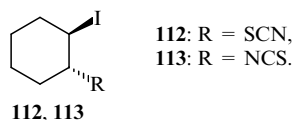
105: R = SCN, R' = I; **106**: R = I, R' = SCN;
107: R = NCS, R' = I; **108**: R = I, R' = NCS.

It is assumed that the reaction products mentioned above are formed as a result of diaxial opening of *cis*- and *trans*-iodonium ions. The regioisomeric ratio indicates that the reaction pathway via a *cis*-iodonium ion is slightly preferred (5:4).⁶

The reaction with 3-*tert*-butylcyclohexene gives *trans*-adduct **109a** and unsaturated compounds **110** and **111**.⁶

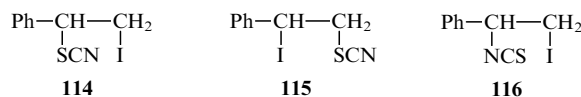


Syntheses of vicinal iodothiocyanates and iodoisothiocyanates were carried out^{75,76} using the ICl –KSCN, I_2 –KSCN, and I_2 –TISCN systems in organic solvents and in a water–organic solvent system in the presence of phase transfer catalysts. Methyltrialkyl(C_8 – C_{10})ammonium chlorides (Adogen 464) or 18-crown-6 ether were used as catalysts. The structure and yields of the reaction products depend considerably on the reaction conditions. The reaction of cyclohexene with the KSCN– I_2 system in a chloroform–sulfolane mixture or in chloroform gives almost exclusively *trans*-2-iodocyclohexyl thiocyanate **112** (96%).



The use of the I_2 –TISCN system in a chloroform–sulfolane mixture at 0–3 °C was found to be optimum for the synthesis of *trans*-2-iodocyclohexyl isothiocyanate. In this case, the yield of isothiocyanate **113** was 60%. In addition, up to 15% of thiocyanate **112** was formed.

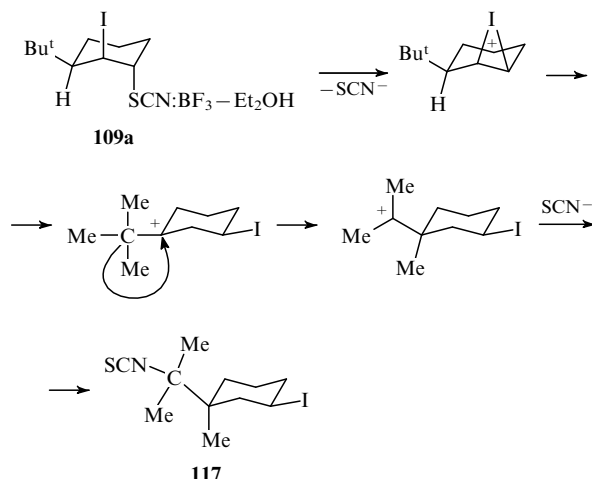
In the reaction with styrene **8c**, the highest yield (72%) of 2-iodo-1-phenylethyl thiocyanate **114** was obtained with the use of the KSCN– ICl system in a chloroform–sulfolane mixture (1:9) at 0–3 °C. The selectivity decreases abruptly under different conditions, and 2-iodo-2-phenylethyl thiocyanate **115**, 2-iodo-1-phenylethyl thiocyanate **116**, and products **9c** and **10c** are formed in addition to adduct **114**. Treatment of iodothiocyanate **114** with boron trifluoride etherate in chloroform gives iodoisothiocyanate **116** in 89% yield.



The reaction of β -methylstyrene with the TISCN– I_2 system in the presence of boron trifluoride etherate occurred most efficiently in $CHCl_3$. In this case, 2-iodo-1-phenylpropyl isothiocyanate (74%) and the product **89** (15%) were isolated.

Thus, performing the reaction in the presence of BF_3 etherate was one of the methods for the selective synthesis of iodoisothiocyanates in the studies cited above.^{75,76} Its addition favours the isomerisation of iodothiocyanates into iodoisothiocyanates. However, this method is not always efficient. For example, such a treatment of thiocyanate **109a** gave compound **117** (26%) instead of the expected isothiocyanate **109b**; the formation of

compound **117** was explained⁶ by the migration of the methyl group in the intermediate carbocation.

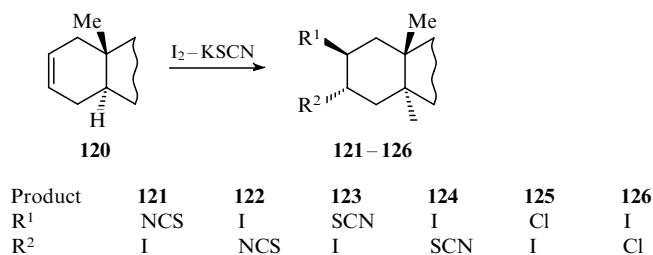


If the reaction is carried out in a chloroform–sulfolane mixture (1:9) in the presence of the ICl–KSCN system, the adduct **109b** (yield 51%) is formed along with a small amount (3%) of the product **117**. Performing the reaction under different conditions did not increase the selectivity of the process.

In order to perform selective iodoisothiocyanation of α -methylstyrene, the reaction was carried out either in a chloroform–water mixture (10:1) in the presence of the phase transfer catalyst Adogen 464 using the KSCN–I₂ system or in sulfolane with the TISCN–I₂ system with an addition of boron trifluoride etherate. In these cases, 1-iodo-2-phenylpropane-2-yl isothiocyanate was formed in 71% and 76% yields, respectively.⁷⁶

Iodoisothiocyanation of indene **36** in sulfolane results in *trans*-2-iodoindan-3-yl isothiocyanate **118** and *trans*-2-iodoindan-3-yl thiocyanate **119**. When the reaction mixture was kept for 2 h, compounds **118** and **119** were isolated in 43% and 26% yields, respectively, while after 23 h, adduct **118** was formed preferentially (88%).⁷⁶ If the reaction was carried out under different conditions, a more complex mixture of products was formed.

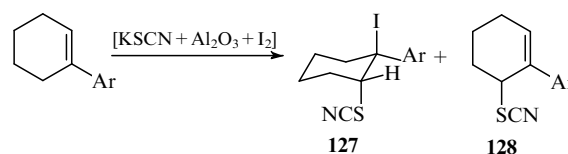
5 α -Androstene **120** reacts very slowly with the systems considered above. The degree of conversion of this steroid was small when it was treated with I₂–KSCN in chloroform in the presence of a phase transfer catalyst. After 92 h, a mixture of products was isolated from the reaction mixture: 3 α -iodo-2 β -isothiocyanato- **121** and 2 β -iodo-3 α -isothiocyanato-5 α -androstanes **122** in the 7:1 ratio (total yield 23%); 3 α -iodo-2 β -thiocyanato- **123** and 2 β -iodo-3 α -thiocyanato-5 α -androstanes **122** in the 5:1 ratio (total yield 34%), as well as 3 α -iodo-2 β -chloro- **125** and 2 β -iodo-3 α -chloro-5 α -androstanes **126** in the 2.4:1 ratio (total yield 2%).⁷⁶



The effect of the metal ion in the system iodine–metal thiocyanate on the reaction with alkenes was studied.⁷ In the reaction of this system with cyclohexene, the maximum yield (88%) of the products **112** and **113** and a high selectivity (**113**:**112** = 91:9) of the process was observed when Hg(SCN)₂ was a component of the system. With TISCN or AgSCN, the total yield and the selectivity decrease dramatically. The reaction does

not occur in the presence of Ni(SCN)₂ and Pb(SCN)₂. The highest selectivity of the formation of the adduct **112** was achieved with KSCN (**113**:**112** = 3:97; total yield 78%). Similar results were obtained for cyclopentene, cycloheptene, and *trans*-hex-3-ene. The reaction with Hg(SCN)₂ gives the corresponding iodoisothiocyanates in 65%–70% yield, and iodothiocyanates are mainly formed (60%–70%) in the reaction with KSCN. It is assumed⁷ that alkenes react with ISC⁺ through a iodonium ion, which reacts with the I(SCN)₂[−] complex ion to give iodoisothiocyanates and with [−]SCN to give iodothiocyanates.

The regioselective synthesis of 2*e*-aryl-2*a*-iodocyclohexyl 1*a*-thiocyanates **127** by the reaction of 1-arylcyclohexenes with a complex system KSCN–Al₂O₃–I₂ in chloroform was carried out.⁷⁷ The yield of thiocyanates **127** was ~40%. In addition to thiocyanates **127**, 2-arylcyclohex-2-enylthiocyanates **128** were obtained in ~60% yield. The formation of the latter is explained⁷⁷ by the elimination of a HI molecule from adducts **127**.



Ar = Ph, 4-MeC₆H₄, 3,4-Me₂C₆H₃, 4-Bu^tC₆H₄, 4-MeOC₆H₄.

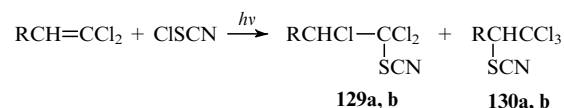
III. Homolytic reactions of thiocyanogen and thiocyanogen halides with alkenes

Homolytic reactions of thiocyanogen and thiocyanogen halides are initiated by ultraviolet irradiation. Under these conditions, thiocyanogen and its halo-derivatives exhibit high reactivity in addition reactions. For example, CISCN reacts with vinyl chloride, 1,1-dichloroethylene, *cis*- and *trans*-1,2-dichloroethylenes, and other similar compounds under UV irradiation; no reaction occurs without UV irradiation.⁷⁸ The yields of reaction products depend on the solvent and the intensity of irradiation. In the reaction of CISCN with *cis*- and *trans*-1,2-dichloroethylenes, the maximum yield of 1,2,2-trichloroethyl thiocyanate (60%) was obtained in acetic acid in a nitrogen atmosphere; the distance of the reactor from the source of irradiation was 1 cm, and the reaction time was 1 h. Under these conditions, tetrachloroethylene was more inert, and the yield of 1,1,2,2,2-pentachloroethyl thiocyanate was only 11% after 12 h.

Tetraphenylethylene and *trans*-ethylene 1,1-dithiocyanate appeared to be inert under these conditions; the latter was transformed into an equilibrium mixture of *cis* and *trans*-isomers.

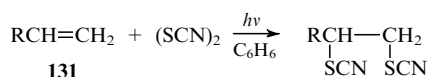
The reaction of CISCN with vinyl bromide affords a mixture of 1-bromo-2-chloro- and 2-bromo-2-chloro-ethyl thiocyanates in 61% and 9% yields, respectively.

Regioisomeric products are also formed in reactions of CISCN with 1,1-dichloro- and trichloroethylenes. In this case, 1,1-dichloroethylene gives a mixture of adducts **129a** (55%) and **130a** (4%), and trichloroethylene forms products **129b** and **130b** in 52% and 6% yields, respectively.

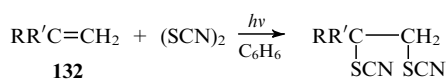


R = H (a), Cl (b).

A comparison of the results of reactions of thiocyanogen with aliphatic and alicyclic alkenes under homolytic⁷⁹ and heterolytic⁴⁰ conditions was carried out. The yields of the products are higher in a radical reaction even after shorter reaction times. The reaction with many alkenes is completely selective, e.g., the reactions of alkenes **131** and **132** gives only α,β -dithiocyanates in 70%–98% yields.⁷⁹



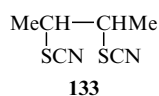
R = H, Me, Bu, Bu^t, Me(CH₂)₇, Me(CH₂)₁₇, Cl, Br, Ph.



R = R' = Me; R = R' = Et; R = Ph, R' = Me.

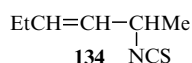
The reaction of thiocyanogen with 3-methylbut-1-ene is less selective. In addition to 3-methylbutane-1,2-diyl dithiocyanate (63%), unsaturated compounds, viz., 2-methylbut-3-ene-2-yl isothiocyanate and 3-methylbut-2-enyl isothiocyanate, are formed.

As could be expected, the stereochemistry of the radical reaction differs from that of the heterolytic reaction. *trans*-β-Methylstyrene reacts with (SCN)₂ to form adducts **89** with *threo*- and *erythro*-configurations in 14% and 80% yields, respectively. The reaction with *cis*- and *trans*-but-2-enes is not stereoselective. A mixture of (±)- and *meso*-diastereomeric adducts **133** is formed from both isomers. The yields of the adducts are 37% and 57% for the *cis*-alkene and 39% and 60% for the *trans*-alkene.



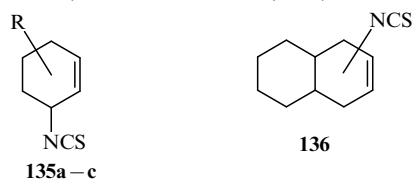
The reaction of thiocyanogen with *cis*- and *trans*-stilbenes is also non-stereoselective. The products of this reaction will be discussed later.

The reaction with *cis*- and *trans*-hex-3-enes occurs in a more complex way. In addition to the adduct **19** (21%), (*E*)-hex-3-en-2-yl isothiocyanate **134** (48%) is formed as a mixture of (±)- and *meso*-diastereoisomers.⁷⁹ A somewhat different ratio of the products of this reaction is given by Maxwell *et al.*⁴⁸ Compounds **134** and **19** were isolated in 45% and 39% yield, respectively, upon thiocyanation of a *cis*-alkene, and in 60% and 33% yields upon thiocyanation of a *trans*-alkene. In addition, insignificant amounts of adducts with the isothiocyano group were obtained (6.5% and 14.5%, respectively, for *trans*- and *cis*-hex-3-enes).



The reaction of *cis*- and *trans*-2,5-dimethylhex-3-enes resulted only in products of the substitution of hydrogen at the allylic position, *trans*-2,5-dimethylhex-3-en-2-yl isothiocyanate and 2,5-dimethylhex-4-en-3-yl isothiocyanate, in ~29% total yield.⁷⁹

Unsaturated compounds of the type **135a–c** are formed as the main products in reactions of (SCN)₂ with cyclohexene and 4-methyl- and 4-*tert*-butylcyclohexenes (yields 40%–50%).⁷⁹ Compounds **135b,c** were obtained as a mixture of isomers, and their structure was not fully determined.⁷⁹ The reaction with *trans*-Δ²-octalin **29** occurs similarly to give a mixture of isomeric compounds of the type **136** (the structure was not determined, yield 45%) and the adduct **30** (40%).

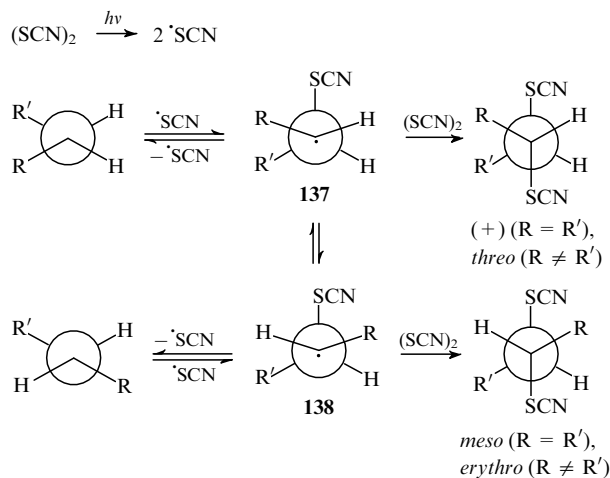


R = H (**a**), Me (**b**), Bu^t (**c**).

The reactions occur much more slowly in the presence of oxygen and other inhibitors of radical processes. A mechanism

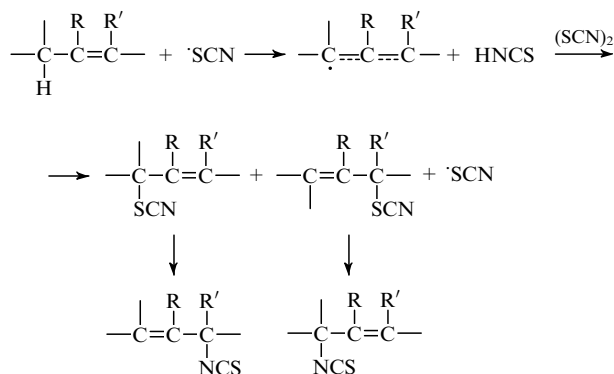
presented in Scheme 1 was suggested on the basis of stereochemical data.⁷⁹

Scheme 1

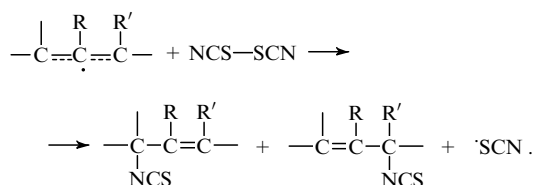


Allylic isothiocyanates are probably formed according to Scheme 2.⁷⁹ The primary reaction products include allylic thiocyanates, which isomerise rapidly into more thermodynamically stable isothiocyanates.

Scheme 2



An alternative scheme was suggested⁷⁹ according to which allylic isothiocyanates are formed directly through the reaction of the allylic radical with the nitrogen atom of thiocyanogen, which is more readily accessible sterically.



An increase in the number of methyl groups at the carbon atom of the double bond increases the time required for the reaction. This also leads to a considerable increase in the fraction of adducts of the type **6** in the reaction mixture.⁸⁰ This trend also holds for alkenes with phenyl substituents. For example, the reaction of *trans*- and *cis*-1,2-diphenylethylenes gives products with the isothiocyanate groups in 16%–18% yields as a mixture of *erythro*- and *threo*-1,2-diphenyl-2-isothiocyanatoethyl thiocyanates **139a**. However, the main reaction direction is the formation of 1,2-diphenylethane-1,2-diyl dithiocyanates **139b** (a mixture of (±)- and *meso*-forms) in 73% yield. The reaction of (SCN)₂ with 1,1-diphenylethylene and triphenylethylene gave 2,2-diphenyl-**140a** and 1,2,2-triphenyl-2-isothiocyanatoethyl thiocyanates **140b**, respectively;⁸⁰ α,β-dithiocyanates were not found in the reaction mixture.

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Chemical approaches to the elucidation of template biosynthesis: study of replication and reverse transcription

D G Knorre, N V Kudryashova, O I Lavrik

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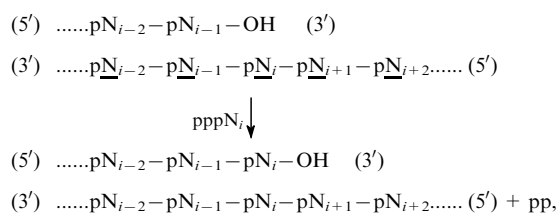
Abstract. Chemical approaches to the elucidation of DNA template biosynthesis using DNA polymerases and reverse transcriptases, predominantly DNA polymerase I from *E. coli* and reverse transcriptase from HIV-1, are considered. Special attention is paid to the comparison of chemical modification and X-ray structural analysis data as well as to quantitative aspects of the interaction of DNA polymerases with templates, primers, and nucleoside 5'-triphosphates. New versions of a catalytically competent labelling method developed in the course of investigation of these enzymes are described. The data obtained in the analysis of replication complexes using primer analogues with photoreactive groups are presented. The bibliography includes 98 references.

I. Introduction

Some general problems concerning the application of chemical approaches to the study of the mechanism of template biosynthesis of nucleic acids and the main results obtained in the study of enzymes that catalyse RNA biosynthesis (transcription) by chemical methods have been reviewed.¹ The present review is devoted to the application of chemical methods to the study of DNA biosynthesis, namely, its replication and reverse transcription.²

The main chemical event in this process, *viz.*, the elongation of the polynucleotide chain, in the case of DNA polymerases is fully identical with that for RNA polymerases considered previously.¹ A nucleoside triphosphate (pppN_i) complementary to the translatable element pN_i of the template (its role is played by single-stranded DNA) phosphorylates the 3'-OH group of the 3'-terminal nucleotide residue of the growing DNA chain. It is in this way that the nucleotide residue is transferred from the triphosphate to

the 3'-OH group of the growing polymeric chain; therefore the enzyme represents a nucleotidyl transferase.



where p is the orthophosphate residue; N_i and N_i are the nucleoside residues in the product and the template, respectively, and *i* is the ordinal number of the residue in the polynucleotide chain starting from the 5'-end of the product and the 3'-end of the template, respectively.

However, this is virtually the last point where the similarity between DNA polymerases and RNA polymerases ends. RNA polymerases interact with double-stranded DNA, which are temporarily unwound under the action of this very enzyme to form a non-extended unwound region (protrusion). One of the unwound strands (on which transcription occurs) becomes involved in the selection of a substrate in the active centre. If the replication is accomplished by DNA-dependent DNA polymerases, the double-stranded DNA is first unwound by a special system mentioned below. DNA polymerase is not directly involved in DNA unwinding.

Transcription begins at a predetermined site of the template and requires preliminary binding of the enzyme in the region where the transcription begins (the promoter region). Following the formation of a complex with an enzyme and specific transcription factors at the required region of DNA subject to transcription the process is initiated, *i.e.*, the synthesis of a dinucleotide occurs. It should be noted that the first dinucleotide residue retains a triphosphate group. Initiation of DNA synthesis in living organisms always begins with the synthesis of a ribooligonucleotide primer the 3'-terminal OH group of which serves as an acceptor of deoxyribonucleotide 5'-phosphate. It is not until this process has been completed that the synthesis of a new DNA chain begins. The 3'-terminal deoxyribonucleotide fragment now acts as a primer. A special enzyme, primase, in prokaryotes and eukaryotes is responsible for the synthesis of a ribooligonucleotide

D G Knorre, N V Kudryashova, O I Lavrik Novosibirsk Institute of Bioorganic Chemistry, Siberian Branch of the Russian Academy of Sciences, prosp. Akad. Lavrent'eva 8, 630090 Novosibirsk, Russian Federation. Fax (7-383) 235 16 65. Tel. (7-383) 235 64 61 (D G Knorre)

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primer; therefore the primary product is a hybrid oligonucleotide, which has a ribooligonucleotide at its 5'-end.

The region where the direct chemical conversion takes place contains a complex of the 3'-terminal nucleotide of the primer with a complementary nucleotide of the template, the protruding single-stranded fragment of the template and the selected substrate. Therefore, it makes no difference whether we deal with an exogenous primer or the terminus of a newly synthesised strand.

In the case of RNA polymerases, the product is a single-stranded RNA fixed by complementary interactions to the strand of the template subjected to transcription only at its 3'-end. In the case of DNA polymerases, a duplex is formed, which is preserved in biological systems up to the beginning of the next replication cycle. In this context, the range of problems that can be solved by chemical methods in respect of DNA polymerases differs from that for RNA polymerases described in the review cited.¹ It is also noteworthy that X-ray data about the spatial structure of DNA polymerases and their complexes with templates and substrates are now more abundant. Therefore, it is expedient to consider the large body of experimental results concerning the chemical (including affinity-based) modification of DNA polymerases in relation to the X-ray data available. Much of the above can be said of the enzymes responsible for reverse transcription, *i.e.*, to RNA-dependent DNA polymerases (reverse transcriptases).

While considering DNA polymerases, special mention should be made of two groups of enzymes differing in their biological functions. One of them is responsible for the synthesis of new DNA molecules, which occurs *via* separation of strands of the parent DNA and the formation of daughter replicas on each of the separated strands. This results, with the accuracy of inevitable errors, in the formation of two double-stranded structures that are identical with the original one. However, this process requires the participation of several additional enzymes and proteins. The unwinding of the double helix is effected by enzymes called helicases. They function in the branching region of the original double helix, namely, in the replication fork. The recombination of the two strands is prevented owing to their binding to a special protein, most commonly referred to as the SSB (single strand binding) protein. Continuous synthesis of a complementary chain towards the replication fork takes place on one of the strands with a 5' → 3' orientation from the replication fork. This strand is usually named the leading strand. The synthesis on the second strand can proceed only in the direction away from the replication fork, and a new initiation must take place at certain intervals of time with the liberation of the template. In other words, the synthesis of a new RNA primer, which is further elongated in the direction away from the replication fork, takes place. Thus, the fragments of the daughter strand with a ribonucleotide at the 5'-end (Okazaki fragments) are the products of synthesis on this lagging strand. A hybrid DNA-RNA duplex is formed at the primer site. Its RNA fragment must be removed from the final replication product. This is achieved, at least partly, with a special enzyme, RNase H, which catalyses the hydrolysis of ribooligonucleotides within this hybrid duplex. The preceding Okazaki fragment can then be elongated with DNA polymerase to reach the 5'-end of the second chain. As a result, the lagging daughter strand is formed with ruptures called nicks. Linking of 5'-phosphate with the 3'-OH group of the preceding fragment requires yet another enzyme, DNA ligase, which catalyses the formation of a phosphodiester bond between these two groups. Thus, a minimum set of replication enzymes and auxiliary proteins includes DNA polymerase itself, helicases, the SSB protein, RNase H, and DNA ligase.

As a matter of fact, this set is even greater. An important feature of the replication process is its processivity. After elongation, the 'template-elongated primer' system is not separated from the enzyme. Instead, a new encoding element of the template and the 3'-end of the elongated primer are transposed relative to the enzyme in such a way that they appear in the active centre of the enzyme. There is a large body of evidence that the processivity is

provided by special auxiliary proteins that consolidate the enzyme complex with the template-primer duplex. These proteins are called 'clamps'.³

The second group of DNA polymerases cannot synthesise complete daughter replicas, but they are necessary to fill short gaps that often appear on one of DNA strands. The classical example of such gaps is the excision of damaged regions of one of DNA strands by special enzymes that play an important role in restoring injured sites (DNA repair). Therefore, DNA polymerases pertaining to this group are often regarded as DNA repair enzymes, although their functions are hardly confined to repair. DNA polymerase I from *E. coli* and human DNA polymerase β are the most well-studied enzymes of this group. The spatial structure of these two enzymes has been established by X-ray structural analysis.

II. The main types of affinity reagents used for the study of replication and reverse transcription

Application of affinity-based modification to the study of enzymes is particularly efficient in two cases. First, when it is necessary to determine the position of a site(s) of modification of an enzyme by a reactive substrate or effector analogue, which points either to a subunit or a region in the protein molecule that interacts with the substrate or the effector. Second, when it is necessary to determine the affinity of a substrate or a cofactor for the protein from the data on the competition between the reagent and the substrate (or the cofactor).⁴ The second case will be considered in more detail in Section V.

DNA polymerases and reverse transcriptases interact with the template, the primer, and deoxynucleoside 5'-triphosphate (further referred to as dNTP). In the case of DNA polymerases, the strands of a double-stranded DNA are first unwound by helicases. Thus, single-stranded DNA serves as a template for replication. There is every reason to believe that reactive derivatives of DNA modify the enzyme at the binding site of the template.

One of the strands in double-stranded structures corresponds to the template, and the other one to the primer. If a complex of two DNA fragments has both a double-stranded and a hanging one-stranded element and the shorter fragment at their junction has a free 3'-OH group, it is this fragment that functions as a primer. Complex 1 is an example which can be useful for further consideration:



1

Apparently, it is the upper strand in this complex that plays the role of a primer. However, the situation with dNTP analogues is not so unambiguous. Even in the framework of a simplified scheme implying the existence of distinctly separated binding sites for a template, a 3'-terminal fragment of the template, and a dNTP, a dNTP analogue will not necessarily form a complex with the binding site of the substrate. It will be shown later (see Section V) that dNMP and dNDP also possess affinity for the binding site of the template. As a result, modification of an enzyme by such an analogue will not allow the unambiguous assignment of the modified region of the protein to the binding site of dNTP because it may be the binding site of the template as well.

Introduction of reactive groups into dNTP can be easily carried out at the γ -phosphate⁵ *via* nucleoside 5'-trimetaphosphate. Using this route, derivatives containing 4-(*N*-2-chloroethyl-*N*-methylamino)benzylamine,^{6,7} imidazole,^{8,9} and *p*-azidoaniline residues¹⁰ were obtained. In the case of alkylating and phosphorylating derivatives, the inactivation proceeded only in the presence of a template-primer complex. This can be regarded as evidence in favour of analogue binding in the substrate-binding site.⁶⁻⁹ In the case of a photoaffinity reagent (*p*-azidoaniline derivative), inactivation was also observed upon irradiation in the absence of the complex, but its presence enhanced inactiva-

tion.¹⁰ A wide variety of dNTP analogues with a photoreactive group in the heterocyclic base have been recently synthesised. Derivatives containing a photoreactive group at position 4 of cytosine, at position 5 of uracil (dTTP analogues), and at positions 2 and 8 of adenine have been described and tested.^{11–20} Table 1 lists the presently known dNTP containing reactive groups in their heterocyclic bases. It is important to mention that some of these

compounds can act as substrates for DNA polymerase. This property makes it possible to use these analogues for specific photoaffinity-based modification of DNA polymerases.

Photoreactive analogues must possess good photochemical characteristics that allow their irradiation at the wavelengths that cause no photoinactivation of proteins and nucleic acids.¹¹ At the same time, these analogues manifest good substrate properties in

Table 1. Derivatives of dNTP containing photoreactive groups in the heterocyclic base.

Photoreactive group	Position of the group in the heterocycle	Substrate properties	Modification (inactivation)
N ₃	Ade-8	–	Modification of Ile765 and Tyr766 in DNA polymerase I from <i>E. coli</i> in the absence of a template–primer duplex ¹⁷
$\text{SCH}_2\text{CC}_6\text{H}_4\text{N}_3\text{-}p$ $\text{O}=\text{C}$	Ade-2	Competitive inhibitor with respect to dTTP ¹⁹	Inactivation of the Klenow fragment in the absence of a template–primer duplex ¹⁸ Inhibition of modification in the presence of poly(dA)–oligo(dT) ¹⁸ Labelling of Asp732 ¹⁸
$\text{CH}_2\text{—CH}_2\text{—NH—C—C}_6\text{F}_4\text{N}_3\text{-}p$ $\text{(FAB)} \quad \text{O}=\text{C}$	Cyt-4	Substrate of DNA polymerase from human α -primase instead of dTTP ²¹ Substrate of reverse transcriptase from HIV-1 instead of dCTP ¹³ and dTTP ¹⁶	Modification of the 165, 59, and 49 kDa subunits (the human complex) ²³ Modification of the 165 and 49 kDa subunits (the human complex, competent labelling) ²³ Modification of the 150, 59, and 48 kDa subunits (the calf thymus complex) ²³ Modification of p66 and p51 ¹⁴ Modification of p66 (competent labelling) ¹⁴
$\text{CH=CHCH}_2\text{NHCC}_6\text{F}_4\text{N}_3\text{-}p$ $\text{(AIFAB)} \quad \text{O}=\text{C}$	Cyt-4	–	Decrease in substrate properties and enhancement of terminating properties
$\text{CH}_2\text{—CH}_2\text{—NH—C—C}_6\text{H}_3\text{N}_2\text{NO}_2$ $\text{(NAB)} \quad \text{O}=\text{C}$	Cyt-4	Substrate of DNA polymerase from α -primase of calf thymus ¹⁵ Substrate of reverse transcriptase from HIV-1 instead of dCTP and dTTP ¹⁶	Decrease in substrate properties and enhancement of terminating properties
$(\text{CH}_2)_2\text{NHCCH}_2\text{ON=CHC}_6\text{F}_4\text{N}_3\text{-}p$ $\text{O}=\text{C}$	Cyt-4	Substrate of reverse transcriptase from HIV-1 instead of dCTP and dTTP ¹⁶	Decrease in substrate properties and enhancement of terminating properties
$\text{C}(\text{CH}_2)_3\text{ON=CHC}_6\text{F}_4\text{N}_3\text{-}p$ $\text{O}=\text{C}$	Cyt-4	Substrate of reverse transcriptase from HIV-1 instead of dTTP ¹⁶	Decrease in substrate properties and enhancement of terminating properties
$\text{NHC}(\text{CH}_2)_4\text{CNH—N=CHC}_6\text{F}_4\text{N}_3\text{-}p$ $\text{O}=\text{C} \quad \text{O}=\text{C}$	Cyt-4	Substrate of reverse transcriptase from HIV-1 instead of dCTP and dTTP ¹⁶	Decrease in substrate properties and enhancement of terminating properties
$\text{CH=CHCH}_2\text{NHCC}_6\text{F}_4\text{N}_3\text{-}p$ $\text{O}=\text{C}$	Cyt-5	Substrate of DNA polymerase from α -primase of calf thymus ²³ Substrate of reverse transcriptase from HIV-1 ¹⁴	Modification of p66 and p51 Modification of p66 (competent labelling) ¹⁴
N ₃	Ura-5	–	Modification of DNA polymerase I from <i>E. coli</i> in the absence of a template–primer duplex ²⁴
$\text{HC=CH—CH}_2\text{—NH—C—C}_6\text{H}_3\text{N}_2\text{NO}_2$ $\text{O}=\text{C}$	Ura-5	Substrate of reverse transcriptase from HIV-1 instead of dTTP ¹⁵	Modification of p66 and p51
$\text{CH=CH—C}_6\text{H}_4\text{—C—CF}_3$ N=N	Ura-5 (ddUTP)	Substrate of reverse transcriptase from HIV-1 instead of dTTP ²⁰	Modification of p66

reactions catalysed by DNA polymerase α from human placenta,²¹ reverse transcriptase from HIV,^{13–16} and DNA polymerase β .¹² These substrates can act as terminators by preventing further elongation of α primer after being incorporated into its 3'-end. In other cases, the presence of a modified residue at the 3'-end does not prevent the addition of the next unit, *i.e.*, further elongation of the chain. These derivatives can be used for conducting the polymerase chain reaction (PCR), which yields a duplex with a large number of reactive groups.²² The corresponding characteristics of reactive dNTP derivatives are listed in Table 1.

Despite the apparent similarity of analogues containing reactive groups at the same positions, their properties as affinity reagents may vary substantially. Thus three dATP analogues containing 4-N₃C₆H₄CH₂S, 4-N₃C₆H₄SS, and 2-NO₂-4-N₃C₆H₃S groups at position 2 of adenine have been described.¹⁹ It was found that only the first of them could inactivate the Klenow fragment of DNA polymerase I upon irradiation (see Section III.1). It should be noted that inactivation does not require the presence of a template–primer duplex. Modification reaches saturation when one residue is incorporated into the enzyme. Although the modifying reagent is based on dATP, its competitive substrate is dTTP. Moreover, this modification is inhibited by the poly(dA)–oligo(dT) duplex, which may attest to the binding of the analogue in the template region of the enzyme.¹⁸

Among other nucleotide analogues having a reactive group in their carbohydrate fragment, 2',3'-epoxyATP has been studied in more detail. In the presence of the duplex **1**, the enzyme was inactivated in accordance with the classical law of affinity-based modification;⁴ its K_d was 21 μ M and the inactivation rate constant was 0.021 s^{−1}. The 2',3'-epoxyAMP residue was incorporated into the primer simultaneously with inactivation. Naturally, the residue incorporated played the role of a terminator. It was shown²⁵ that the duplex carrying this residue at its terminus did not modify the enzyme; its inhibitory effect is due to the enhanced stability of a triple complex with the enzyme.

Sometimes, DNA derivatives designed for modification of DNA-binding sites of an enzyme can be obtained by direct introduction of a reactive group into the DNA molecule or its fragment. Thus the decanucleotide d(pT)₂pC(pT)₇ modified at the N(3) atom of the cytosine residue with *cis*-aquahydroxodiammineplatinum, *i.e.*, containing the *cis*-{(NH₃)₂Pt[N(3)-dC](OH)} fragment, was used as an affinity reagent for the matrix site of DNA polymerase α from human placenta and the Klenow fragment of DNA polymerase I.^{26–28} Incubation of this decanucleotide with the enzyme results in gradual inactivation of the latter. This inactivation is competitively inhibited by deoxyoligonucleotides of various lengths and structures.

Since both the template and the primer have sufficiently extended contacts with the enzyme, when used as the affinity reagents (DNA analogues), it is especially desirable to obtain a series of derivatives with a reactive group at different predetermined positions of DNA. Two main approaches to the synthesis of these derivatives have been developed. One of them is based on the introduction of a reactive group during the synthesis of the corresponding oligonucleotide. Naturally, this approach can be used only for derivatives with a reactive group in their heterocycles. One can also synthesise DNA or an oligonucleotide derivative containing a group where the reactive residue will be introduced in the final stage of the synthesis. As an example, we can mention the synthesis of a series of primer analogues with a photoreactive group at different positions relative to the 3'-end of the growing chain.²⁹ Thus a thymidine analogue containing a (CH₂)₃NHCOCF₃ residue at position 5 of uracil was introduced instead of thymidine into a specific position of the primer during the synthesis.²⁹ After removal of the trifluoroacetyl group by mild alkaline hydrolysis, the primer was treated with 5-azido-2-nitrobenzoic acid *N*-hydroxysuccinimide ester. Then the modified primer was hybridised with DNA from phage M13 used as a template and elongated by one unit with DNA polymerase from

phage T4 using [α -³²P]ddATP as a substrate. The final procedure sharply diminishes the risk of cleavage of the 3'-terminal residue due to 3' → 5' exonuclease activity inherent in the enzyme and allows simultaneous introduction of the radioactive label into the primer. This step is essential for the affinity-based modification with this compound. Using this approach, primers with a photoreactive arylazide group at positions 3, 9, 13, 18, 22, 27, and 46 relative to the 3'-terminal fragment have been obtained.²⁹ When the corresponding template–primer duplex is used, the reactive residues can be introduced into the specific positions of the primer by the enzymic method using dNTP analogues bearing a reactive group as DNA polymerase substrates.^{12, 14, 15, 23}

The second approach to the synthesis of DNA with a predetermined position of the label can be exemplified by the synthesis of a series of derivatives of oligonucleotide primers with different positions of the fluorescent label relative to the 3'-end of the primer. A set of such derivatives were obtained³⁰ from one oligonucleotide with a thymidine analogue U* at a definite position; this analogue contained the fluorescent 5-dimethylaminonaphthalene-1-sulfonyl group at position 5 instead of the methyl group. The starting duplex had the structure **2**.



2

The structure of the template allowed the elongation of the primer in the presence of DNA polymerase, by one unit (compound **3**) with dCTP, by three units (compound **4**) with dCTP + dATP, and by six units (compound **5**) with dCTP + dATP + dGTP. The fluorescent label was translocated at a certain distance from the enzyme active centre.



3



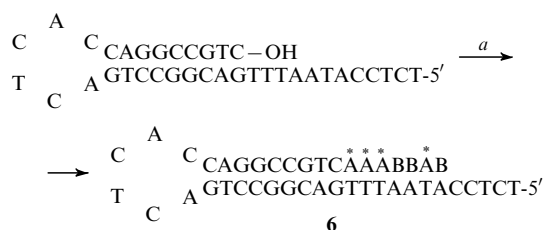
4



5

In some experiments, it was possible to use a hairpin structure with a hanging single-stranded fragment instead of a template–primer duplex. Such a structure mimics the template–primer duplex and the short fragment of the hairpin stem can be elongated in the presence of DNA polymerase. When photoreactive dNTP are used for elongation, a photoreactive stem mimicking the photoreactive duplex can be obtained.

This approach was used in particular for the synthesis of a hairpin containing several residues of bromodeoxyuridine (compound **6**).³¹



6

*A is the radiolabelled dAMP residue,

B is 5-bromodeoxyuridine;

(a) DNA polymerase, [α -³²P]dATP + BrdUTP (BrdUTP is 5-bromodeoxyuridine triphosphate).

This hairpin structure has been used for photoaffinity-based modification of DNA polymerase γ (mitochondrial DNA polymerase) from frog (*Xenopus*) and DNA polymerase ϵ from calf thymus.³²

III. Study of the interaction of DNA polymerases with templates, primers, and nucleoside 5'-triphosphates using group-specific and affinity-based chemical modification. Structural aspects

1. DNA polymerase I from *E. coli* and the Klenow fragment

This enzyme is made up of one polypeptide chain (M_r is 103 kDa, 928 amino acid residues) and forms three domains. The N-terminal domain (1–330) comprises an active centre for 3' → 5' exonuclease activity and catalyses stepwise hydrolysis of nucleotides from the 5'-end. The central domain (residues 331–514) contains an active centre for 5' → 3' exonuclease activity and catalyses the cleavage of the 3'-terminal nucleotide from the growing polynucleotide chain. It is noteworthy that this cleavage is directed predominantly against the residue that is not complementary to the template and thus prevents preservation of an erroneously incorporated monomer. The 515–928 domain contains the DNA polymerase centre itself.³³ Mild treatment of the enzyme with a protease (subtilisin) results in the splitting of the 5' → 3' exonuclease domain to form the so-called Klenow fragment, which retains only two activities and which is now the subject of the most active studies.³⁴

X-Ray structural analyses of the Klenow fragment and of its complexes with a model DNA duplex and with dCTP have been carried out with a resolution of 3.9 Å (Fig. 1).^{35,36} This figure clearly demonstrates the presence of both domains. The N-terminal 5' → 3' exonuclease domain is formed by seven α -helices A–G and four β -structures 1–4. The C-terminal polymerase domain of the Klenow fragment is formed by three subdomains, which have been termed the 'palm', the 'fingers', and the 'thumb' by anatomic analogy with the right hand (Fig. 1). The 'palm' domain consists

of six β -structures 7–9 and 12–14, the 'thumb' domain comprises four α -helices H–K, and the 'fingers' domain is made up of five α -helices L–P. The regions of the other two subdomains that are the most remote from the 'palm' come together to form a cleft where DNA binding takes place. The bottom of this cleft contains carboxy groups of two aspartic acid residues (Asp705, Asp882) and one glutamic acid residue (Glu883) (Fig. 2), which are supposed to coordinate the triphosphate group of the substrate through Mg^{2+} ions. Magnesium ions play an important role in the main catalytic process, being responsible for the transfer of the monophosphate residue to the 3'-OH group of the primer. Similar triads of dicarboxylic acid residues were also detected in other DNA polymerases the spatial structures of which have been studied. Special mention should be made of DNA polymerase β ; its structure in the complex with a dCTP and dATP was established with high resolution both in the presence and in the absence of a template–primer complex.^{37,38} The most detailed information about the contact sites of the template–primer complex with the enzyme was obtained by Modak *et al.*³⁹ These authors performed direct photo-cross-linking of two [5'-³²P]-labelled oligonucleotides, containing 25 and 37 monomeric units the 3'-termini of which formed a hairpin structure with the enzyme. The stem of the hairpin mimicked the template–primer complex. The main modification involved the peptide fragment corresponding to the DNA polymerase fragment 759–775 at Ile765, Tyr766, Ser769, and Phe771 residues in the O helix of the 'fingers' domain.

To obtain information about the binding site for the substrate, a series of investigations were carried out using reactive derivatives of dNTP. These studies began with direct photo-cross-linking of the enzyme with dTTP by irradiation of the enzyme–substrate complex with light at $\lambda = 254$ nm.⁴⁰ It was shown that photoaddition occurred at the His881 residue. As can be seen from

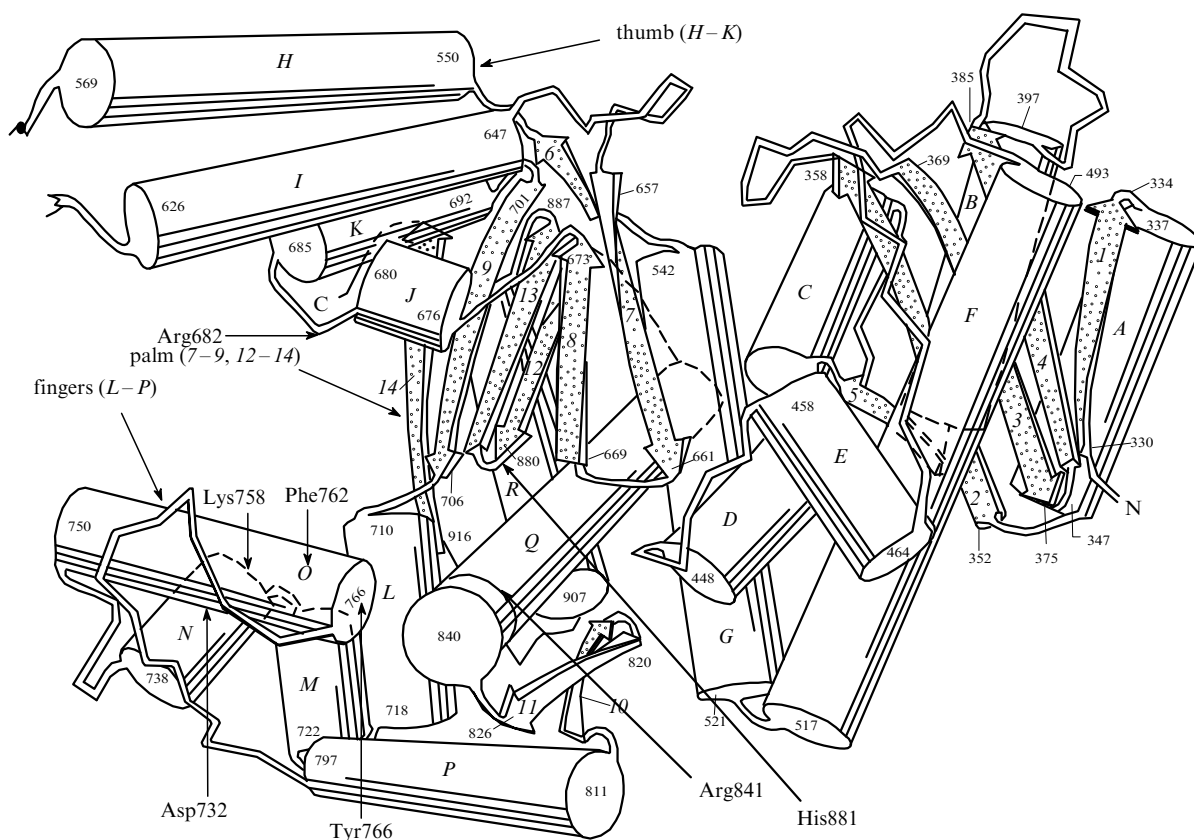


Figure 1. A scheme of the three-dimensional structure of the Klenow fragment of DNA polymerase I from *E. coli*. The α -helical regions of the polypeptide are shown as cylinders; the β -pleated sheet, as ribbons, with arrows indicating the direction of the chain in the folds from the N- to the C-end. The arrows indicate the amino acid residues detected by affinity-based modification.

Fig. 1, this residue is localised between the 12th and 13th β -structures of the 'palm' subdomain. When the Klenow fragment was modified with 8-azido-dAMP, photoaddition occurred predominantly at Tyr776 localised in the α -helix of the 'fingers' subdomain.¹⁷ It is interesting to note that the same tyrosine residue was modified upon irradiation of the enzyme in the complex with the template and the primer analogue 7.⁴¹

3' d(AGCGTCGGCAGGTTCCCAA)
5' d(TCGCAGCCGU*)

7

U* is the residue of the dTMP analogue containing a 5-azido-2-nitrobenzoyl group linked *via* a spacer, (CH₂)₃NH, at position 5.

This coincidence shows that Tyr766 is localised directly in the catalytic centre. Evidence in favour of the presence of a tyrosine residue in the catalytic centre can also be derived from the results of chemical modification of the Klenow fragment by *N*-acetylimidazole, a specific reagent for the OH group of tyrosine. This modification was accompanied by a loss of the enzymic activity. The enzyme could be protected from inactivation only in the presence of a complete template–primer–dNTP complex. The latter must be complementary to the template used.^{4,42}

Even this example shows that chemical modification data do not fit into a simplified pattern of statistical distribution of substrate binding sites. Comparison of these data with the spatial structure of DNA polymerase obtained from X-ray analysis shows that the distance between the Tyr766 residue modified by 8-azido-dAMP and the His881 residue modified by dTTP is rather large (9 Å). This suggests that the orientation of the latter is different in different nucleotides, at least in the binary enzyme–dNTP complex.

In addition to dNTP analogues, other reagents, such as pyridoxal 5-phosphate (which often behaves as a nucleotide analogue) and 5'-*p*-fluorosulfonylbenzoyl adenosine (the size of the FSO₂Bz-fragment of which is close to that of the triphosphate group), were used for modification of DNA polymerase (the Klenow fragment). In the former case, the modification affected Lys758,⁴³ in the latter case, Arg682.⁴⁴ It should be noted that the latter modification was performed in the presence of a template–primer complex modelling the complex of the Klenow fragment with the template–primer and dNTP.

If one assumes that the residues thus revealed are directly related to the active centre of the enzyme, it would be reasonable to suppose that the positively charged residues of both Lys758 and Arg682 will interact with the triphosphate fragment of dNTP. However, this interpretation, too, is inconsistent with the enzyme structure obtained from X-ray analysis. Indeed, Lys758 is localised in the *O* helix pertaining to the 'fingers' domain, while Arg682 is located in the 'thumb' domain, *i.e.*, in the opposite side of the cleft (Fig. 1). At the same time, the triad of amino dicarboxylic acid residues localised in the 'palm' domain is the most probable participant in the binding of the triphosphate fragment. Moreover, these assumptions are at variance with the results obtained by photo-modification of the Klenow fragment with 2-(4-azidophenacylthio)-dATP.¹⁸ It was found¹⁸ that the modification affected the Asp732 residue localised in the helix *N*.

When conducting a simultaneous analysis of the X-ray and chemical or affinity-based modification data, one should bear in mind that these results may not be adequate from the theoretical standpoint. X-Ray analysis is carried out on crystalline preparations and gives an optimised structure. It is obvious, however, that the conformation of the protein backbone may fluctuate to some extent, and the crystal conformation deduced from X-ray analysis will not necessarily be optimum for the binding of dNTP or its triphosphate fragment. In an even greater degree this applies to the results of chemical modification. It was found⁴⁵ that the thermodynamically optimum structure of an affinity reagent–enzyme complex will hardly provide the optimum mutual orientation of the reactive fragment and the amino acid residue of the target. The use of the molecular mechanics method for the analysis

of the process occurring in the duplex formed by complementary oligonucleotides one of which carries the *N*-2-chloroethylamino group showed⁴⁶ that the energetically optimum conformations do not provide sufficient approximation of the heterocycle to be alkylated and the intermediate ethyleneimmonium cation that formed from the original alkylating group. To provide the transition from the thermodynamically optimum to the kinetically optimum structure, it is necessary to overcome a certain energetic barrier. The term 'store-conformation' has been introduced to describe energetically minimised structures able to pass (easily but not freely) to a kinetically optimum conformation.⁴⁶ Therefore, a small inconsistency between the X-ray and chemical data, which does not exceed several Angström, can only reflect the conformational differences between the structure of the enzyme with the optimum arrangement of the substrate and of the modifying agent.

It was shown⁴⁷ that the treatment of the Klenow fragment with [7-¹⁴C]phenylglyoxal, which specifically reacts with the arginine residues, inactivates the enzyme. Incorporation of four residues of the reagent into the protein gives a 95% inactivation. Since each arginine residue can react with two phenylglyoxal molecules, this implies that the inactivation occurs upon modification of two arginine residues. Only the template–primer complex can protect the enzyme from inactivation by phenylglyoxal. The main site of modification is Arg841. This residue is localised in the *Q* helix near Tyr766, Lys758, and His881, which, as mentioned previously, take part in the interaction with dNTP or their analogues. The position of amino acid residues within the three-dimensional structure of the Klenow fragment of DNA polymerase I from *E. coli* revealed by affinity-based modification is shown in Fig. 1. The triad of dicarboxylic amino acid residues is marked by black circles in Fig. 2.

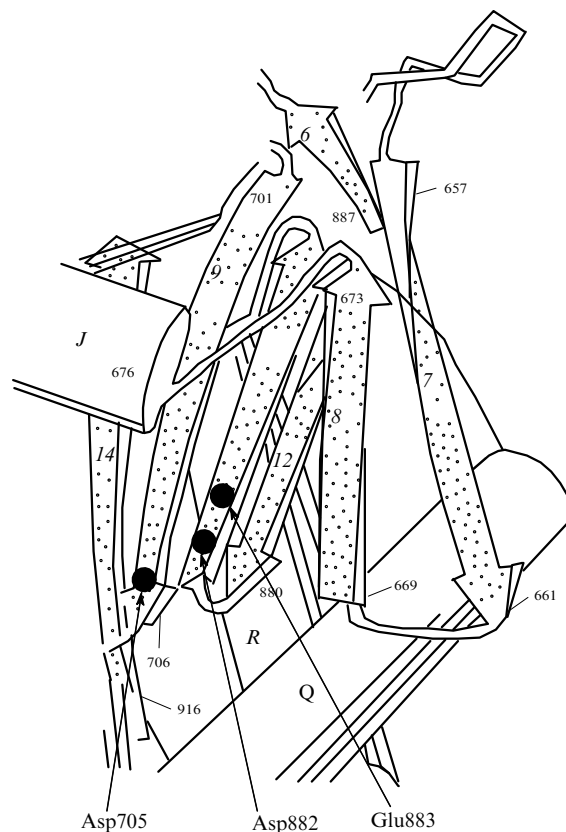
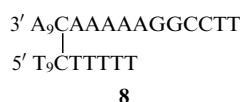


Figure 2. The position of the triad of dicarboxylic amino acids in a three-dimensional structure of the Klenow fragment of DNA polymerase I from *E. coli*.

An unexpected result was obtained in the study of the structure of the Klenow fragment of DNA polymerase I. It was found that the active centre where the elongation of the primer takes place and the site of the 3' → 5' exonuclease activity are at a large (about 30 Å) distance from one another. According to the generally accepted and well-rationalised experimentally viewpoint concerning the centre of the 3' → 5' exonuclease activity, the newly attached 3'-terminal fragment must undergo 'testing' in the exonuclease centre after each elongation act. This requires the translocation of the terminal fragment of the primer by several units. This problem was studied using a template–primer duplex 8 with covalently cross-linked chains as a model.⁴⁸



Here, the amino groups of the two cytosine residues are linked through an ethylene bridge. Such a cross-linking is achieved by introducing a cytidine analogue (instead of cytidine) containing a highly reactive three-membered ethyleneimine ring at position 4 into a matrix oligonucleotide. This analogue easily alkylates an opposite amino group of the primer chain. It was found that only the 5th (starting from the cross-linking site) dTMP residue of the primer can be split off by exonuclease. Splitting of the 4th residue is strongly hindered (the rate constant for this reaction is two orders of magnitude lower than that for the 5th residue). At the same time, this shortened cross-linked primer, the 3'-OH group of which is at a distance of four nucleotides from the cross-linking site, is still a good substrate for elongation. Hence, the difficulty in separating the strands affects only one of the enzyme activities. This result can be regarded as an experimental proof that the 3'-terminal fragment of the strand that is synthesised should be translocated at a large distance for correction.⁴⁸

Some data about the contact sites of the enzyme and nucleic acid components were obtained with the use of fluorescent methods. A series of duplexes 2–5 were used to study the contact sites of a template–primer duplex with the enzyme.³⁰ These duplexes contained a dTMP analogue with the fluorescent 5-dimethylaminonaphthalene-1-sulfonyl group (instead of the methyl group) at position 5 introduced into a predetermined position of the primer component. Thus the fluorescent label was set aside at a certain distance (which was different for different duplexes) from the enzyme active centre. The fluorescence lifetime and the inner rotation correlation time measured for all the samples showed that at least six primer residues interact with the enzyme. The label becomes more remote from the 3'-end of the primer, some changes in its fluorescent properties were observed, which reflect the changes in both the label accessibility for the solvent and its closeness with the protein.

Introduction of fluorescent labels into the protein, DNA, and dNTP was used to calculate the distances between the specific site in the enzyme, DNA, and dNTP using the Förster theory based on the resonance energy transfer. 4-Amino-7-nitrobenzo-2,1,3-oxadiazole can be introduced into the Klenow fragment as an energy acceptor at Cys907 through the CH₂C(O)OCH₂CH₂ spacer. A similar acceptor can be introduced into position 5 of uracil through the trimethylene spacer, and a DNA fragment can be synthesised on the basis of the thymidine fragment thus obtained. The fluorescent 5-aminonaphthalene-1-sulfonate group can be introduced as an energy donor into position 5 of uracil through the SCH₂C(O)NHCH₂CH₂ spacer. This can serve as a basis for obtaining a mononucleotide, a nucleoside triphosphate, and a DNA fragment carrying a donor group. This study made it possible to determine the distances between dNMP, dNTP, DNA, and Cys907 as well as the distance between DNA and dNMP.⁴⁹

Studies of the active centres of other DNA polymerases by affinity-based modification are still in their infancy. Human DNA polymerase β for which high resolution X-ray data are now available seems to be a tempting object of investigation.^{37,38} An attempt was made to localise the dNTP-binding site by modification with 8-azido-ATP and 5-azido-dUTP.⁵⁰ However, these experiments were carried out in the absence of the template–primer complex. This may account for the modification of the 8 kDa subdomain involved in the interaction with single-stranded DNA.⁵⁰ Recently, catalytically competent labelling of DNA polymerase β was performed using FAB-dCTP.¹² Given that the site(s) of modification are established, they can be more reliably associated with the dNTP-binding site.

2. Reverse transcriptases

Enzymes responsible for reverse transcription, *i.e.*, catalysing template biosynthesis of DNA on RNA templates, are characteristic of a large group of viruses called retroviruses. Some investigations based on the use of chemical methods were carried out with reverse transcriptases of the avian myeloblastosis virus (AMV) and the Moloney murine leukemia virus (MuLV). Identification of reverse transcriptase in the human immunodeficiency virus (HIV-1) has given a strong impetus to intensive studies of these enzymes. Reverse transcriptase is regarded as a promising target in the fight against AIDS; therefore this section will largely deal with the HIV-1 enzyme.

Normally, reverse transcriptase is made up of two subunits designated according to their molecular weights (in kDa) as p66 (555 amino acid residues) and p51 (446 amino acid residues). The smaller subunit (p51) represents a shortened subunit of p66 devoid of the fragment 447–555.^{51–53} This enzyme catalyses several reactions. Its functioning begins with reverse transcription of genomic viral RNA expressed in the virion by two molecules, 9750 nucleotides each.⁵⁴ Like all other DNA polymerases, this enzyme requires the presence of a primer. Host-cell tRNA is a natural primer and human tRNA^{Lys,3} is a primer for the HIV-1 enzyme. In a definite (final) stage of reverse transcription, which results in the formation of a minus-replica of DNA, the enzyme begins to function as an ordinary DNA polymerase by forming a plus-strand of DNA from the information contained in the minus-strand. The formation of the minus-strand is accompanied by gradual destruction of the genomic viral RNA under the action of another activity inherent in the enzyme, namely, that of RNase H. It is this enzymic activity that is present in the 447–555 domain, which is absent from the p51 subunit.^{53,55} In principle, homodimers made up of identical subunits can be obtained under special conditions instead of the p66/p51 heterodimer.

X-Ray structural analysis of the heterodimer revealed⁵⁶ that the p66 subunit consisted of several subdomains. They form a structure similar to that of the Klenow fragment of DNA polymerase I represented by the 'fingers', 'palm', and 'thumb' subdomains. The residues corresponding to these subdomains, which are linked to the C-terminal subdomain responsible for the RNase H activity through a linker subdomain, were identified in the primary sequence of reverse transcriptase.⁵⁶ The 'palm' subdomain contains three Asp residues (110, 185, 186) that seem to play the same role as the corresponding triads in DNA polymerases I and β.

The first three domains form a polymerase domain which, like the Klenow fragment, has a cleft for the binding of the template–primer duplex. However, unlike the Klenow fragment, the polymerase domain is formed by the N-terminal part of the polypeptide chain but not by its C-terminal part.⁵⁷

The contact site of the duplex with the enzyme was studied in most detail using footprinting with the •OH radicals.⁵⁸ Several probes were prepared on an artificial template–primer duplex (its central part is shown below) by elongation of the primer with the corresponding dNTPs and one ddNTP.

```

....d(AAACCCTTCTGGTTCCCC...)(3') (78 units)
          d(GGGG...)(5') (35 units)
          ddAGGGG...
          ddGAAAGGGG...
          ddCAAGGGGAAAGGGG...
          ddTGGAAGACCAAGGGGAAAGGGG...

```

Using this approach, a series of duplexes with the terminating fragment at a distance of 1, 4, 10, and 19 units from the original fragment were obtained. For example, the 10-nucleotide-shift was achieved by adding dATP, dGTP, and ddCTP to the duplex--enzyme mixture. Since the incorporation of the terminator occurs in the active centre of the enzyme, complexes with the duplex at the same position relative to the active centre but with different nucleotide environment were formed in all the cases studied. In all these cases the enzyme protected the sites from +3 to -15 on the template strand and the primer residues from -1 to -15 (the numbering is given relative to the terminator incorporation site). At the same time, the sites from -9 to -11 of the template and the sites from -8 to -10 of the primer are not protected. In addition, a pair with a strongly enhanced sensitivity to modification neighbours (with respect to the 5'-end of the primer) the sequence protected from the $\cdot\text{OH}$ radicals (Fig. 3). The dark area designates the regions in the primer and the template between positions +3 and -15 protected by the enzyme from free radicals. The hypersensitive spot is the site of enhanced cleavage of the template chain induced by changes in the template structure owing to the interaction of the HIV-1 reverse transcriptase heterodimer with the RNase H domain. The region of the duplex where this conformational change takes place is near the contact site for RNase H. It is therefore probable that it is the RNase H domain that induces a conformational transition in this region of the duplex. Similar, although not identical results were obtained in enzymic footprinting studies. Irrespective of the site where the synthesis is stopped by the terminator, the template residues from +7 to -23 and the primer residues from -1 to -25 are protected from DNase I. This site becomes accessible for the DNase attack at the junction of the regions forming the polymerase and RNase H centres (nucleotides -20 of both the template and the primer).⁵⁹

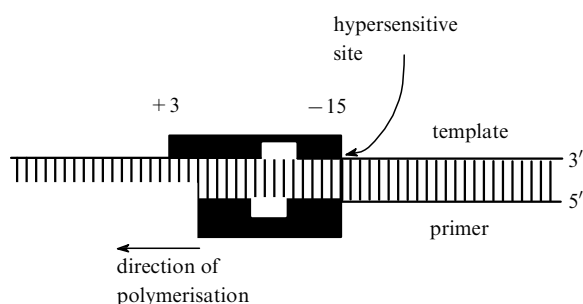


Figure 3. A scheme of footprinting with the hydroxyl radicals of the template and the primer chains.

One of the most intriguing properties of reverse transcriptases is the use of definite host-cell tRNAs as primers for reverse transcription. The 3'-terminal sequences of these tRNAs are always complementary to the site of the primer binding with genomic RNA. However, some other domains of this tRNA are also involved in the binding with both genomic RNA and the enzyme itself. Studies with *trans*-Pt[(NH₃)₂Cl₂] as a bifunctional cross-linking reagent⁶⁰ revealed that the anticodon loop of tRNA^{Lys,3} appears to be linked to reverse transcriptase of HIV-1. Using the same reagent, it was shown that cross-linking of the anticodon loop with reverse transcriptase of HIV-1 also takes place when tRNA is synthesised by transcription of the encoding gene by RNA polymerase from phage T7, which does not contain modified heterocycles, *viz.*, 5-methoxycarbonyl-

methyl-2-thiouracil and *N*-(2-methylthiopurin-6-yl)threonine. This implies that this interaction is not due to the presence of specifically modified heterocycles in the anticodon loop.⁶¹

In order to identify tRNA^{Lys} fragments that make contact with the enzyme, tRNA analogues with specifically incorporated 4-thiouridine residues were used.⁶² In most cases, irradiation of the enzyme-tRNA complex with light at $\lambda = 365$ nm resulted in the cross-linking of tRNA with the protein. It was found that in the case of tRNAs containing a photoactive residue at positions -1 and +16, *i.e.*, within the acceptor stem and the dihydrouridil loop, the cross-linking occurred exclusively with the p66 subunit. If the thiouridine residue was at position 36 (the anticodon loop), the cross-linking occurred with both subunits, although the reaction with p66 was predominant. When the thiouridine residue was at position 43 (the anticodon stem), no photo-cross-linking of tRNA with the enzyme took place. These results give an idea of which regions in the tRNA primer are in a direct contact with the enzyme.

Chemical modification with reagents specifically interacting with single-stranded sites of nucleic acids, *viz.*, dimethyl sulfate, *N*-cyclohexyl-*N'*-[2-(*N''*-methylmorpholinium)ethyl]-carbodiimide, diethyl pyrocarbonate,⁶³ made it possible to carry out a detailed analysis of the interaction of the primer binding site (PBS) of genomic RNA of HIV-1 and tRNA^{Lys}. The absence of or a drastic decrease in the level of modification of some particular sites of genomic RNA suggest their involvement in the formation of complementary nucleotide pairs. It was found that 18 nucleotide residues at the 3'-end of tRNA form a double helix with the 179-196 site of genomic RNA. The results obtained with the use of simpler unnatural systems, *e.g.*, poly(rA)-oligo(dT) duplexes, indicate that reverse transcription does not require such a complicated and specific primer. Nevertheless, the 3'-end of this primer not only corresponds to a definite site in viral genomic RNA, *i.e.*, fulfils the function of a primer, but also forms a complex with other fragments of tRNA and the template. The hexanucleotide fragment 33-39 of this primer, which forms an anticodon loop, is linked to the complementary 162-167 site of the template with a fall-out of one minor nucleotide from the two-helical site of the loop. The 40-47 site forms duplexes with the 140-143 and 158-160 sites of viral RNA.⁶³

Thus, the use of chemical methods for the study of reverse transcriptase of HIV-1 has made it possible to identify the regions of the template and the product located on the enzyme in the vicinity of its catalytic centre as well as the sites of the natural primer interacting with the enzyme and genomic RNA. The regions interacting with the primer were also established for genomic RNA.

The information obtained from the analysis of functionally important protein regions by chemical methods was more scarce and sometimes controversial. Of undoubted interest are the results obtained with affinity reagents and related to the distribution of modification sites between the subunits. Direct photo-cross-linking of dTTP with the enzyme occurs only on the p66 subunit.⁶⁴

The same results were obtained by photoaffinity labelling of the enzyme in the template (18-, 21-meric oligomers)-primer (12 units) complexes elongated with 4-thiouridine triphosphate⁶⁵ and with poly(dA)-oligo(dT) used as the primer-template and 2',3'-dideoxy-(5*E*)-[4-(3-trifluoromethyl-3*H*-diazirin-3-yl)styryl]UTP as a dTTP analogue.²⁰ Direct photo-cross-linking was performed⁶⁶ for the duplex formed by a 40-meric 5'-terminal fragment of genomic RNA and a 20-meric DNA primer. In this case, the primer was added exclusively to the p66 subunit. At the same time, after elongation of the primer to 40 nucleotides, the cross-linking occurred also with the p51 subunit. Presumably, this indicates the presence of a common pocket, which binds the primer and which is formed by both subunits of the enzyme.⁶⁶ In any case, it is obvious that the p51 subunit begins to interact with the primer at a sufficiently large distance from the enzyme active centre.

Similar results were obtained by Lavrik *et al.*⁶⁷ In these studies, the enzyme was irradiated with light at $\lambda = 266$ nm in the presence of [^{32}P]d(pT)₁₀ with or without a complementary template [poly(rA)] added; radioactivity was found only in the p66 subunit. At the same time, when the d(pT)₁₀ derivative containing a photoreactive residue of 2-nitro-5-azidobenzamide or β -alanyl-lamidoethidium linked by a phosphamide bond with the 5'-terminal phosphate was used, the photoinduced binding occurred with the both subunits. This can be interpreted as a result of remoteness of the photoreactive group from the enzyme active centre where the opposite 3'-terminal residue of the nucleotide has to be localised. At the same time, introduction of a dCTP analogue residue with a photoreactive azidoperfluorobenzoyl group linked with C(5) of cytosine through the spacer $\text{CH}=\text{CH}-\text{CH}_2-\text{NH}$ (AlFAB-dCTP), or with the amino group of cytosine through the spacer $\text{CH}_2-\text{CH}_2-\text{NH}$ (FAB-dCTP) to the 3'-end of the primer also results in cross-linking of the primer with both subunits upon irradiation.¹⁴

This change in the distribution pattern upon introduction of a relatively small fragment separating the photoreactive group and the primer shows that the p51 subunit is located near the catalytic site of p66. X-Ray data for an HIV-1 reverse transcriptase–DNA complex together with computer simulation suggest the involvement of the p51 subunit in the interaction between revertase and the template–primer complex.^{56, 57, 68}

Studies of reverse transcriptase of the avian myeloblastosis virus, which is also made up of two subunits, show their non-equivalence. This enzyme is used as a natural primer for tRNA^{Trp}. It was found⁶⁹ that tRNA^{Trp} oxidised with periodate at the 3'-terminal *cis*-diol group inactivates the enzyme. When the modification is not brought to completion, all the tRNA^{Trp} appears to be bound with only one of the two subunits designated as α . The latter is probably a p66 analogue of the HIV-1 enzyme because it contains all the activities inherent in this enzyme including that of RNase H.

Some studies provide evidence about the sites or regions of reverse transcriptase of HIV-1 that either interact with affinity reagents or are essential for manifestation of catalytic functions. In the above experiment with direct photo-cross-linking of the enzyme with dTPP, the main modification point was determined to be a Lys73 residue localised in the 'fingers' subdomain.⁶¹ In contrast, in the template (18–21 units)–primer (12 units) complex elongated with 4-thiouridine triphosphate, photoaffinity-based labelling was restricted to the peptide fragment 313–423.⁶² This fragment corresponded to the lower part of the 'thumb' subdomain and the linker domain. It was found also that modification with phenylglyoxal, which is specific for arginine, results in complete inactivation of the enzyme.⁷⁰ The presence of a template–primer complex prevents the inactivation; the Arg277 residue appears to be protected from modification. This residue is also present in the 'thumb' subdomain, but at its opposite end (relative to the peptide), and is modified with 4-thiouridine.

To establish the binding site for the primer, (pdT)₁₆ was directly cross-linked with a homodimer made up of two p66 subunits.⁷¹ Analysis of tryptic hydrolysates revealed that a peptide 288–307 localised in the upper part of the 'thumb' subdomain is the main binding site for oligo(dT). Fragments Leu289–Thr290 and Leu295–Thr296 were identified as the most probable sites of modification. This region also comprises a polynucleotide-binding domain for the homodimer of reverse transcriptase of HIV-1.⁷²

It should be noted that some photoactivated groups in the primer modify both the protein and the template DNA, which results in the cross-linking of the primer and template chains. This phenomenon was observed in enzyme–template–primer systems of reverse transcriptase of HIV-1 and of a DNA polymerase α complex with primase when primers with a FAB-dCTP residue were used.^{13, 14, 21}

IV. Catalytically competent labelling of DNA polymerases

The method of catalytically competent labelling of template enzymes was first actively applied to the study of DNA-dependent RNA polymerases. The main principle of this method consists in chemical modification of the enzyme by some unlabelled reactive analogue followed by elongation of a covalently attached substrate with a second substrate bearing a radioactive label. In this case only those residues of the first substrate analogue will contain the radioactive label the orientation of which allows them to take part in subsequent catalysis due to covalent binding. These residues are usually referred to as 'catalytically competent'.^{1, 73}

For the first time, this principle was applied to DNA polymerase I.⁷⁴ Oligothymidylate analogues with an alkylating group linked to the 5'-terminal phosphate were used as affinity reagents (Fig. 4). Affinity-based modification of DNA polymerase I was carried out by covalent binding of a reactive thymidylate analogue in the presence of a poly(dA) template. After covalent binding, a radioactive label was introduced by elongation of oligothymidylate with [α - ^{32}P]dTTP. This approach made use of the catalytic competence of the oligonucleotide primer covalently attached at its 5'-end. The most intense labelling was observed in the peptide Asn832–His928 located in the polymerase region of the enzyme. As the 3'-OH group of the primer must be in the active centre of the enzyme during catalytically competent labelling, more detailed localisation of the binding site at the 5'-end of the primer might allow establishing of the orientation of the primer relative to the enzyme. The orientation of the primer complex with DNA polymerases is currently a matter of vivid discussions.^{38, 75}

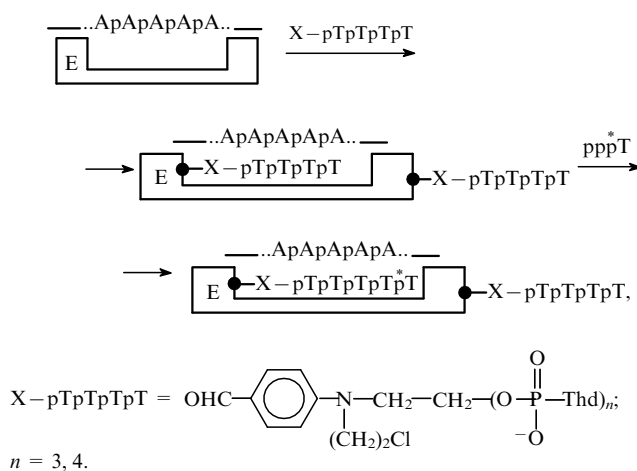


Figure 4. A scheme of highly efficient affinity-based modification of DNA polymerase I from *E. coli*: p^* is the radiolabelled phosphorus atom; X–pTpTpTpT is the affinity reagent; X is the affinity reagent residue covalently bound with the enzyme; E is the enzyme.

An analogous approach was used⁶⁷ in a study of the contribution of revertase subunits to the interaction with the template–primer complex. It is interesting to note that covalent binding of the primer at its 5'-end did not prevent subsequent attachment of at least four thymidine residues to the growing chain. Therefore, one should not rule out the possibility of translocation of the enzyme relative to the template–primer duplex. This system appears to be an interesting model for translocation studies. The same result was obtained for primase from *E. coli*⁷⁶ where the covalent attachment of adenosine trimetaphosphate followed by elongation with [α - ^{32}P]GTP was used for competent labelling. Elongation with [α - ^{32}P]GTP, together with other dNTP, yielded tetra- and pentanucleotides.

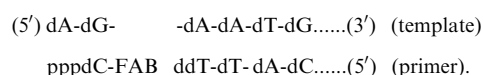
In this case, too, the covalent binding did not prevent several elongation acts to be accomplished.

A new version of catalytically competent labelling was carried out using photoreactive analogues of dNTP with arylazido groups linked with a heterocyclic base of the nucleotide through spacers. In contrast with the above-described versions of catalytically competent labelling where immobilisation was carried out at the 5'-end of a monomer or an oligonucleotide, the triphosphate group of dNTP does not take part in substrate immobilisation on the enzyme and thus remains unmodified. Hence, it can participate in the reaction with the 3'-OH group of the primer added.

This possibility was studied using a series of photoreactive analogues the substrate activity of which had been tested beforehand (see Table 1, Refs 11, 12, 14–16, 23). It was found that in all the cases studied the dNTP analogues covalently linked to DNA polymerase through a heterocyclic base could interact with the template–primer complex. In the presence of [^{32}P] phosphate at the 5'-end of the primer, this resulted in competent labelling of the binding site of the dNTP analogue. In other studies, a non-labelled template–primer complex was added to a DNA polymerase conjugate with a dNTP analogue followed by addition of [$\alpha\text{-}^{32}\text{P}$]dNTP corresponding to the template. In this case labelling of the conjugate also took place. Thus, the template–primer complex immobilised through a heterocyclic base can participate in the elongation of the primer.^{12, 14, 21, 23}

According to some data, binding of such reagents can increase the selectivity of modification. Modification of HIV-1 reverse transcriptase with a template–primer complex carrying a FAB-dCTP or AIFAB-dCTP residue at the 3'-end of the primer is described in Section III.¹⁴ In these studies, the photoreactive group was introduced into the primer enzymically, *i.e.*, with the help of a free substrate. This resulted in modification of both subunits. In analogous experiments, the same photoreactive groups were introduced into the primer with the help of preimmobilised analogues of dNTP. In this case, modification was more selective and affected only the p66 subunit. In the case of NAB-dUTP, the use of this approach did not increase the selectivity. The label was detected in the subunits both after preliminary immobilisation and without it.¹⁵ This provides additional evidence for the close localisation of the p51 subunit and the active centres of the p66 subunit.

That the triphosphate group of an immobilised dNTP retains substrate activity may be of considerable interest in the study of an enzyme centre involved in the catalysis of the nucleotidyl-transferase reaction. It is therefore important to preserve at a maximum the ability of the immobilised dNTP to take part in the elongation of the primer. One of the approaches has been checked for the example of FAB-dCTP and reverse transcriptase of HIV-1.¹² To this end, photoaddition of the reagent was carried out in the presence of a template–primer complex with the corresponding dideoxynucleotide at the 3'-end of the primer component. A fragment of this system is shown below:

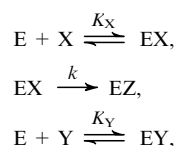


The duplex used could not undergo elongation due to the absence of the OH-group at the 3'-end of the primer. In other features, it fully mimicked the functional duplex. After irradiation, the dideoxy analogue of the primer was replaced with an excess of an ordinary ^{32}P -labelled primer. The level of catalytically competent binding of the enzyme in the presence of a template and a primer was determined by the amount of the label bound with the enzyme. It was found that the level of labelling of the p66 subunit increased substantially (severalfold) in comparison with that observed upon photo-cross-linking of the same analogue in the absence of the other components. It is interesting to note that analogous experiments with human DNA polymerase β did not reveal any increase in the level of FAB-dCTP binding with the

enzyme. This may indicate a lesser dependence of the interaction of dNTP with the active centre of this enzyme on the template.¹² The primer (both covalently attached to the 3'-end by catalytically competent elongation and containing a photoreactive group in the 3'-terminal unit after covalent attachment) can be further elongated with an [$\alpha\text{-}^{32}\text{P}$]dNTP.^{12, 14} This approach can also be used for the analysis of the translocation mechanism of DNA polymerases.

V. Study of interactions of DNA polymerases with templates, primers and nucleoside 5'-triphosphates by affinity-based chemical modification. Quantitative aspects

As mentioned above, affinity-based modification of biopolymers, *i.e.*, modification by reagents with a specific structure that is recognised by a biopolymer and carrying a reactive group, is widely used for selective modification of those groups of a biopolymer that are localised at the site of its interaction with the ligand. In other words, affinity-based modification is used as a tool for the study of the structural organisation of active centres of enzymes. The kinetics of affinity-based modification can be studied by measuring either the degree of the reagent binding with the biopolymer or a decrease in the biopolymer activity in the course of the reaction. Kinetic data provide information about the reagent affinity for the biopolymer. The measurements performed in the presence of a ligand competing with the reagent for the binding to the enzyme active centre allow one to determine the affinity for the competing ligand. The methods used to estimate the dissociation rate constants (K_d) for the ligands competing with affinity reagents have been generalised in the reviews.^{4, 77} In the simplest form, the affinity-based modification of an enzyme (E) by a reagent (X) in the presence of a competing ligand (Y) can be represented as follows:



where EX is the enzyme–reagent complex; EZ is the modification product; EY is the enzyme–Y complex; k is the rate constant for the conversion of EX into EZ; K_X is the rate constant for the dissociation of the EX complex, and K_Y is the rate constant for the dissociation of the EY complex.

At a sufficiently large excess of the affinity reagent X, modification occurs as a first-order reaction. The values of apparent rate constants for the modification (k_{app}) at various concentrations of the reagent and the competing ligand can be determined from the dependence of the degree of modification or the residual activity of DNA polymerase on the time of its incubation with a reactive analogue of an oligonucleotide. The dependence of k_{app} on the initial concentration of the reagent X_0 and the concentration of the competing ligand Y_0 can be written as equation (1):

$$\frac{1}{k_{\text{app}}} = \frac{1}{k} + \frac{K_X}{[kX_0(1 + Y_0/K_Y)]}, \quad (1)$$

where k_{app} is the apparent rate constant for the modification, k is the rate constant for the conversion of EX into EZ, K_X is the rate constant for the dissociation of the EX complex, and K_Y is the rate constant for the dissociation of the EY complex.

Using this anamorphosis, it is not difficult to obtain the constant K_Y from the dependence of k_{app} on Y_0 at constant X_0 .

This method was used to study the interaction of DNA polymerases with templates, primers, and deoxynucleoside 5'-triphosphates. The affinity reagent (pdT)₂p((NH₃)₂Pt[N(3)-

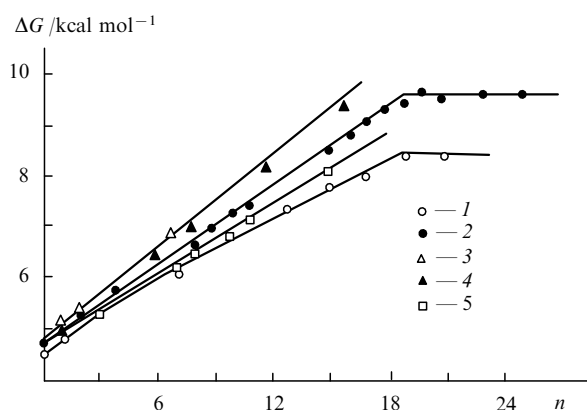


Figure 5. Dependence of ΔG^0 for the complex of the Klenow fragment with oligocytidylate (1), oligothymidylate (2), oligoguanylate (3), and oligoadenylate (4), and for the complex of DNA polymerase α from human placenta with oligothymidylate (5) on the length of the oligonucleotide.

dC(OH)}(pdT)₇ was used to study the binding site of the template. Its reaction with the enzyme was followed by monitoring the changes in the activity of DNA polymerase.⁷⁴ A broad array of oligonucleotides of various lengths and composition were used as competitive inhibitors. The values of the dissociation constants for the DNA polymerase α complex and the Klenow fragment with oligonucleotides and the corresponding standard free energies of binding (ΔG^0) were established.^{28, 78, 79} The dependence of ΔG^0 on the length n was determined for a series of homooligonucleotides (Fig. 5). This dependence is linear up to about $n = 20$. This suggests that the length of the region in which the template binds with the enzyme is about 20 nucleotide residues. For decathymidylates this dependence is described by equation (2).

$$\Delta G^0 = -6.0 - 0.32n \text{ (kcal mol}^{-1}\text{)}. \quad (2)$$

This means that the contribution of each nucleotide unit is 0.32 kcal mol⁻¹. For other types of nucleotide units these values are different. Thus for the most hydrophilic pdC, this value is -0.28 kcal mol⁻¹, whereas for more hydrophobic pdA and pdG it is -0.40 kcal mol⁻¹ (see Ref. 74). The linear dependence (2) makes it possible to calculate the value of ΔG^0 for the interaction of DNA polymerase with an oligonucleotide with a random sequence of the monomers (Table 2). The calculated values are in good agreement with those obtained experimentally.

Table 2. K_d values for the complexes of the Klenow fragment of DNA polymerase I from *E. coli* with oligonucleotides of various lengths and structures.²⁸

Oligonucleotide	K_d / μ M	
	calculated	experimental
d(pTpApApTpApCpGpA)	0.140	0.170
d(pCpTpGpCpGpTpTpApC)	0.120	0.130
d(pApApTpCpApTpGpGpTpCpApT)	0.013	0.015
d(pCpA) ₅	0.070	0.060
d(pGpA) ₅	0.024	0.015
d(pGpA) ₃	0.400	0.450
d(pGpT) ₆	0.011	0.009

The correlation between the nature of the oligonucleotide and its role in the interaction with the enzyme suggests that this interaction is hydrophobic rather than electrostatic. It is interesting to note that according to direct photo-cross-linking data, the 759–774 region of the Klenow fragment, which interacts directly with the DNA duplex, does not contain charged amino acid

residues,³⁹ but has eight highly hydrophobic residues (Ile760, Phe762, Leu764, Ile765, Tyr766, Met768, Phe771, and Leu773).

This finding was confirmed in experiments with oligothymidylates esterified (ethylated) at internucleotide phosphates, *i.e.*, devoid of the negative charge.²⁶ The dissociation constants (K_d) for the complex of human placenta DNA polymerase α with the octanucleotide d(Tp)₇T and the octanucleotide d[Tp(C₂H₅)Tp]₃Tp(C₂H₅)T ethylated at four internucleotide phosphates are 0.4 and 0.33–0.39 μ M, respectively (depending on the configuration of the chiral phosphorus atoms). In other words, elimination of four charges in the oligonucleotide molecule does not affect its affinity for the enzyme. At the same time, on complete esterification of the octanucleotide d[Tp(C₂H₅)]₇T the affinity drops by one order of magnitude ($K_d = 2.8 \mu$ M).²⁶

It is noteworthy that this dependence is not extrapolated to zero at $n = 0$. This implies that the free energy ΔG^0 of the interaction of the enzyme with orthophosphate is -6.0 kcal mol⁻¹. This was also confirmed by direct experiments where enzyme inactivation by the reagent was inhibited in the presence of orthophosphate. Moreover, neutral triethyl phosphate ($\Delta G^0 = -4.5$ kcal mol⁻¹) acted as a competitive inhibitor of the inactivation reaction. This fact illustrates the role of hydrogen bonds in the interaction of the phosphate fragment with DNA. The experimental data altogether allow a conclusion to be made about the significant contribution of only one internucleotide phosphate in the formation of a template–DNA polymerase complex.

In studies of the interaction of DNA polymerase with a primer to form a complex, the Michaelis constant, K_m , was used to characterise the primer affinity for the complex. In preliminary affinity-based modification experiments, it was shown that K_m differed slightly from the dissociation constant of the primer complex. A series of experiments was performed aimed at the enzyme inactivation by 2',3'-anhydroATP.⁸⁰ This was shown⁸⁰ to inactivate the enzyme in the presence of a template–primer [(poly(dT)–oligo(dA))] complex, the rate of inactivation being dependent on the concentration of this complex. Since the latter depends on the concentration of the primer, one may calculate the value of the dissociation constant for the primer complex. The equation used for calculation (3) was obtained on the assumption⁸⁰ that the primer and 2',3'-anhydroATP bind independently with the dissociation constants K_Y and K_X , respectively, but the reaction proceeds only when both the primer and the reagent are present simultaneously:

$$\frac{1}{k_{app}} = \frac{(1 + K_X/X_0)(1 + K_Y/Y_0)}{k}. \quad (3)$$

Table 3 gives the values for several oligodeoxyadenylates and human placenta DNA polymerase α . As is seen, the differences between these constants are small. This suggests that the Michaelis constant can be used as a measure of the primer affinity. For the Klenow fragment this coincidence is even better. Therefore, the main regularities of the interaction of DNA polymerases with the

Table 3. The K_d and K_m values for the complexes of human DNA polymerase α and the Klenow fragment of DNA polymerase I from *E. coli* with primers.

Primer	DNA polymerase α		Klenow fragment	
	K_d / μ M	K_m / μ M	K_d / μ M	K_m / μ M
d(pA) ₂	70	—	120	—
d(pA) ₅	9	32	30	34
d(pA) ₆	10	20	15	16
d(pA) ₇	1.8	6.5	—	—
d(pA) ₈	1.5	4.7	7	8
d(pA) ₁₀	0.33	0.44	1.2	1.3
d(pA) ₁₂	0.2	0.37	—	—

primer were analysed preferentially for the poly(dA)-oligo(dT) system using the K_m values.^{78,81} The latter were determined conventionally from the dependence of the rate of the primer elongation on its concentration. The dependence of $-\log K_m$ on the primer length (the number n of the nucleotide residues) was found to be linear up to $n = 9-12$. The K_m values for a series of oligothymidylates ethylated at internucleotide phosphates were compared. It was shown that the primer affinity for the enzyme--template complex strongly depends on the presence of a charged phosphate group at the 3'-terminal nucleotide residue. Ethylation of all the other internucleotide phosphates has practically no effect on K_m . The presence of the OH group at the 3'-end of the primer is a crucial factor. The oligonucleotide d(pT)₉p(ddT), which carries a 2',3'-dideoxythymidylate residue at its 3'-end and is devoid of the OH group, is a noncompetitive inhibitor of the primer. In these experiments with variable concentrations of the template, the oligonucleotide d(pT)₉p(ddT) behaved as a typical competitive inhibitor. This result testifies to its binding to the matrix site of the enzyme.^{81,82}

The dependence of $-\log K_m$ on the length of the primer is extrapolated to ~ 4 at $n = 1$. This suggests that the mononucleotide, too, can serve as a primer for DNA polymerase. This was demonstrated in direct experiments on human placenta DNA polymerase α where poly(dT) was used as a template, dATP as a substrate, and [³H]dAMP as a primer. As was shown by reversed phase chromatography of the reaction mixture, the dinucleotide d(pA)₂ was predominantly formed together with smaller analogues of longer oligomers. The substantial predominance of the dimer over longer oligomers attests to the distributive character of the synthesis. Similar results were obtained when [³H]dATP was used as a primer. This implies in fact that DNA polymerases can initiate DNA synthesis *in vitro*, although as has already been mentioned, in all cases studied the initiation of DNA synthesis *in vivo* begins with the synthesis of a ribooligonucleotide primer.⁸¹ These results are in favour of general regularities in the interaction of a DNA duplex with prokaryotic and eukaryotic DNA polymerases and fit well into a nonspecific sequence-independent model of DNA recognition. Indeed, the contribution of hydrophobic interactions of bases is crucial for single-stranded sites, whereas the interaction of the sugar-phosphate backbone is a critical factor in the case of DNA duplexes. It is noteworthy that the number of electrostatic interactions of both template and primer chains with the enzyme is limited. X-Ray data for the complexes of the Klenow fragment of DNA polymerase I with DNA³⁶ and of DNA polymerase β with DNA³⁸ are consistent with the conclusion about the limited number of contacts between the charged amino acid residues and DNA. For example, only one charged residue, *viz.*, Arg254, was found in DNA polymerase β . Presumably, this residue forms a hydrogen bond with the phosphate of a 3'-terminal dNMP newly introduced into the primer.³⁸ Simulation of the interaction of a DNA duplex with reverse transcriptase of HIV-1 carried out on the basis of X-ray data also revealed a limited number of electrostatic contacts, *viz.*, one or two lysine residues in the binding site of the 3'-end of the primer and several (but no more than 5-6) residues in the template region.⁶⁸ These data are consonant with the idea about the electrostatic nature of the DNA-binding site of DNA polymerases and the presence of a strong electrostatic field in this region.⁸³ This structure may be necessary for primary diffusion of DNA; however, the number of genuine 'strong' contacts can be restricted in order to provide the 'mobility' of DNA during the translocation and dissociation of the products.

The mechanism of interaction of dNTP with DNA polymerases was analysed by affinity-based modification of enzymes with γ -P-imidazolides of deoxynucleoside 5'-triphosphates and P-imidazolides of deoxynucleoside 5'-monophosphates.^{79,84,85} It is noteworthy that these reagents inactivated DNA polymerases only in the presence of both the template and the primer and only when the template was complementary to the reagent base. This suggests that the reagents bind to the site where the substrate is

selected for subsequent transfer of the nucleotide residue to the 3'-terminal hydroxy group of the primer. Quantitative estimation of nucleotide binding with a different number of phosphate groups was carried out on the basis of the protective effect of poly(dA) and oligo(dT)₁₅ on enzyme inactivation by dTMP-imidazolide. The values of dissociation constants for the complexes of dNMP, dNDP, and dNTP with human DNA polymerase α determined by this method are given in Table 4.⁸⁵ According to these data, the K_d values for different dNMP and dNDP are very similar, which suggests that β -phosphate hardly contributes much to the formation of dNTP complexes with DNA polymerase.

Table 4. K_d Values for the complexes of human DNA polymerase α with nucleotides in the presence of a template [poly(dA)] and a primer [d(pT)₁₅].⁸⁴

Base	$K_d (K_i \text{ or } K_m)/\mu\text{M}$				
	dNMP	dNDP	dNTP	NTP	γ -methylamide dNTP
C	15	11	7(15)	3	—
T	9 (28)	7	0.06(3.1)	0.05	0.03
G	7 (6)	6.0	0.3(0.64)	0.3	—
A	3 (7.8)	—	0.8	0.7	0.3

The affinity of dNMP for the enzyme increases in the following order: dCMP < dTMP < dGMP < dAMP. There was a linear correlation between ΔG^0 for dNMP binding and the retention time of the corresponding nucleosides on a reversed-phase adsorbent. Hence, the α -phosphate group of various dNMP makes an equal contribution to the total efficiency of complex formation with the enzyme. The difference in the affinity of both dNMP and dNDP for the active centre of DNA polymerase is largely due to the difference in the efficiency of hydrophobic interactions of their bases with the enzyme and does not reflect their complementarity to the template. At the same time, the situation is quite different for triphosphates. The base of dTTP is complementary to that of the template in the enzyme-poly(dA)-oligo(dT) complex and this nucleotide possesses the highest affinity for the complex. The affinity of all of the dNTP is higher than that of di- and mono-phosphates. This leads to a conclusion that the integrity of the triphosphate group of dNTP is required to enable the complementary interaction of nucleotides with the template.

Similar results were obtained for the Klenow fragment.⁸⁶ It should be emphasised, however, that the integrity of the triphosphate group is also important for the formation of a nonspecific complex between dNTP and DNA polymerases; this follows from the above data, especially for dATP and dGTP. The conclusion about the essential role of the triphosphate group for the recognition of dNT was confirmed by X-ray data, according to which the catalytic centres of DNA polymerases contain three carboxy groups that determine the Mg^{2+} -mediated orientation of the triphosphate fragment of dNTP.^{37,87}

VI. Chemical methods for the study of replicative complexes

As mentioned earlier, the functioning of the enzymes catalysing replication occurs within complicated multisubunit structures. The two main problems currently arising in this respect are concerned with the detection of contacts between the polynucleotide components and individual polypeptides of the complex, on the one hand, and between individual polypeptides, on the other hand.

In this context, replicating DNA polymerase from *E. coli* (DNA polymerase III), which actually represents a replicative complex, has been studied in most detail. This enzyme is made up of ten subunits, *viz.*, α , ϵ , β , τ , γ , δ , δ' , χ , ψ , and θ .⁸⁸ Partial

dissociation of the total complex usually takes place during its isolation; therefore, studies are carried out with intermediate incomplete complexes, *viz.*, complex III, which includes α , ϵ , and θ subunits; complex III', which contains additionally the subunit τ , and complex III*, which contains all subunits except for β . Complex III represents the nucleus of the total DNA polymerase. It comprises DNA polymerase α , 3',5'-exonuclease ϵ , and the subunit θ the function of which has not been finally established. These subunits are responsible for the two most important functions, *i.e.*, the binding of complex III' at the initiation site including the 3'-end of the primer bound with the template, and subsequent migration of the enzyme along the template without any dissociation of the enzyme–template complex.

In order to determine the subunits to which DNA binds in the course of elongation, a series of primers with a photoreactive group at different positions relative to the 3'-end of the growing chain were synthesised and assayed.²⁹ Their synthesis is described in Section II. Primers with a photoreactive arylazide group at positions 3, 9, 13, 18, 22, 27 and 46 relative to the 3'-terminal fragment were used for this purpose. After formation of the enzyme–template–primer complex, this was irradiated. This resulted in the cross-linking of a definite nucleotide residue with the enzyme. Analysis of subunits of the irradiated complex showed that the presence of a photoreactive group at positions 3 and 9 resulted in labelling of the α -subunit; at position 13, of the α - and γ -subunits; at position 18, of the γ -subunit alone, and at position 22, of the γ - and β -subunits. Primers with a photoreactive group at positions 27 and 46 from the 3'-end did not cross-link with any of the subunits. Assuming that in all these complexes the 3'-end of the primer is at the same position relative to the enzyme, the results obtained can be interpreted as evidence in favour of translocation of the product relative to the components of the complete enzyme.

The second system more or less thoroughly characterised was DNA polymerase in a complex with auxiliary proteins of bacteriophage T4. Bacteriophage T4 contains about 150 genes including those encoding proteins of the replicative complex. They are usually marked by numbers corresponding to the gene number and by the symbol gp (gene product). An efficiently functioning system contains DNA polymerase gp43 itself and the auxiliary proteins gp44, gp62, and gp45. Moreover, it requires the presence of a protein that binds single-stranded DNA (gp32). The auxiliary proteins fulfil the function of a clamp. The prerequisite for the formation of a stable complex between the 3'-end of the template–primer complex and three auxiliary proteins is the presence of ATP γ S, a non-hydrolysable analogue of ATP that contains the S atom at the γ -atom of P. It should be noted that DNA polymerase does not bind with this complex; its binding takes place only when a normal, hydrolysable ATP is added to the system.⁸⁹

This system was studied by determining direct photo-cross-links upon powerful laser irradiation (one or several 8 ns pulses, irradiation power was $5-8 \times 10^{16}$ photons). The most intense cross-linking was observed for the protein gp32. In this case, (dT)₁₀ is cross-linked with a far greater efficiency than (dC)₁₀. Direct photo-cross-linking of (dT)₁₀ occurs also with the individual proteins gp43 and gp45, although less intensely; no modification of gp44 and gp62 takes place. At the same time, in a system comprising an ensemble of all the three auxiliary proteins, photomodification affects only gp62. It is worth noting that its modification requires the presence of ATP.⁹⁰

A strong effect of ATP was also established in studies using a template–primer complex with a photoactive analogue of thymidine (NAB-dTTP) at several predetermined positions relative to the 3'-end of the primer.⁹¹ Addition of ATP and DNA polymerase resulted in significant changes in the contacts between the auxiliary proteins and the primer. For example, the binding of gp62

with the primer in the presence of all of the other auxiliary proteins was much stronger in the presence of ATP γ S, but not of ATP. This suggests that the addition of ATP results in its hydrolysis, which initiates a conformational transition, which either displaces gp62 to a larger distance from the primer or completely displaces it from the system.

In the case of eukaryotes, the fragment of a replicative complex containing DNA polymerase α and primase was studied first. Each of these enzymes consists of two subunits, which can be easily isolated as a single complex composed of four subunits, *viz.*, a 180 kDa subunit (DNA polymerase itself, or sometimes as a 165 kDa subunit formed upon partial proteolysis), a 72 kDa subunit (its function is unknown), and 60 and 50 kDa subunits (γ - and δ -subunits of primase). After direct photo-cross-linking of [α -³²P]ATP with a complex from yeast, the label is detected only in the δ -subunit.⁹² After modification of the complex with adenosine triphosphate *P*-*p*-formylphenyl ester followed by identification of modification points by catalytically competent labelling, the radioactive label was found in both subunits. Modification of an analogous complex from human placenta with adenylate *P*-*p*-formylphenyl esters with subsequent introduction of the radioactive label using [α -³²P]ATP revealed that the ATP ester was bound exclusively with the δ -subunit in the presence of poly(dT) and with both subunits of primase in the absence of poly(dT).⁹³

In studies of a DNA polymerase–primase complex from human placenta, a template–primer duplex (25 and 10 units, respectively) was elongated with FAB-dCTP. It was found that the primer was photoadded not only to the 165 kDa subunit of DNA polymerase but also to primase subunits. However, the 72 kDa polypeptide was not labelled under these conditions. Photoaddition of FAB-dCTP to the complex with subsequent attachment of the primer (catalytically competent labelling) resulted in modification of only the 165 kDa subunit of DNA polymerase and the minor (50 kDa) subunit of primase.²¹ Similar results were obtained for a DNA polymerase–primase complex from calf thymus. However, in the latter case the use of catalytically competent labelling did not result in labelling of the primase subunits at all.²³ These results suggest that photoaffinity modification can be used for gaining information about the role of various subunits of the complex in the formation of active structures and the change-over from the primase function to elongation of a newly synthesized DNA.²¹

Photoaffinity modification was also used to study the interaction of a eukaryotic replication factor (RPA) with DNA. RPA is made up of three subunits with molecular weights of 70, 32, and 14 kDa. Its functions are to stabilise the configuration of denatured DNA and to establish specific interactions of DNA with other proteins involved in replication, repair, and recombination of DNA.⁹⁴ The interaction of RPA subunits with a DNA duplex having an extended template chain, was studied by introducing a photoreactive group into the 3'-end of a radiolabelled primer using DNA polymerases α or β with 5-(5-azido-2-nitrobenzoyl)-deoxyuridine 5'-triphosphate as a substrate.⁹⁵ The p32 and p70 subunits underwent the most intense labelling upon UV irradiation. The minor (p14) subunit was not modified under these conditions. Based on the results obtained, a model for the interaction of RPA subunits with the DNA duplex was proposed (Fig. 6). It is supposed that the p70 subunit interacts with the single-stranded site of the DNA duplex, the p32 subunit is near the 3'-end of the primer, while the p14 subunit is remote. This scheme is very efficient for the studies of DNA interaction with other replication factors, such as PCNA and RFC, as well as for the study of formation of the whole replicative ensemble in the course of DNA synthesis.

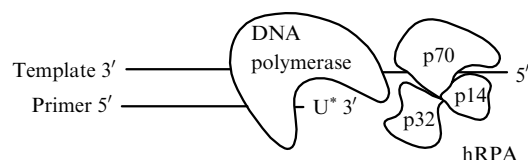


Figure 6. The interaction of the eukaryotic replication factor (hRPA) with a DNA duplex containing a photoreactive residue, dNMP(U*), introduced into the 3'-end of the primer by DNA polymerase; p70, p32, and p14 are the RPA subunits.

VII. Conclusion

Chemical approaches to the study of the mechanism of action of enzymes are not confined to the use of chemical modification for the analysis of template biosynthesis of DNA. Various substrate analogues obtained mostly by chemical methods have found wide use in enzymological studies. With respect to DNA polymerases, this approach has been successfully developed in studies by Kraevsky.^{96,97}

The data presented in this review demonstrate that the use of chemical (particularly, affinity-based) modification to elucidate the nature of active centres of DNA polymerases is a very practicable approach. However, the results obtained by this method must be analysed together with X-ray data. Analysis of these data together with the results obtained by site-directed mutagenesis is no less important. Most recent studies resort to methods of computer simulation more and more often because they allow a more detailed interpretation of information obtained by experimental methods.

The processes catalysed by DNA polymerases are characterised by a high degree of dynamism. The same can be said of the stage of the monomer selection where the monomer is tested for complementarity to the encoding element of the template prior to the nucleotidyl transferase reaction), to the translocation stage, where the template-elongation product complex migrates relative to the active centre of the enzyme, and to the repair stage involving 3' → 5'-exonuclease where the 3'-end of the synthesised chain is translocated from the polymerase to the exonuclease centre. These events occur over milliseconds; one of the few possible ways to monitor these transient changes in the contact sites of enzymes, templates, and products is fast photochemical labelling of the enzyme by photoreactive analogues of the substrate or the primer. This can be done for a millisecond interval using pulse irradiation. Although these experiments have just begun, a considerable chemical ground for this method including the synthesis of photoreactive analogues of dNTP and introduction of photoreactive nucleotide residues into definite positions of the primer chain has been created.

An important and very promising result of the most recent investigations is the elaboration of new techniques for catalytically competent labelling of enzymes with dNTP derivatives carrying a reactive group in their heterocyclic base. These derivatives retain their triphosphate fragment after covalent cross-linking with the enzyme and can sometimes act as donors of the nucleotide residue. This opens up interesting possibilities for the study of the mechanism of the nucleotidyl transferase reaction catalysed by the enzyme. Studies of elongation of primers covalently immobilised on the enzyme also seem to hold much promise. Since this system allows simultaneous realisation of several elongation acts and, as a consequence, of several translocation acts, it remains to be hoped that a convenient model for the study of the translocation mechanism will be developed despite limited mobility of the primer.

One of the peculiarities of studies of nucleic acid polymerases by the chemical modification method is the simultaneous presence in the system of single- and double-stranded nucleic acids and a protein (or a group of proteins). As mentioned above, simulta-

neous modification of the enzyme and the template was observed for primers carrying an azidoperfluorobenzoyl group linked to a heterocyclic base.^{14,21} In some cases, this can impede the interpretation of results of affinity-based modification, *e.g.*, due to the impossibility of separation of DNA chains or because simultaneous binding of two or more photoreactive groups of the primer with the template and the enzyme yields products that cannot be easily identified. Therefore, preference may be given to reagents endowed with the ability to selectively modify proteins without any cross-linking of the primer with the matrix, *e.g.*, when the primer contains NAB-dUMP residues.¹⁵ Studies on a model system in which the amino acid residue and the photoreactive group (azidoperfluorobenzoyl, 5-azido-2-nitrobenzoyl or *p*-azidoanilide) are artificially converged by addition to the 3'- and 5'-terminal phosphates of complementary oligonucleotides, respectively, showed that only in the former case can the cross-linking also take place in the absence of the amino acid residue at the 3'-end.⁹⁸ Therefore, among other arylazides used for protein modification, derivatives with a 5-azido-2-nitrobenzoyl or *p*-azidoanilide groups are more preferable.

Chemical approaches, in the first place, covalent cross-linking of reactive primer-template complexes with reactive fragments at predetermined positions of these complexes are an indispensable tool in the study of both RNA polymerases and transcription complexes, on the one hand, and replicative complexes, on the other hand. In particular, they are used for the study of the mutual arrangement of individual components of the above complexes (*e.g.*, eukaryotic DNA polymerase and auxiliary proteins, such as SSB, PCNA, RFC) and their translocation relative to the template-primer complex in the course of elongation.

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Generation of the second harmonic of laser radiation in noncentrosymmetrical polymeric systems

A V Vannikov, A D Grishina, R W Rychwalski, A T Ponomarenko

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Abstract. Second-order nonlinear optical properties in polymeric media and the mechanisms of generation and relaxation of the second harmonic of a polarised laser beam are discussed. The relationships between the chemical structures of the polymeric systems and the transport characteristics of the charge carriers are considered and the influence of the captured charges on the parameters of the second harmonic relaxation are analysed. It is shown that the kinetics of second harmonic relaxation in the polymeric systems of the host–guest type is determined entirely by the decay kinetics of the surface potential. The bibliography includes 98 references.

I. Introduction

Optical second harmonic generation (SHG) consists in the medium assisted transformation of two photons with the frequency ω into one photon with the frequency 2ω . The generation of the second harmonic (SH) results from the dispersion of light in the medium and occurs under the action of polarised laser radiation, as a rule, in the spectral range of polymer transparency where both single- and multi-photon absorption by the medium are absent. This range corresponds to the radiation of the near-IR lasers. Physicochemical basis of SHG is considered in detail in several monographs^{1–4} and reviews^{5–8} and numerous papers. Preparation of polymeric systems with nonlinear optical properties that are used for SHG requires first of all that an oriented molecular structure was formed. These structures are produced under the action of an external electric field. The charges left after the electric field is switched off determine in some cases kinetic characteristics of SHG.

A V Vannikov, A D Grishina A N Frumkin Institute of Electrochemistry, Russian Academy of Sciences, Leninskii prosp., 31, 117071 Moscow, Russian Federation. Fax (7-095) 952 08 46. Tel. (7-095) 952 24 28.

E-mail: vanlab@glas.apc.org (A V Vannikov)

R W Rychwalski Chalmers University of Technology, S-41296 Gothenburg, Sweden. Fax (31) 772 38 72

A T Ponomarenko Institute of Synthetic Polymeric Materials, Russian Academy of Sciences, ul. Profsoyuznaya 70, 117393 Moscow, Russian Federation. Fax (095) 420 22 29

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This review is devoted to the analysis of the influence of captured charges in polymers on the characteristics of the SH relaxation. Some general information on the mechanism of the SH generation and relaxation in polymeric media is considered at the beginning of the paper.

The SHG phenomenon is caused by the nonlinear polarisability of conjugated molecules containing donor and acceptor *para*-substituents when the electric field is applied. It is known that a dipole moment is induced in a molecule placed in the electric field E

$$\vec{p} = ex = \alpha E \cos \theta, \quad (1)$$

where e is the electronic charge, x is the displacement of a bound electron in the electric field, α is the polarisability, θ is the angle between the direction of the electric field and the induced dipole moment. In the rectilinear coordinates, the projections of the vector $\vec{p}$ are equal to

$$p_i = \alpha_{ix}E_x + \alpha_{iy}E_y + \alpha_{iz}E_z, \quad i = x, y, z, \quad (1a)$$

where α_{ij} is the coefficient of linear polarisation along the axis i with electric field acting along the axis j ; this is a second rank tensor or the tensor of linear polarisability

$$\alpha_{ij} = \begin{vmatrix} \alpha_{xx} & \alpha_{xy} & \alpha_{xz} \\ \alpha_{yx} & \alpha_{yy} & \alpha_{yz} \\ \alpha_{zx} & \alpha_{zy} & \alpha_{zz} \end{vmatrix}$$

Macroscopic polarisation (P) per unit volume of a substance containing N chromophore molecules along the direction of the applied field is the sum of the projections of dipole moments for each individual molecule onto this direction under conditions of dipole–dipole interaction. Under the action of the laser radiation, nonlinear effects along with linear dependence $P = \chi^{(1)}E$ take place in donor–acceptor systems

$$P = \chi^{(1)}E + \chi^{(2)}EE + \chi^{(3)}EEE + \dots \quad (2)$$

Here $\chi^{(1)}E$, $\chi^{(2)}EE$, and $\chi^{(3)}EEE$ are the polarisations, and $\chi^{(1)}$, $\chi^{(2)}$, $\chi^{(3)}$ are the susceptibilities of the first, second, and third order, respectively. The nonlinear terms, $\chi^{(2)}EE$ and $\chi^{(3)}EEE$, are also called hyperpolarisabilities of the second and third orders.

Under the action of a monochromatic electromagnetic wave $E(\omega) = E_1 \cos(\omega t) = 0.5E_1(e^{i\omega t} + e^{-i\omega t})$, dipoles oscillating with a frequency ω in small fields appear provided $P(\omega) \approx \omega^{(1)}E_1 \cos(\omega t)$. The donor–acceptor systems discussed below exhibit nonlinear

response to laser radiation, which is caused by the nonlinear electronic polarisation

$$P(\omega) = \chi^{(1)}E(\omega) + \chi^{(2)}E(\omega)E(\omega) + \chi^{(3)}E(\omega)E(\omega)E(\omega) + \dots (3)$$

or

$$P(\omega) = \chi^{(1)}E_1\cos(\omega t) + 0.5\chi^{(2)}E_1^2\cos(2\omega t) + \dots (3a)$$

$$+ 0.5\chi^{(2)}E_1^2 + \frac{\chi^{(3)}}{4}E_1^3[\cos(3\omega t) + 3\cos(\omega t)] + \dots$$

The expressions for the nonlinear polarisation in media with symmetrical polarisability with respect to the inversion centre, where $P(+E) = -P(-E)$, cannot contain even terms, i.e., $\chi^{(2)} = 0$ in Eqns (3) and (3a). In such media, nonlinear effects are caused by the third order polarisation. The second-order polarisation is induced in noncentrosymmetrical systems, where $P(+E) \neq -P(-E)$. According to the formula (3), the nonlinear response of a centrosymmetrical system causes the generation of the third harmonic (3ω) of the fundamental frequency of the laser radiation. In a noncentrosymmetrical medium, the radiation spectrum of the assembly of the oscillating dipoles contains a second harmonic caused by the second order nonlinear polarisation

$$P(2\omega) = 0.5\chi^{(2)}E_1^2\cos(2\omega t). (3b)$$

The anharmonic character of the polarisation induced by the polarised light $E(\omega)$ is illustrated in Fig. 1.^{1,8} The polarisation along a donor–acceptor molecule D–B–A (D is the donor fragment, B is the bridging spacer group with the system of conjugated π -bonds, A is the acceptor fragment) is caused by the fact that the charge displacement from A to D is smaller than in the opposite direction. In this case, an expression for the polarisation is represented by a Fourier series. The terms of the series possess the frequencies $\omega, 2\omega \dots 0$ (see Fig. 1).

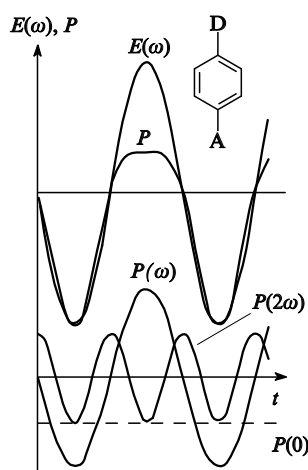


Figure 1. Polarisation (P) in a molecule D–B–A induced along the direction from A to D by the electric field $E(\omega)$ of a light wave (upper x axis) and the expansion of $P(\omega)$ as a Fourier series with the frequencies $2\omega, \omega$, and 0 (bottom x axis).

$$P = P(\omega) + aP(2\omega) + \dots + \epsilon P(0).$$

The dipole oscillations with the frequency 2ω (second term of the series) induce the generation of the second harmonic 2ω under the action of the fundamental frequency ω .

II. The relationship between microscopic and macroscopic polarisation

The dipole polarisation of an isolated chromophore molecule in a linear range can be written as follows [see formula (1a)]

$$p_i(\omega) = \alpha_{ij}(\omega)E_j(\omega).$$

Here i and j are the molecular coordinates that fix the orientation of the induced dipole moment $p_i(\omega)$ and the direction of the electric field $E_j(\omega)$, respectively. In the range of the appearance of the nonlinear effects, the expression for the dipole polarisation takes the form

$$p_i(\omega) = \alpha_{ij}(\omega)E_j(\omega) + \beta_{ijj}(-2\omega, \omega, \omega)E_j(\omega)E_j(\omega) + \gamma_{ijjj}(-3\omega, \omega, \omega, \omega)E_j(\omega)E_j(\omega)E_j(\omega) + \dots (4)$$

Here $\beta_{ijj}(-2\omega, \omega, \omega)$ and $\gamma_{ijjj}(-3\omega, \omega, \omega, \omega)$ are the polarisabilities of the second and third orders or hyperpolarisabilities of the second and third orders (the coefficients β_{ijj} and γ_{ijjj} are the tensors of the third and fourth rank), respectively.

In the macroscopic coordinates XYZ , the macroscopic polarisation of a dielectric, e.g., in the direction Z , is determined by the local internal field $F_Z(\omega)$, which is linked with the external field by the expression

$$F_Z(\omega) = E_Z(\omega) + \frac{4\pi}{A}P_Z(\omega) = E_Z(\omega) \left[1 + \frac{4\pi}{A}\chi_{ZZ}^{(1)}(\omega) \right],$$

where A is a coefficient depending on the system geometry: for sphere $A = 3$, for ellipsoids of polarisation this factor is tabulated and can be found in the reference books. Using the relationship between the dielectric constant $\epsilon_Z(\omega)$ and the susceptibility

$$\epsilon_Z(\omega) = 1 + 4\pi\chi_{ZZ}^{(1)}(\omega),$$

the expression in square brackets can be written in the form⁵

$$f_Z(\omega) = 1 + \left[\frac{\epsilon_Z(\omega) - 1}{A} \right] (5)$$

and

$$F_Z(\omega) = f_Z(\omega)E_Z(\omega). (5a)$$

If $A = 3$, then

$$f_Z(\omega) = \left(\frac{\epsilon_Z(\omega) + 2}{3} \right), (5b)$$

where $\epsilon_Z(\omega) = n^2(\omega)$, and $n(\omega)$ is the refractive index for the fundamental frequency. It thus follows that the linear polarisation can be represented by the relation [see also formula (1)]

$$P_Z(\omega) = N\alpha_{ij}f_Z(\omega)E_Z(\omega)\langle \cos\theta_{Zi} \rangle.$$

Thus, the first-order susceptibility is linked with the linear polarisability of an individual molecule α_{ij} by the relation

$$\chi_{ZZ}^{(1)}(\omega) = N\alpha_{ij}f_Z(\omega)\langle \cos\theta_{Zi} \rangle. (6)$$

Consequently, the second-order macroscopic polarisation is linked with β_{ijj} by the relation

$$P_Z(2\omega) = N\beta_{ijj}E_Z(\omega)f_Z(\omega)\langle \cos\theta_{Zi} \rangle E_Z(\omega)f_Z(\omega)\langle \cos\theta_{Zi} \rangle f_Z(2\omega)\langle \cos\theta_{Zi} \rangle,$$

where $f_Z(2\omega)$ is determined according to the formula (5b) at the frequency 2ω .

The second-order polarisability along the direction of the macroscopic axis Z , which is averaged along all orientations of the individual molecules D–B–A, is determined by the expression

$$\beta_i = \beta_{iii} + \frac{1}{3}[\sum(\beta_{ijj} + \beta_{jji} + \beta_{jji})].$$

The molecules D–B–A are chromophores, since they contain donor and acceptor groups, and a conjugated chain; they absorb visible light. Below we call these molecules nonlinear optical NLO-chromophores or just chromophores.

A component of the second-order susceptibility along the direction Z is determined by the polarisability β_i according to the relation

$$\chi_{ZZZ}^{(2)} = N\beta_i(-2\omega, \omega, \omega)f_Z(\omega)\langle\cos\theta_{Zi}\rangle f_Z(\omega)\langle\cos\theta_{Zi}\rangle f_Z(2\omega)\langle\cos\theta_{Zi}\rangle,$$

i.e., in a quasi one-dimensional molecule (in which dipole moment is directed along the axis of symmetry and the β_{iii} dominates)

$$\chi_{ZZZ}^{(2)} = N\beta_{iii}(-2\omega, \omega, \omega)f_Z^2(\omega)f_Z(2\omega)\langle\cos^3\theta_{Zi}\rangle, \quad (7)$$

$$\begin{aligned} \chi_{ZXX}^{(2)} &= \chi_{ZYY}^{(2)} = \\ &= \frac{1}{2}N\beta_{iii}(-2\omega, \omega, \omega)f_Z^2(\omega)f_Z(2\omega)(\langle\cos\theta_{Zi}\rangle - \langle\cos^3\theta_{Zi}\rangle). \end{aligned} \quad (7a)$$

III. The polarisability of polymeric donor-acceptor systems

Doubling of the laser radiation frequency was observed for the first time for quartz crystals⁹ ($d_{33} = 0.5 \text{ pm V}^{-1}$)[†]. Nowadays, a large number of inorganic crystals that generate the SH of the fundamental frequency of the laser radiation are known. However, of special interest are polymeric systems as that it is in these media the maximum intensities of the SH corresponding to $d_{33} = 200 \text{ pm V}^{-1}$ are obtained. Organic polymers are processable and blend well with integrated film optical systems.

Polymeric matrices containing low-molecular-weight chromophores and polymers containing chromophores in the side groups or in the main chain belong to the polymeric media that include D–B–A chromophores.^{1,5} It is essential that these molecules possess dipole moments in the ground state. As a rule, the initial polymeric films are disordered and, consequently, are centrosymmetrical systems. Intensive studies of the second harmonic generation in the polymeric donor–acceptor systems began after 1979,^{10–12} when an earlier developed rather simple method for transformation of the centrosymmetrical systems into noncentrosymmetrical ones due to predominant orientation of the dipole chromophore molecules under the action of a constant electric field at the glass transition temperature T_g was applied to the polymers (see references cited in the Ref. 6). A decrease in the temperature of such orientational poling in a constant field down to 20 °C and below can be achieved if the polymer layer is plasticised by the introduction of the CO₂ under high pressure. After polarisation the CO₂ is removed by the evacuation, and the polymer is restored its to initial glassy state that is now polarised.¹³

When the constant field E is applied, the potential energy of a molecule with the dipole moment μ is changed by the quantity

$$U(\theta) = -\mu F \cos\theta,$$

where $F = Ef(0)$, $f(0) = (1/3)(\epsilon + 2)$ [cf. formulas (5) and (5a)] and ϵ is the dielectric constant of the polymeric matrix. According to the Boltzmann distribution law the number of particles oriented at an angle θ to the direction of the field E is proportional to $\exp(-U(\theta)/kT)$ and the mean values of $\langle\cos^n\theta\rangle$ are determined according to the formula

$$\langle\cos^n\theta\rangle \equiv L_n\left(\frac{\mu F}{kT}\right) = \frac{\int_0^\pi \left\{ \exp\left[\frac{-\mu F \cos\theta}{kT}\right] \cos^n\theta \cdot \sin\theta \right\} d\theta}{\int_0^\pi \left\{ \exp\left[\frac{-\mu F \cos\theta}{kT}\right] \sin\theta \right\} d\theta},$$

[†] The second harmonic nonlinear coefficient $d_{ZZ} = 0.5\chi_{ZZZ}^{(2)}$ is often used as the SHG characteristics in equations (3a) and (3b). In the studies that are aimed at practical application, the symbols 123 are used, as a rule, instead of XYZ for the designation of the nonlinear coefficient coordinates; i.e., $d_{ZZ} \equiv d_{33}$.

representing the Langevin functions $L_n(\mu F/kT) \equiv L_n(u)$. This function is represented¹ in the form of the Legendre polynomial $L_n(u)$, where $u = \mu F/kT$ when the mean values of $\langle\cos^n\theta\rangle$ are calculated. For $n = 1$,

$$L_1(u) = \frac{u}{3} - \frac{u^3}{45} + \dots \simeq \frac{u}{3},$$

Hence, in the first approximation $\langle\cos\theta\rangle \approx \mu F/3kT$ in the relation (6). For $n = 3$,

$$\begin{aligned} L_3(u) &= \left(1 + \frac{6}{u^2}\right)L_1(u) - \frac{2}{u} + \dots = \\ &= \left(1 + \frac{6}{u^2}\right)\left(\frac{u}{3} - \frac{u^3}{45} + \dots\right) - \frac{2}{u} + \dots \simeq \frac{u}{5}, \end{aligned}$$

i.e., $\langle\cos^3\theta\rangle \approx \mu F/5kT$ in the relation (7).

Thus,

$$\chi_{ZZZ}^{(2)} = N\beta_{iii}(-2\omega, \omega, \omega)f_Z^2(\omega)f_Z(2\omega)f_Z(0)\frac{\mu E}{5kT} \quad (7b)$$

and

$$\chi_{ZXX}^{(2)} = \chi_{ZYY}^{(2)} = \frac{1}{3}\chi_{ZZZ}^{(2)}.$$

If a constant electric field E is applied the second harmonic may contain a contribution of the third-order nonlinearity

$$\Delta P(2\omega) = N\gamma(-2\omega, \omega, \omega, 0)f_Z(2\omega)E_Z^2(\omega)f_Z^2(\omega)Ef(0),$$

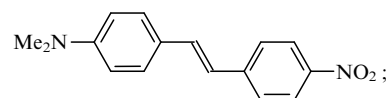
where $N\gamma(-2\omega, \omega, \omega, 0)f_Z(2\omega)f_Z^2(\omega)f(0)$ is the contribution of the third-order susceptibility.

In this case, the constant electric field E excites rather than orients the molecule. Thus,¹⁴

$$\begin{aligned} \chi_{ZZZ}^{(2)} &= NEzf(0)f_Z(2\omega)f_Z^2(\omega)[\beta_{iii}(-2\omega, \omega, \omega)\frac{\mu E}{5kT} + \\ &+ \gamma(-2\omega, \omega, \omega, 0)]. \end{aligned} \quad (7c)$$

The contribution of the third-order nonlinearity expressed by the term $\gamma(-2\omega, \omega, \omega, 0)$ appears and disappears simultaneously as the constant electric field E is switched on and off irrespective of the degree of orientation of the chromophores.

Considerable attention is paid to the D–B–A chromophores such as *para*-substituted stilbenes, where B is $-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{C}_6\text{H}_4-$, for example, 4-dimethylamino-4'-nitrostilbene (DANS),



arylamines, where B = $-\text{C}_6\text{H}_4-$, polyconjugated systems with B = $-\text{C}_6\text{H}_4(\text{CH}=\text{CH})_n-\text{C}_6\text{H}_4$ ($n \geq 2$), $\text{C}_6\text{H}_4-\text{N}=\text{CH}-\text{C}_6\text{H}_4$ or $\text{C}_6\text{H}_4-\text{N}=\text{N}-\text{C}_6\text{H}_4$, etc. J-Aggregates of dyes are also effective chromophores.¹⁵

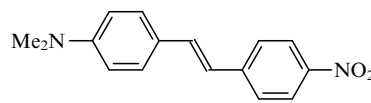
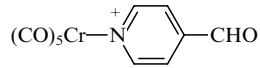
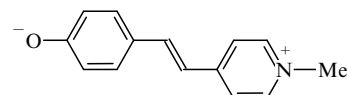
For the molecules D–B–A it is established^{16,17} that the second-order polarisability β can be represented in the form of two terms

$$\beta = \beta_{\text{ad}} + \beta_{\text{ct}},$$

where β_{ad} is the additive part resulting from the interaction between the substituents and the systems of conjugated bonds, and β_{ct} is the contribution for which the donor–acceptor interaction is responsible. As the molecular structure in the case of full charge transfer from D to A corresponds to the structure of the excited molecule then according to the concepts developed in the publications^{5–8, 16–24}

$$\beta_{\text{ct}} = \frac{3e^2\hbar^2}{2m} \frac{W}{[W^2 - (2\hbar\omega)^2][W^2 - (\hbar\omega)^2]} f\Delta\mu_{\text{ex}}, \quad (8)$$

Table 1. β Values for the chromophores with different relationships between μ_e and μ_g .

Chromophore	Relationship between μ_e and μ_g	μ_g/D	μ_e/D	$10^{-30}\beta/\text{cm}^5\text{C}^{-1}$
	$\mu_e > \mu_g$	+ 9.85	+ 23.5	+ 73
	$\mu_e \approx \mu_g$	+ 7.84	− 10.5	− 12
	$\mu_e < \mu_g$	+ 22.6	+ 13.7	− 100

Note. Signs + and − denote the direction of the vectors $\vec{\mu}$ and $\vec{\beta}$ in chromophore.⁸

where h is the Planck constant, m is the mass of an electron, W is the distance between the ground-state level and the first excited level of an intramolecular DA-complex, ω is the fundamental frequency of the laser radiation, f is the oscillator strength for the transition from the ground state to the excited state, $\Delta\mu_{ex} = -\mu_e - \mu_g$ is the difference in dipole moments of the DA-complex in the ground state and excited state, respectively.

It follows from formula (8) that weak ($\mu_e \gg \mu_g$) and weak ‘reverse’ complexes ($\mu_e \ll \mu_g$), where the electron transfer is only possible in one direction from D to A or from $A^{-\cdot}$ to $D^{+\cdot}$, respectively should exhibit the highest nonlinearity. On going to the molecules $D^{\delta+}A^{\delta-}$ with the degree of transfer $\delta \approx 0.5$, $\mu_e \approx \mu_g$, the charge displacement in both directions is possible where upon application of the electric field, one should expect the weakening of nonlinear characteristics. Indeed, when the weak complexes ($\mu_e < \mu_g$) are replaced by molecules with close values of μ_e and μ_g , the contribution of β_{ct} decreases drastically, but on going to the reverse complexes ($\mu_e > \mu_g$) this contribution increases considerably (Table 1).

The oscillator strength f is proportional to $(eRV_{01})^2/W$, where R is the distance between the groups D and A, V_{01} is the energy of the exchange interaction between D and $A^{-\cdot}$: $V_{01} = V(R_0)\exp[-(R-R_0)/\zeta]$, R_0 is the sum of Van der Waals radii of D and $A^{-\cdot}$, ζ is the parameter of damping of the wave functions.^{20,21} Taking this into account, one can represent formula (8) as follows

$$\beta \propto (eRV_{01})^2 \frac{\Delta\mu_{ex}}{W^2}$$

[in a static approximation, $h\omega = 0$ (see Ref. 8)]. The parameter ζ decreases if delocalised π -electrons of the bridging group B in the molecule D–B–A take part in the exchange interaction

$$V_{01} = V_{01}(D, M^{-\cdot})V_{01}(M^{-\cdot}, A^{-\cdot}).$$

The parameter ζ is determined by the structure of the bridging group. Weakening of the exchange interaction at a large distance between D and A leads to the decrease in β_{ct} .

It is seen from the formula (8) that the contribution of β_{ct} increases with a decrease in the distance between the ground and excited levels, which determines the longwave optical absorption of the intramolecular DA complex. The experimental data showing the increase in $\log \beta_{ct}$ with the increase in the wavelength of the optical absorption for *para*-substituted benzenes and stilbenes are presented by Kanis *et al.*⁸

The charge displacement from D to A in the D–B–A molecules in the ground state is determined by the difference in the Hammett constants (σ_x). For example, for *para*-substituted π -conjugated molecules⁸

$$\sigma_n = \sigma_{n,a} - \sigma_{n,d},$$

where σ_n is the empirical Hammett constant, $\sigma_n = \log K_X - \log K_H$, where K_X and K_H are the ionisation constants for *para*-substituted and unsubstituted benzoic acids, respectively. The Hammett constants are positive for the acceptors [$\sigma_{n,a}(\text{NO}_2) = 0.778$] and negative for the donors [$\sigma_{n,d}(\text{NH}_2) = -0.66$].²⁵ It is shown^{8,26} that β_j increases linearly from $\sim 4 \times 10^{-30}$ to $40 \times 10^{-30} \text{ cm}^5 \text{ C}^{-1}$ at $h\omega = 0.65 \text{ eV}$ as σ_n increases from 0.4 to 1.5 for mono- and di-substituted stilbenes (the axis Z is directed along the dipole moment of a molecule).

IV. Typical experimental procedure

A typical SHG process includes two stages: the first one is orientational polarisation of a polymer in the external electric field, and the second one is the measurement of the intensity of the SH in the course of the polarisation or after the electric field is switched off. Two methods for the potential application to the polymeric film are used. The first one is a contact method where the potential difference is applied to the transparent electrodes with the polymeric film placed between them. $\text{In}_2\text{O}_3/\text{SnO}_2$ (ITO) or a semitransparent metal film, for example, gold are used as the transparent electrodes. The second method is the corona discharge, the charges are deposited onto the free surface of a polymer instead of the upper contact electrode. These charges result from the corona discharge (ionisation of a gas in the measurement chamber by high voltage applied to the corona electrode). This method is well developed in electrophotography.²⁷ The principal scheme of the experimental set-up for second harmonic generation with the potential application of the corona discharge method is shown in Fig. 2.²⁸ The specimen consists of a transparent ITO electrode as a substrate and a polymeric layer that generates the second harmonic. A positive or negative charge is applied to the surface of the polymeric layer by the corona discharge method. The surface potential U is registered using the ring electrode and an electrometer.

Linearly polarised laser radiation with the fundamental wavelength λ (as a rule, λ lies, in the near-IR range and is equal to 1064 nm) is applied to the sample. The intensity of the second harmonic $I(-2\omega)$ that is selected by the $\lambda/2$ interference filter (532 nm) is measured with a photomultiplier and a digital voltmeter. The effects due to the fluctuation of the incident radiation can be excluded if the intensity of the second harmonic is measured relative to the intensity of the fundamental wavelength signal taken out by the reference channel (see Fig. 2).

The intensity $I(-2\omega)$ is related to the second-order susceptibility by the expression^{1,29}

$$[I(-2\omega)] \propto [\chi_{ZZZ}^{(2)} E(\omega) E(\omega)]^2. \quad (9)$$

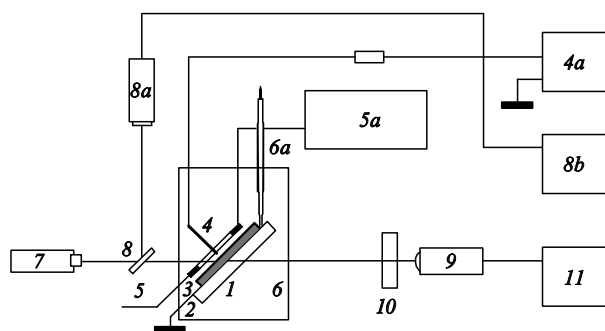


Figure 2. Schematic diagram of the experimental set-up for the second harmonic generation with the potential application by the corona discharge.

(1) — substrate, (2) — transparent electrode, (3) — polymeric layer, (4) — corona electrode, (4a) — source of stabilised voltage, (5) — ring electrode, (5a) — electrometer, (6) — temperature controlled chamber, (6a) — thermometer, (7) — laser, (8) — laser beam splitter, (8a) and (9) — photomultipliers, (8b) and (11) — pulse voltmeters, (10) — interference light filter for 532 ± 10 nm.

V. Relationship between the second harmonic and the relaxation characteristics of a polymeric matrix

A detailed analysis of studies on the second harmonic generation in polymeric systems performed before 1994 is presented in a review by Burland *et al.*⁵ It is noted that one of the main problems in the consideration of the nature of SHG in polymeric materials is the elucidation of the role of charges in the stabilisation and kinetic characteristics of the second-order susceptibility.

The coincidence of the decay of the second-harmonic intensity when the corona discharge is switched off and decay of the surface potential U in a poly(vinyl acetate) film containing 2 mass % of DO3 (Table 2) is established.²⁸ The plots $[I(-2\omega, t)]^{0.5}$ and $U(t)$ (Fig. 3) coincide over all time of measurement (22 min) after the corona electrode is switched off and correspond to a biexponential dependence. Thus, the susceptibility $\chi^{(2)}$ is completely controlled by the surface potential U . A biexponential decay of the surface potential in the polymeric films is observed for a large number of polymers³⁰ and can be associated with two processes, *viz.*, autolocalisation of the charge carriers in the polymeric dielectric

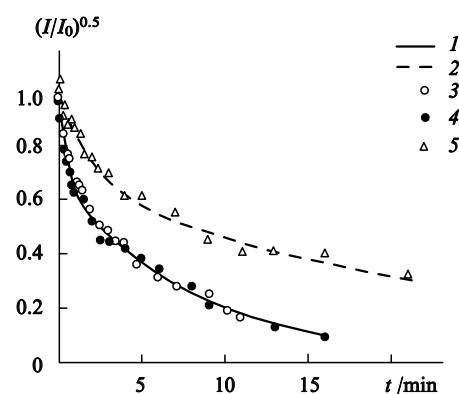


Figure 3. The kinetics of the decay of the second harmonic signal after the switch-off of the corona discharge for the sample of PVAC + 5 - mass % of DO3.

(1) equation (19) with parameters $\phi = 0.33$, $\tau_1 = 0.52$ min, $\tau_2 = 8.3$ min; (2) equation (19) with parameters $\phi = 0.35$, $\tau_1 = 2.1$ min, $\tau_2 = 28$ min; (3) keeping at 43°C for 5 min, then charging by the corona discharge for 2 min at 35°C , measurement at 35°C ; (4) keeping at 43°C for 5 min, then charging by the corona discharge for 2 min at and then 2 min at 35°C , measurement at 35°C ; (5) keeping at 43°C for 5 min, then keeping at 35°C for 4 h, charging by the corona discharge for 2 min at 35°C , measurement at 35°C .

responsible for the initial fast region (τ_1), and a charge carrier drift responsible for the decay of the potential with the time constant τ_2 .

Only in a few studies^{31–35} the kinetics of the decay of the susceptibility $\chi^{(2)}$ and a decrease in the residual electric field were measured simultaneously³⁵ to take account of the effect of trapped charges in the relaxation processes. It was assumed earlier that the contact method entirely excludes the influence of the residual electric field after the cut-off of the potential difference. However, the electric current passing through a cell with poly(isobutyl methacrylate) (PIBMA) and a chromophore DANS (1 mass %) placed between the ITO electrodes has been registered.^{32–34} It was concluded that ITO is an injecting electrode and the current is caused by the ionic impurities in the polymeric matrix. In this case, a residual charge, which can significantly influence the characteristics of the SH relaxation remains in the sample. An attempt was made to exclude the influence of captured electrons on the SH relaxation introducing an insulating SiO_2 interface between the ITO anode and the polymer.^{32–34}

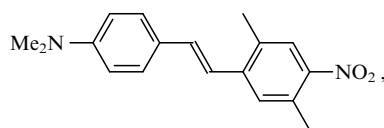
The effect of traces of solvent (chloroform) on the kinetics of SH decay was observed.³³ In the authors' opinion, the solvent

Table 2. Relative contribution of the third-order nonlinearity into $\chi_{ZZZ}^{(2)}$ (see Ref. 37).

Chromophore	Name	Abbreviation	$\frac{\gamma}{\gamma + \beta\mu/5kT}$
	4-dimethylamino-4'-nitrostilbene	DANS	0.2 ± 0.03
	(N-ethyl)-N-(2-hydroxyethyl)-4-(p-nitrophenylazo)aniline, dispersion red dye 1	DR1	0.12 ± 0.02
	4-(p-nitrophenylazo)aniline, dispersion orange dye 3	DO3	0.16 ± 0.03
	4-(dimethylamino)benzylidene-malononitrile	DMN	0.06 ± 0.02

diffuses from a nonpolar polymer into a microvolume that surrounds the chromophore with a high dipole moment. This leads to the change in the dielectric constant and also to the significant decrease in viscosity in the microenvironment of the chromophore. As a consequence, this results in a decrease in the activation energy of the chromophore orientational relaxation. The content of traces of solvent is difficult to monitor. Therefore, the experimental results are often irreproducible. In this connection, one should pay attention to the dry process for the fabrication of films with oriented chromophores by spray-coating the polymer onto the electrode.³⁶

According to the formula (7c), the second harmonic contains the contribution of the third-order nonlinearity, which has to be taken into account in the analysis of the relaxation processes. The kinetics of the decay of $\chi_{ZZZ}^{(2)}$ in polymeric matrices (PMMA, poly(methyl methacrylate) (PEMA), and PIBMA) containing 2 mass % of a chromophore at 30 °C was measured after the constant electric field was switched off.³⁷ Depending on the nature of the chromophore (see Table 2), the susceptibility $\chi_{ZZZ}^{(2)}$ decreases by 6%–20% over the period 10^{-4} –0.5 s and then slowly diminishes over 10^3 – 10^4 s. Fast decrease in the susceptibility after the cut-off of the constant field E is related to the disappearance of the contribution of the third-order nonlinearity. This contribution $\gamma/(\gamma + \beta\mu/5kT)$ for different donor-acceptor molecules are also listed in Table 2. The value of this contribution depends only slightly on the nature of the polymeric matrix: in the PEMA and PIBMA containing 2 mass % of 4-tricyanovinyl-*N*-ethyl-*N*-(2-hydroxyethyl)aniline (TC1) this contribution was 4% at 30 °C.³⁸ For polyamide [–CONH–X–HNCO–(CH₂)–]_{*n*}, where the chromophore X was of the following structure,



the initial fast decay of the second-harmonic intensity $[I(-2\omega, t)/I(0)]^{0.5}$ down to 25% of the initial value was also explained³⁹ by the disappearance of the contribution of the molecular third-order susceptibility γ . Here $I(0) \equiv I(-2\omega, 0)$ is the second-harmonic intensity at the moment of the polarising field cut-off. This decay continues for ~ 20 s after the cut-off of the constant electric field. Possibly, such a delay is caused by the gradual drain of the surface charge deposited by the corona discharge.⁴⁰

The rate of the decay of the second-harmonic intensity after the real removal of the electric field is caused by the orientational relaxation of the chromophore and is determined by its structure, the character of the linkage with the polymer, and free volume of the polymer. The investigation of the kinetics of this process is an informative method of analysis of the polymer dynamics. The measurement of the SH after the switch-off of the electric field may last from ~ 0.5 s to an indefinitely long time. Different mechanisms of the relaxation of the system chromophore–polymer are found in the measurement.

As a rule, the study of the second-harmonic relaxation is based on the concept that these processes are caused by the rotational diffusion of chromophore. When the electric field is applied, they are described in the framework of the Smoluchowski model by equation^{5,31,41}

$$\frac{\partial G(\theta, t)}{\partial t} = D_{\text{rot}} \frac{1}{\sin \theta} \frac{\partial}{\partial \theta} \left\{ \sin \theta \left[\frac{\partial}{\partial \theta} G(\theta, t) + \frac{G(\theta, t)}{kT} \frac{\partial}{\partial \theta} V(\theta, t) \right] \right\}, \quad (10)$$

where $G(\theta, t)$ is the distribution function of the orientations of the dipole moment of the chromophore as the projection of the solid angle θ at the moment t ; θ is the angle between the macroscopic axis Z normal to the film surface and coinciding with the direction

along the constant electric field E , and the long axis of the chromophore, $D_{\text{rot}} = \langle [\theta(t) - \theta(0)]^2 \rangle / 4\tau$ is a coefficient of the rotational diffusion of the chromophore, τ is the relaxation time, and $V(\theta, t) = -\mu E \cos \theta$ is the potential energy of the chromophore. The change in the chromophore orientation after the switch-off of the constant field at the moment $t = 0$

$$\frac{\partial G(\theta, t)}{\partial t} = D_{\text{rot}} \frac{\partial G(\theta, t)}{\partial (\sin \theta d\theta)^2} \quad (11)$$

(the second Fick law) determines kinetics of the decay of the second-order susceptibility according to the expression^{5,40–42}

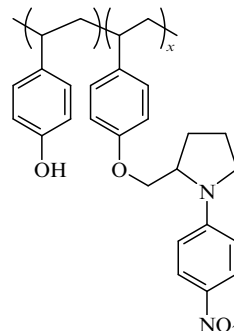
$$\frac{\chi^{(2)}(-2\omega, \omega, \omega, t)}{\chi^{(2)}(-2\omega, \omega, \omega, 0)} = A \exp(-2D_{\text{rot}}t) + B \exp(-12D_{\text{rot}}t). \quad (12)$$

Here [see Eqn (7)],

$$\frac{\chi^{(2)}(-2\omega, \omega, \omega, t)}{\chi^{(2)}(-2\omega, \omega, \omega, 0)} \equiv \left(\frac{I(-2\omega, t)}{I(0)} \right)^{0.5} \equiv \frac{\langle \cos^3 \theta, t \rangle}{\langle \cos^3 \theta, 0 \rangle}.$$

The representation of the function $G(\theta, t)$ in the form of the Legendre polynomial is used in the calculation and the same D_{rot} value is assumed for all chromophores. The latter condition is more characteristic of the temperatures higher than T_g .

The kinetics of the decay of the second harmonic intensity ($\lambda/2 = 532$ nm) in the polymer with the pendent chromophoric groups has been studied by Firestone *et al.*^{40–42} Polyhydroxystyrene (PHS) with the portion of hydroxy group (x) esterified with *N*-(4-nitrophenyl)-(S)-proline [(S) = NPP] was the object of the investigations



The kinetics was measured over a wide range of temperatures near the T_g of the polymer, which depends on the degree of substitution x , and decreases from 146 °C at $x = 12\%$ to 134 °C and 96 °C at $x = 36\%$ and 90%, respectively.⁴¹

The calculations have shown^{5,40} that the relationship between pre-exponential factors in Eqn (12) depends on the poling field strength and at $E = 2.5 \times 10^5$ V cm⁻¹ (at $D_{\text{rot}} = 1.5 \times 10^{-5}$ rad² s⁻¹) the kinetics of the decay of the $\chi_{ZZZ}^{(2)}$ is mainly characterised by the stretched exponent: $A \simeq 1$, $B \simeq 1.5 \times 10^{-5}$ at 130 °C. If the poling field increases by an order of magnitude the contribution of the fast exponent increases to $B = 0.0712$. Thus, one should expect the first-order exponential orientational relaxation of the chromophores after the switch-off of the constant field. The experimentally measured decay of the SH intensity $[I(-2\omega, t)]^{0.5}$ in (S)-NPP-PHS with $x = 36\%$ at temperatures higher than the T_g for this polymer (134 °C) after the cut-off of the field $E = 1.1 \times 10^6$ V cm⁻¹ is mainly characterised by the fast exponent only at 153 °C: $B = 0.998$, $A \simeq 0.0016$, and $D_{\text{rot}} = 9.7 \times 10^{-3}$ rad² s⁻¹ [or in Eqn (12) the relaxation time $\tau_2 = (1/12)D_{\text{rot}} = 8.6$ s]. The contribution of the slow relaxation increases with the decrease in the temperature of the measurement: at 149 °C $B = 0.88$, $A \simeq 0.12$, and $D_{\text{rot}} = 8.7 \times 10^{-3}$ rad² s⁻¹ ($\tau_2 = 9.6$ s), and at 134 °C $B = 0.52$, $A \simeq 0.43$, and $D_{\text{rot}} = 2.3 \times 10^{-3}$ rad² s⁻¹ ($\tau_2 = 36.2$ s). Revealing the biexponential relaxation instead of the calculated monoexponential process suggests in the authors' opinion^{40–42} the presence of two fractions

in the structure of the polymer, *viz.*, the liquid one responsible for the fast relaxation and the glassy one responsible for the slow orientational relaxation of chromophores.

The contribution of the liquid fraction increases with the increase in temperature and prevails at $T_g + 19$ °C. It was also noted that this two-fraction consideration is possibly unnecessary as the model of rotational diffusion itself predicts the biexponential relaxation according to the relation (12).

The temperature dependence of the orientational relaxation of chromophores in the range higher than T_g does not obey the Arrhenius law and is well described by the Williams–Landel–Ferry formula

$$\lg\left(\frac{\tau(T)}{\tau(T_g)}\right) = -\frac{C_1(T - T_g)}{C_2 + (T - T_g)}, \quad (13)$$

where C_1 and C_2 are empirical coefficients, and τ is the relaxation time. The values $C_1 = 17.44$ and $C_2 = 51.6$ °C are typical of polymers. In the measurement of the kinetics of $\chi_{ZZZ}^{(2)}$ decay at different temperatures these coefficients are as follows: $C_1 = 1.94$ and $C_2 = 39.1$ °C, *i.e.*, measurement of the second harmonic gives information on the relaxation in the local chromophore micro-environment rather than the universal macroscopic relaxation.^{40, 42}

In viscous media, the individual chromophores differ in their orientational relaxation time and a distribution of the relaxation processes can be represented by the empirical Kohlrausch–Williams–Watts (KWW) function⁴²

$$\frac{\chi_{ZZZ}^{(2)}(t)}{\chi_{ZZZ}^{(2)}(0)} = \left(\frac{I(-2\omega, t)}{I(0)}\right)^{0.5} \equiv G(t) = \exp\left(-\frac{t}{\tau_{KWW}}\right)^b, \quad (14)$$

where τ_{KWW} is the mean relaxation time [the time counted from the moment of the field cut-off to the moment of a 2.7-fold decrease in the distribution function $G(t)$], parameter b characterises the width of the distribution of chromophores according to the orientational relaxation time. The values of the coefficient b vary from 0 to 1. At temperatures higher than the glass transition temperature $b \approx 1$, *i.e.*, all chromophores are characterised by the same τ_{KWW} . The decrease in b as the temperature decreases indicates a growing deviation of the relaxation time of the individual chromophore from the mean value. In a number of publications (see, for example, Ref. 13), difficulties in the transformation of the experimental results to the form of function (14) using a single value of τ_{KWW} are noted. It is suggested to use of a bimodal representation in order to avoid difficulties

$$G(t) = \varphi_1 \exp\left(-\frac{t}{\tau_{1,KWW}}\right)^{b_1} + \varphi_2 \exp\left(-\frac{t}{\tau_{2,KWW}}\right)^{b_2}. \quad (14a)$$

Here, parameters $\tau_{1,KWW}$, b_1 , and $\tau_{2,KWW}$, b_2 show the presence in the polymer of domains with the fast and slow relaxations distributed according to the energies.

The relationships of the type (14a) bear little information as they contain a large number of parameters and, naturally, allow one to describe any experimental dependence.

The process of the chromophore orientation immediately after the switch-on of the poling constant field can be represented by the modified KWW function

$$[I(-2\omega, t)]^{0.5} = 1 - \exp\left(-\frac{t}{\tau_{KWW}}\right)^b. \quad (14b)$$

It was mentioned above that the exponential dependence corresponding to $b = 1$ in Eqn (14) is found in (S)-NPP-PHS with $x = 36\%$ at $T_g + 19$ °C.⁴⁰ As temperature decreases, b gradually decreases, which indicates a deviation of the relaxation time of individual chromophores from the mean value. The empirical functions (14) and (14b) describe well the process of the depolarisation/polarisation at the temperatures smaller than

T_g . The decay of the second harmonic intensity measured after the switch-off of the poling field ($E = 1.25 \times 10^6$ V cm⁻¹, poling time 20 min) at $T_g = 134$ °C corresponds [see Eqn (14)] to the values $\tau_{KWW} = 63$ s, $b = 0.61$, and at 120 °C $\tau_{KWW} = 972$ s, $b = 0.5$. The growth of $[I(-2\omega, t)]^{0.5}$ after the switch-on of the field corresponds to the dependence (14b) with the parameters $\tau_{KWW} = 79.8$ s, $b = 1$ at T_g and $\tau_{KWW} = 3126$ s, $b = 0.41$ at 120 °C.⁴² The decrease in the coefficient b with the decrease in temperature, *i.e.*, the broadening of the distribution function of the chromophores according the orientational relaxation times and the increase in the mean duration of relaxation τ_{KWW} in both processes (polarisation and depolarisation) indicate the heterogeneous character of the distribution of the microdomain sizes at temperatures below T_g .

An Arrhenius-type temperature dependence of the orientational processes was established at temperatures below T_g .^{40, 42}

$$\lg\left(\frac{\tau}{\tau_0}\right) = \frac{E_a}{kT}, \quad (15)$$

where τ_0 is a constant, E_a is the activation energy. In the samples of (S)-NPP-PHS with $x = 36\%$ $E_a = 24.7 \pm 2.6$ kcal mol⁻¹ either at a growth or decay of $[I(-2\omega, t)]^{0.5}$, *i.e.*, upon switch-on and off of the poling field.

According to the principles developed by Turnbull and Cohen and Chalykh,^{43–45} molecular diffusion is determined by the free volume of the polymer. Migration of a molecule in amorphous media becomes possible if a microcavity the volume of which exceeds some critical value $V' \simeq V_m$ (V_m is the volume of the diffusing molecule) appears in the vicinity of the diffusing molecule as a result of the thermal redistribution of the free volume.⁴⁴ In this case, the diffusion coefficient (D) is proportional to the probability of redistribution of the free volume and is determined by the relation

$$D \propto \tau^{-1} \propto \exp\left(-\frac{cN_A V'}{V_{fr}(T)}\right), \quad (16)$$

where $c \approx 0.5–1$ is a factor of the overlap of the microcavities, $V_{fr}(T) = [V(T) - V_v]$ is the molar free volume of the polymer repeating unit, $V(T)$ is the molar volume of the polymer at given temperature, and V_v is the Van der Waals molar volume of the repeating unit.

An analysis of the decay kinetics carried out by Firestone *et al.*^{40–42} demonstrated the link between the characteristics of the second harmonic and relaxation processes in the polymer. However, the authors failed to rationalise the disagreement between theoretical order of the exponential dependence of the orientational relaxation of chromophores using diffusional model and the measured biexponential dependence of the decay of the susceptibility $\chi_{ZZZ}^{(2)}$. In the authors opinion, the theoretical consideration carried out is simplified as it does not take into account different specific effects, for example, the interaction of the chromophore dipoles with the polymeric matrix or with each other.

An analysis of the relaxation processes gives a good correspondence³⁵ between the experimental results and calculations based on a Gaussian distribution of the activation energy E_a (see Refs 32–34) or according to Eqn (15)

$$\begin{aligned} \Phi(t) &= \left(\frac{I(-2\omega, t)}{I(0)}\right)^{0.5} = \int_{-\infty}^{\infty} \Gamma(\ln \tau) \exp\left(-\frac{t}{\tau}\right) d \ln \tau = \\ &= \pi^{-1/2} \int_{-\infty}^{\infty} \exp(-u^2) \exp\left[\left(-\frac{t}{\tau_G}\right) e^{-\sigma_G u}\right] du. \end{aligned} \quad (17)$$

Here $\Gamma(\ln \tau) = (\pi \sigma_G^2)^{-1/2} \exp(-u^2)$ is the Gaussian distribution of $\ln \tau$, $u^2 = (\ln \tau - \ln \tau_G)^2 / \sigma_G^2$, σ_G is the half-width of the distribution at $\Gamma_{\max}/2.7$, and τ_G is the most probable relaxation time. Verbiest

*et al.*³⁵ have used the Eyring theory of absolute reaction rates according to which

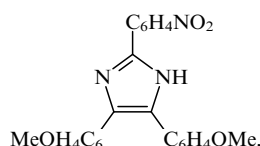
$$\ln \tau = \ln \frac{2\pi h}{kT} - \frac{\Delta S}{R} + \frac{\Delta H}{RT},$$

where R is the gas constant, ΔS and ΔH are the entropy and enthalpy of activation, respectively. Therefore, the thermal characteristics of the processes are estimated according to the dependence

$$\ln(\tau T) = \ln \frac{2\pi h}{k} - \frac{\Delta S}{R} + \frac{\Delta H}{RT}.$$

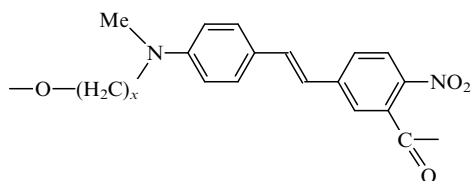
On the basis of the fact that $E_a = \Delta H + RT$ and in majority of cases $\Delta H \gg RT$ the authors suppose that $E_a \approx \Delta H$.

The distribution function (17) and the empirical KWW function (14) are characterised by two parameters, *viz.*, τ_G , σ_G and τ_{KWW} , b , respectively. The parameters of the Gaussian distribution τ_G and σ_G were compared with the coefficients τ_{KWW} and b for the decay curves $[I(-2\omega, t)]^{0.5}$ measured at different temperatures in a polyetherimide containing chromophore lophine 1 (L1)³⁵

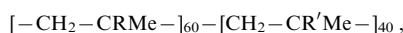


and also in PMMA containing dye DR1 (see Table 2). It was shown that as the temperature increases the increase in b from 0.2 to 1 corresponds to a decrease in σ_G from 10 to 0. In the range of $\sigma_G = 0-2$ the value of $\ln(\tau_{KWW}/\tau_G)$ is equal to zero and then decreases linearly down to -1.3 with an increase in σ_G to 10.

The characteristics of the orientational relaxation of chromophores in co-polymers consisting of the repeating units (P1, $x = 2$ and 6) with the following structure



and polymers including DANS, whose donor fragment is incorporated into the main chain (P2), and also containing DR1 (see Table 2) in the side chain (P3)



where $R = -C(O)-O-(CH_2)_2-R''$ ($R'' = \text{carbazolyl}$) and the chromophore $R' = -C(O)-O-(CH_2)_2-N(Et)-C_6H_4-N=N-C_6H_4-NO_2$ are the side substituents have been studied.⁴⁶ The susceptibility was measured when the poling electric field was switched on at room temperature, then the temperature was gradually increased to T_g , the sample was kept at this temperature until the constant value of $\chi^{(2)}$ was achieved, then the temperature was decreased again to 20 °C. The decrease in the temperature was accompanied, according to relation (7a) by an increase in the susceptibility to the limiting value $\chi_{\max}^{(2)}$, which could be achieved upon prolonged poling at the temperatures near the T_g . Then the poling electric field was switched off. It is established that in all polymers $\chi^{(2)}$ was increased up to 60% of $\chi_{\max}^{(2)}$ in 30 s at 20 °C. As this value exceeds a possible contribution of the third-order susceptibility (20%, see Table 2) the fast rise of $\chi^{(2)}$ was related⁴⁶ to the local motion of the chromophore in the free volume of the polymer. It was found that upon cut-off of the electric field in the samples cooled down to room temperature the value of the fast decay is less than 60%; for the P1 polymer this value is $\sim 20\%$ of

$\chi_{\max}^{(2)}$. In the authors opinion such a decrease in the contribution of the fast component of $\chi^{(2)}$ is caused by the decrease in the free volume, which resulted from the poling at T_g . The 'memory effect'[‡] in PIBMA containing DANS, *i.e.*, the increase in the duration of the decay of the second harmonic intensity τ in repeated cycles on-off of the polarising field at $T = T_g + 27$ °C [for the relationship between τ and V_{fr} , see Eqn (16)] was explained by the decrease in the free volume.³⁴ A gradual increase in τ_{KWW} after keeping a poly(arylene ether) composition doped by 10% of chromophore DANS ($T_g = 185$ °C) in a constant electric field at 45 °C (*i.e.*, at $T_g - 140$ °C) was also related to the decrease in the free volume.⁴⁷ The composition was preliminarily poled for 25 min at 190 °C (*i.e.*, at $T_g + 5$ °C). It was shown that upon keeping at 45 °C τ_{KWW} increases from 0.27 to 4.06 h after 31 h.

Polymers with $T_g = 82.7$ °C containing donor carbazole groups in the main chain substituted at positions 2 and 3 by acceptor substituents have been synthesised.⁴⁸ In contrast to the majority of polymeric systems with quasi-unidimensional chromophores, the direction of the dipole moment vector in these polymers does not coincide with the direction of the charge transfer, which results in an contribution of a nondiagonal coefficient of the second harmonic d_{ZX} is increased. The authors assume that the biexponential decay of $[I(-2\omega, t)]^{0.5}$ after the cut-off of the poling electric field measured at temperatures from 20 °C to 100 °C ($T_g + 17.3$ °C) is caused by two effects, *viz.*, the fast decay is determined by the movement of chromophore in a local free volume, and the slow decay is related to the recombination of the injected charges.⁴⁸

The values of τ_{KWW} and b in Eqn (14) obtained in the measurement of the second harmonic decay and an analysis of the electrochromic relaxation at 85–105 °C of a system consisting of PMMA and 1 mass % of nitroaminostilbene (NAS) ($T_g = 117$ °C), have been compared.^{49,50} These compositions possess electrochromic properties, *i.e.*, upon application of the poling field the optical density of the chromophore decreases reversibly. It is established⁵⁰ that the relaxation time (τ) of the NAS chromophores after the switch-off of the electric field estimated from the decay of the second harmonic intensity coincides with the time of the electrochromic relaxation. For such polymers as PMMA, poly(vinyl chloride) (PVC), and polycarbonate (PC) the time τ increases by an order of magnitude near the T_g on going from PVC to PMMA in the series $PVC < PC < PMMA$. This increase is believed to be caused by the decrease in the free volume of polymers [see relation (16)].⁵⁰ Such a conclusion provokes objections that the free volume is increased rather than decreased as on going from PVC to PMMA and makes up 18.56 and 23.17 cm³ mol⁻¹ at 20 °C, respectively (see Ref. 51). As the thermal extension coefficients for these polymers are similar $[(2.7-2.9) \times 10^4 \text{ K}^{-1}]$ (see Ref. 52), and the T_g of (PVC + NAS) is equal to 59 °C (see Ref. 49), which is almost half the T_g of (PMMA + NAS) (117 °C), the relation $V_{fr}(PVC) < V_{fr}(PMMA)$ holds and at elevated temperatures, too. It is possible that the captured charges determine the significant increase in the relaxation time on going from PVC to PMMA. It is to the accumulation of charges captured during poling that the memory effect in these compositions is related.⁵⁰

In the high-temperature corona poling, the sharp initial increase in $[I(-2\omega, t)]^{0.5}$ is followed by its gradual decay both in the polymers with the chromophores in the main chain⁵³ and in the doped polymers.³¹ Such behaviour of the polarisation curves can be caused by the decrease in the surface potential under equilibrium conditions due to the penetration of deposited charge into the bulk of the polymer and the increase in the film electric conductivity in the constant field due to the thermal increase in the crystallinity of the materials.

‡ The manifestation of this effect is that the repetition of the cycles polarisation/cut-off of the electric field results in the increase in the time of electrochromic relaxation, while optical density is not restored to the initial value.⁵⁰

The dynamics of the dipole reorientation at different temperatures in pure polymers, *viz.*, PMMA, PC, and polyimide (PI, $T_g = 207^\circ\text{C}$) not-doped with chromophores has been investigated.⁵⁴ The characteristics obtained by the method of the generation and decay of the second harmonic (532 nm) and by the method of the dielectric relaxation were compared. The values of $\chi^{(2)}$ appeared to be small, however, it was established that the decay plots of $[I(-2\omega, t)]^{0.5}$ can be described by the dependence (14). Two effects have been found. The first one lies in the fact that the decay time of the second harmonic τ_{KWW} measured in PI is increased by an order of magnitude when the same on-off cycle is repeated. The temperature dependences of the decay time for the second harmonic intensity $\tau(\text{SH})$ and the dielectric relaxation time $\tau(\text{DR})$ at the temperatures higher than T_g for all polymers are described by Eqn (13). The second effect is illustrated by the example of PVC where $\tau(\text{SH})$ is five orders of magnitude higher than $\tau(\text{DR})$ at $T_g + 23^\circ\text{C}$. This difference gradually decreases as the temperature decreases, and $\tau(\text{SH}) \approx \tau(\text{DR})$ at T_g . Both effects were explained by the influence of the captured charges on the decay time of $[I(-2\omega, t)]^{0.5}$ after the cut-off of the poling electric field. Presumably, the significant difference in the relaxation times is caused by the fact that at temperatures higher than T_g the polymeric chains are mobile and only captured charges hold the dipole in the oriented state thereby decreasing the orientational relaxation time $\tau(\text{SH})$.⁵⁴ At T_g , where the mobility of the polymeric chains is restricted, the role of the captured charges in the stabilisation of the oriented dipoles decreases.

Unfortunately, as a rule, in the studies mentioned above the decay of the potential was not measured simultaneously with the relaxation. Therefore, the suggestion of the influence of the captured charges on the characteristics of the relaxation processes are sufficiently justified, but are not proved.

VI. The influence of the captured charges on the characteristics of second harmonic generation and relaxation

The analysis of nonlinear optical characteristics of the polymeric materials presented above leads to the conclusion that a preferred orientation of the dipole chromophores is required to obtain noncentrosymmetrical structures in the optically transparent uniform polymeric films. The chromophores can be introduced in the polymeric chain or can be present as the side substituents in the macromolecule. Also, they can participate in the formation of a host-guest system as a low-molecular-weight additive to the polymeric matrix. The orientation of the chromophore groups results from the application of the poling electric field to the polymer film in the direction normal to its surface.

It is usually assumed that the contact polarisation method allows one to observe the nonlinear effects in the pure form, *i.e.*, without the influence of the residual charge after the cut-off of the poling field. However, in the electrode poling the current is passing through the film, even if an additional dielectric layer of SiO_2 is deposited between the anode and the polymer, see above. This indicates unambiguously the charge penetration into the film.³³ Even in the absence of the external potential difference, the charge up to $\sim 10^{-8} \text{ C cm}^{-2}$ is deposited on the surface of the dielectric polymeric film, when it comes in a contact with the metal owing to contact charging.^{55, 56}

It is shown³³ that the SHG characteristics are independent of the film conductivity, if the charge carrier concentration is several orders of magnitude smaller than the concentration of the chromophore. For example, for the film PIBMA + 1 mass % of DANS these concentrations are $10^{10} - 10^{15}$ and $5 \times 10^{19} \text{ cm}^{-3}$, respectively. In addition, the residual solvent (chloroform) even after careful removal is retained in the film at a concentration of five molecules per one DANS molecule, which influences significantly the kinetic characteristics of the SH decay. If nonpolar toluene is used as a solvent, the effect of the solvent traces on the

SHG characteristics is considerably less. It is assumed that the polar solvent affects significantly the local field factor, which is often estimated according to the Lorentz equation

$$f(\omega) = \frac{\varepsilon(\omega) + 2}{3}$$

or in a more accurate approximation through the Onsager equation

$$f(\omega) = \frac{(\varepsilon_\infty + 2)\varepsilon(\omega)}{\varepsilon_\infty + 2\varepsilon(\omega)}.$$

These expressions are strictly correct for a spherical symmetry and a continuum approximation for the dielectric medium surrounding the chromophore molecule. Thus, the decrease in the SH intensity is not necessarily associated with the change in the mean orientation of the chromophore molecules [see Eqn (7)]. However, the orientation can also be changed because of the change in the local electric field owing to molecular inhomogeneity.³³ All together, this differs from the concepts according to which the decrease in the SH intensity after the cut-off of the poling field (usually the experiment is carried out in such a way) is related only to the change in the mean orientation of the chromophore. The authors' conclusion³³ is made on the basis of the fact that the decrease in the SH intensity was observed experimentally when the poling field was not switched off.

The study of the decay of the SH intensity after the cut-off of the poling electric field seems to be most interesting. The characteristic time of the SH decay determines the stability of the operation of the nonlinear optical element. The features of the SH decay kinetics allow one to obtain information on the relaxation processes of polymeric chains and low-molecular-weight additives oriented by the poling electric field. It has been mentioned above that the great variety of these decay features were found in different studies: the exponential with saturation,³³ the sum of two exponents [see Eqn (12)],^{5, 40-42} the stretched exponent represented by the empirical function (14), the sum of two stretched exponents [see Eqn (14a)],^{13, 57} *etc.*

It should be noted that all effects connected to the SHG and observed upon multiple charging of the polymeric film, or upon changes in the solvent content in the sample, or after the cut-off of the poling field depend to a considerable degree, and sometimes crucially, on the value and kinetics of the surface charge relaxation. Thus, in order to obtain correct conclusions one should follow the change in the external electric field connected with the charges captured on the surface and in the bulk of the polymeric film and the SHG characteristics simultaneously. A simple relation exists between the surface potential, the external electric field $E(t)$ and the captured charge

$$E(t) = \frac{U(t)}{d},$$

$$U(t) = \frac{d\sigma(t)}{\varepsilon\varepsilon_0} + \frac{1}{\varepsilon\varepsilon_0} \int_0^d (d-x)\rho(x, t)dx, \quad (18)$$

where d is the film thickness, $\sigma(t)$ is the charge density of the film surface, ε is the dielectric constant, ε_0 is the permittivity of free space, and $\rho(x, t)$ is the charge density of the same sign in the polymer bulk at a distance x from the surface.

Simultaneous measurement of the decay kinetics of the second-order susceptibility and the surface potential of a PMMA film containing 4 mass % of DANS after charging by the corona discharge was performed by Liu *et al.*³¹ for the first time. It was established that at the temperatures of measurement higher and lower than T_g ($T_g = 88^\circ\text{C}$) the change in the relaxation of the normalised surface potential U/U_0 and normalised susceptibility χ/χ_0 are similar. The experimental results in the polymeric host-guest system studied could be explained if a

dynamic model that takes into account the Brown motion of the chromophores, the influence of the electric field, and the limitations imposed by the polymer matrix was used. The model contains four parameters, viz., D_{rot} (coefficient of the rotational diffusion); $a = \mu E/kT$; $b = v(g_1 - g_2)(E^2/kT)$, and θ_0 (the angle of the cone within which a chromophore molecule vibrates). Here, μ is the constant dipole moment of the chromophore, $v(g_1 - g_2)$ is the difference in the polarisability in the directions parallel and normal to the axis of the chromophore molecule. Small difference in the decay kinetics of U and $\chi^{(2)}$ is explained by the fact that the change in $\chi^{(2)}$ is more probably related not to the surface potential, but rather to the mean rotational moment $\langle T \rangle$ acting on the chromophore dipole in the external electric field,

$$\langle T \rangle = \int_0^\pi T(\theta) p(\theta, t) \sin \theta d\theta,$$

where $T(\theta) = \mu E \sin \theta - E^2 \cos \theta \sin \theta v(g_1 - g_2)$.

The coincidence of the decay curves for $\chi^{(2)}$ and $\langle T \rangle$ hardly should be paid great attention as the parameter $v(g_1 - g_2)$ was obtained from the experimental $\chi^{(2)}$ values rather than from independent data. In any case, in the experiments considered the decay kinetics of $\chi^{(2)}$ were determined either directly or through $\langle T \rangle$ using the decrease in the surface potential. The problems of the reason for the decrease in U and of the mechanism of this phenomenon are discussed neither in the paper cited (see Ref. 31) nor in other publications.

Practically, the main goals of the studies considered were the fabrication of the polymeric films with large values of $\chi^{(2)}$ that did not change with time and under the action of external factors. The decrease in $\chi^{(2)}$, fast or retarded, for different polymers at room temperature, indicates different thermal disordering of the chromophore orientation. Thus, it is possible to expect that the electric field results in the orientation of chromophores not only at high T_g , but at room temperature, as well. Consequently, it is possible to obtain polymeric films with nonlinear characteristics that can be manipulated by changing the external electric field in usual conditions. Using a simple system of PMMA + 2-methyl-4-nitroaniline (MNA) two components of the SHG response were registered at room temperature⁵⁸ when an alternating voltage of variable frequency was applied to the specimen comprising a film deposited on a glass substrate, and two metallic electrodes with a gap of 25 μm between them. The first component related to the orientation of the chromophore molecules is slow, and is observed up to 3×10^2 Hz. It lags in phase and decreases in the amplitude as the frequency of sinusoidal voltage increases. The second component, which seems to be caused by the third-order $\chi^{(3)}$ contribution into the SHG, is fast. This is characterised by the constant amplitude up to the maximum alternating field frequency 2×10^4 Hz and coincides with it in phase. The change in the slow component of the SH signal is determined by the rotational relaxation time of the oriented chromophores in the PMMA matrix, which is $\sim 10^{-2}$ s at room temperature.

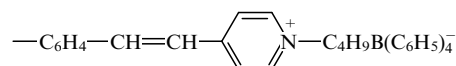
The polymeric films of the type considered can be used for the elaboration of fast nonlinear optical devices of a new type controlled by the external electric field. In order to obtain stable SHG it is necessary to stabilise the oriented state of the chromophores because the process of the electric poling disturbs the equilibrium of the system, and after the cut-off of the corona discharge the dipole chromophores tend to disorder their orientation. This inevitably leads to the decrease in the second harmonic intensity, especially if a rapid decrease in the surface potential takes places. Several methods that allow one to minimise disordering of the chromophores are suggested.

1. The synthesis of polymers with high T_g , and consequently with small free volume at room temperature. This ensures low mobilities of the charged particles and prolonged preservation of the surface potential and nonlinear properties. Polyimides with $T_g > 200$ °C can be mentioned as an example. However, the necessity to use high temperature for the poling leads to the

evaporation of the chromophore in the host – guest systems based on such polymers. In addition, in the host – guest systems the chromophore concentration is limited as it is crystalline and plasticises the polymer at high concentrations.

2. Chemical or photochemical cross-linking of a polymer containing the corresponding cross-linking groups in the macromolecule in the poling at T_g . The mechanism of the influence of cross-linking on the charge of the SHG characteristics is the same as in the former case. However, this method leads to an increase in optical losses because of nonuniformity of cross-linking reaction in the polymer bulk.

3. The synthesis of polymers the macromolecules of which contain chromophores and the groups that favour strong intermolecular interaction and consequently high rigidity of the system. The simultaneous investigation of the SHG and the surface potential in a polymeric system of the third type has been carried out.⁵⁹ A polyurethane (PU) $[-1,3-\text{C}_6\text{H}_4(4\text{-CH}_3)-\text{NH}-\text{CO}-\text{O}-(\text{CH}_2)_2-\text{NR}-(\text{CH}_2)_2-\text{O}-\text{CO}-\text{NH}-]_n-$ was synthesised, where the side substituent R has the following structure



High chromophore group concentration (68 mass %) was the reason for high $\chi^{(2)}$ values: up to 200 pm V⁻¹ ($d_{33} = 100$ pm V⁻¹, see Table 3). The formation of hydrogen bonds between neighbouring macromolecules favours an increase in the polymer hardness and the stabilisation of noncentrosymmetrical structure. In the corona discharge, $\chi^{(2)}$ and U are changed in the following way: at room temperature after the discharge is switched on, $\chi^{(2)}$ is increased sharply; $\chi^{(2)}$ and U remain constant as the temperature increases up to 145 °C ($T_g = 121$ °C), and at this temperature fast increase in $\chi^{(2)}$ is observed. Further heating to 190 °C leads to the decrease in the $\chi^{(2)}$ and U to zero, and the film becomes electroconducting. Subsequent cooling of the film starting from 170 °C to 145 °C is accompanied by the significant increase in the $\chi^{(2)}$ and U . In the process of cooling to room temperature, $\chi^{(2)}$ and U were little changed. At room temperature, after the switch-off of the corona discharge, the decrease in the surface potential to zero and the increase in the $\chi^{(2)}$ by $\sim 20\%$ were observed. The latter is possibly related to the noncolinearity of the dipole moment vector (that follows the direction of the electric field) and the largest component of the β tensor, which after the cut-off of the field can take the position corresponding to the increased value of $\chi^{(2)}$. After such treatment, the value of $\chi^{(2)}$ remained constant for at least 33 days. Consequently, strong intermolecular interaction providing for the system rigidity causes the preservation of the chromophore group orientation in the absence of the external electric field.

The relationship between kinetic parameters of the surface potential U and susceptibility $\chi^{(2)}$ was studied in the films of poly(vinyl acetate) (PVAC) doped with the chromophore DO3.^{28,60} It was shown for this system^{61–63} that the stepwise temperature decrease from $T_g = 41.5$ °C to 35 °C results in isothermal relaxation of the specific volume over 4 h. The decay of the normalised value of the second-order susceptibility after the cut-off of the corona discharge immediately after the temperature jump, and after 4 h is illustrated in the Figure 3. As is seen, the decay of $\chi^{(2)}$ in both cases is well approximated by the biexponential function

$$\left[\frac{I(-2\omega, t)}{I(0)} \right]^{0.5} = \varphi \exp\left(-\frac{t}{\tau_1}\right) + (1 - \varphi) \exp\left(-\frac{t}{\tau_2}\right). \quad (19)$$

Complete relaxation of the specific volume leads to the significant retardation of both fast and slow components: at 35 °C, in the case of nonrelaxed film the kinetic curves of the $\chi^{(2)}$ decay are characterised by the parameters $\varphi = 0.35 \pm 0.05$,

Table 3. Nonlinear second harmonic coefficients (d_{ZX}) in different media oriented at T_g . The measurements were performed after the cut-off of the constant electric field and the establishment of the steady-state characteristics.

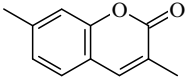
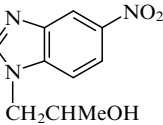
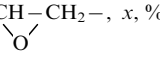
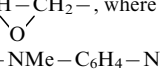
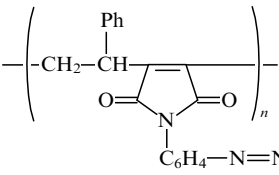
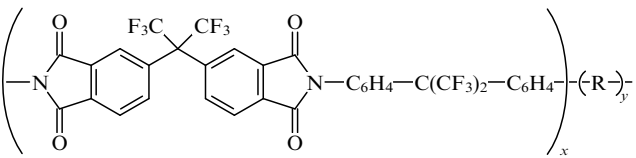
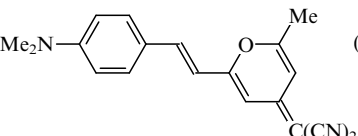
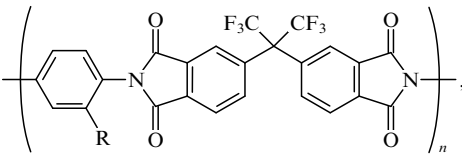
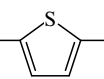
No.	Compound	λ /nm	d_{ZX} /pm V ⁻¹	Ref.
1	α -Quartz	1064	$d_{11} = 0.4 - 0.5$	5, 70, 72–74
2	BaTiO ₃	1064	$d_{51} = 17$	73
3	LiTaO ₃	1064	$d_{33} = 19$	73
4	LiNbO ₃	1064	41	73
5	Host — PMMA, guest — DANS (2 mass %)	1064	1	5
6	Host — spray-coated polytetrafluoroethylene, guest — DANS (10 mass %)	1064	6.2	75
7	Host — PMMA, guest — DO3	1064	5.8	5
8	Host [—O—C(O)—3-C ₆ H ₃ (OH)—5-C(O)—(CH ₂) ₂ —NR—(CH ₂) ₂ —], where R = (C ₆ H ₄ SO ₂ (CF ₂) ₈ F; guest — chromophore NMePr—C ₆ H ₄ SO ₂ C ₈ X ₁₇ , where X = H ($T_g = 80$ °C), F ($T_g = 83$ °C)	1064	$d_{33} = 3.4$ 3.0	77
9	Host — PMMA, guest — DR1	1064	$d_{33} = 9$	5
10	—[—CHR—CH ₂ —O—C ₆ H ₄ —CMe ₂ —C ₆ H ₄ —O—CH ₂ —CHR—CH ₂ — —NR'—CH ₂ —], where R = —O—C(O)—CH=CHPh — pendent groups, NR' — chromophore, R' = —C ₆ H ₄ CN	1064	4.2	76
11	—[—CH ₂ —CHPh—], _x —[CH ₂ —CRMe—], _y —, where chromophore R = —C(O)—O—(CH ₂) ₂ —C ₆ H ₄ —CH=N—C ₆ H ₄ —NMe ₂	1064	$d_{33} = 12.25$	78
12	Copolymer of C(CO ₂ Me)Me=CH ₂ and the chromophore Et ₂ N—X—C(O)—NH—(CH ₂) ₂ —O—C(O)—CMe=CH ₂ , where —X— = 	1064	$d_{33} = 13$	79
13	PA	1542	$d_{33} = 40$	39
14	—[CH ₂ —CRMe—], _n , where R = —C(O)—O—(CH ₂) ₂ —NEt—C ₆ H ₄ —N=N—C ₆ H ₄ —  ($T_g = 151$ °C)	1064	$d_{33} = 16.5$	80
15	(S)-NPP-PHS (see text), x (%): 36 48 62 75 90	1064	$d_{33} = 17.8$ 23.7 26.6 29.0 32.0	41
16	—[CH ₂ —CMeR—], _x —[CH ₂ —CMeR'—], _y —, where pendent chromophore is R = —C(O)—O—(CH ₂) ₂ —NEt—C ₆ H ₄ —N=N—C ₆ H ₃ R''—NO ₂ , (a) R'' = H; R' = —C(O)—OMe, x/y = 1; (b) R'' = —COOH; R' = —C(O)—O—CH ₂ —CH—CH ₂ —, x, %: 8  17 30	1320	$d_{33} = 29$ 10.2 24.0 29.0	81
17	—CH ₂ —CMe ₂ —CRMe—C(O)—O—CH ₂ —CH—CH ₂ —, where pendent  chromophore is R = C(O)—O—CH ₂ —NMe—C ₆ H ₄ —N=N—C ₆ H ₄ —NO ₂	1320	$d_{33} = 47$	82
18	—[CH ₂ —CMeR—], _{0.9} —[CH ₂ —CMe(COR')—], _{0.1} — R = —C(O)—O—(CH ₂) ₂ —NEt—C ₆ H ₄ —N=N—C ₆ H ₄ —NO ₂ , R' = —NH—C ₆ H ₃ -3-MeNO ₂	1064	$d_{33} = 60$	83
19	—[CH ₂ —CMe(CO ₂ Me)—], _x —[CH ₂ —CRMe—], _y —, where R = —C(O)—O—CH ₂ —C ₆ H ₄ —X=X—C ₆ H ₄ CN, —X=X— = —CH=CH—; y (%): 10.3 16.4 22.5 43.0 —X=X— = —N=N—; y (%): 11.9 16.4 31.5 44.0 49.0 71.7 100.0	1064	$d_{33} = 8.8$ 11.5 12.0 12.0 5.2 21.0 68.0 45.0 32.0 31.0 26.0	84
20	Host — polyimide, guest — DANS or Et ₂ —C ₆ H ₄ —(CH ₂) ₂ —  —C(CN)=C(CN) ₂	1300	$d_{33} = 2.5$ 40	85

Table 3 (continued).

No.	Compound	λ /nm	d_{ZZ} /pm V ⁻¹	Ref.
21	 $(T_g = 137^\circ\text{C})$	1338 1542	$d_{31} = 23$ 15	86
22	Host —  (R is the group, which undergoes cross-linking upon photochemical or thermal action), guest —  (20 mass %)	1064	$d_{33} = 13$	87, 88
23	P1 P2 P3 (see text)	1064	$d_{33} = 30$ 90 100	46
24	 where R = $-\text{O}-(\text{CH}_2)_2-\text{NEt}-\text{C}_6\text{H}_4-\text{CH}=\text{CH}-\text{C}_6\text{H}_4-\text{SO}_2\text{Me}$ ($T_g = 240^\circ\text{C}$); $-\text{O}-(\text{CH}_2)_2-\text{NEt}-\text{C}_6\text{H}_4-\text{X}-\text{C}_6\text{H}_4-\text{NO}_2$, where $-\text{X}- =$  ($T_g = 227^\circ\text{C}$) $-\text{X}- = -\text{CH}=\text{CH}-$ ($T_g = 229^\circ\text{C}$) $-\text{X}- = -\text{N}=\text{N}-$ ($T_g = 235^\circ\text{C}$)	1064	$d_{33} = 51$ 103 146 169	89 90 90, 91 90
25	Linear polyurethane with chromophores directed normally to the main chain	1064	$d_{33} = 67$	92
26	PU (see text)	1064	100	59
27	PU $[-\text{O}-(\text{CH}_2)_2-\text{NR}-(\text{CH}_2)_2-\text{O}-\text{C}(\text{O})-\text{NH}-\text{C}(\text{O})-]_n$, where R = $-\text{C}_6\text{H}_3(\text{Me}-\text{N}=\text{N}-\text{C}_6\text{H}_3\text{Me}-\text{NO}_2)$	1064	140–223	93
28	Langmuir–Blodgett films of 2,4-bis[4-(N,N-dibutylamino)phenyl]squaraine (C_4H_9) ₂ N–C ₆ H ₄ –C ₄ O ₂ –C ₆ N ₄ –N(C ₄ H ₉) ₂	1064	$d_{33} = 125$	94

$\tau_1 = 0.6 \pm 0.1$ min, $\tau_2 = 8 \pm 0.5$ min, while for the relaxed film $\varphi = 0.35 \pm 0.05$, $\tau_1 = 2 \pm 0.3$ min, $\tau_2 = 28 \pm 2$ min.

The measurement of the decay kinetic curves for $\chi^{(2)}$ and U at 23°C (Fig. 4) have practically have shown their virtually complete identity; $\varphi = 0.3 \pm 0.05$, $\tau_1 = 2.1 \pm 0.3$ min, and $\tau_2 = 110 \pm 5$ min. Consequently, the SHG in the PVAC + DO3 films is completely governed by the surface potential, *i.e.*, by the charges deposited on the films by the corona discharge in the range from T_g to 23°C . A direct proof of this conclusion was obtained using an effective method for the removal of the surface charge: the film was immersed for 15 s in a saturated aqueous NaCl solution, which led to the disappearance of SHG and the surface potential (see Fig. 4, points on the x axis). Preliminary experiments have shown²⁹ that other known methods of the surface potential removal, namely, keeping in a moist atmosphere, contact with the grounded metallic electrode, *etc.*, are ineffective. With a PMMA + DO3 film non-swelling in water as an example it was shown that the disappearance of the surface charge is not

connected to the swelling and plasticisation of the PVAC immersed for a short time in an aqueous solution. The SHG behaviour of this film after the removal of the surface charge is similar to that in the PVA + DO3 film (see Fig. 4).⁶⁴ For the latter system, it was sufficient to use even distilled water, *i.e.*, the charged particles are water-soluble; the cycles 'discharge in water – charging by the corona discharge' can be repeated many times without change of nonlinear optical and electrical characteristics; the charged film retains constant surface potential and $\chi^{(2)}$ for several months (time of observation) while kept in ordinary conditions. The unambiguous conclusion can be made on the basis of these results that all charge is concentrated on the film surface. In such a case, the surface potential is determined by the first term in Eqn (18).

Charging the film by the negative corona discharge results in predominant deposition of the CO_3^- ions onto the surface (see Refs 65, 66). The subsequent fate of the deposited ions depends on the characteristics of the polymeric system. First, the existence of

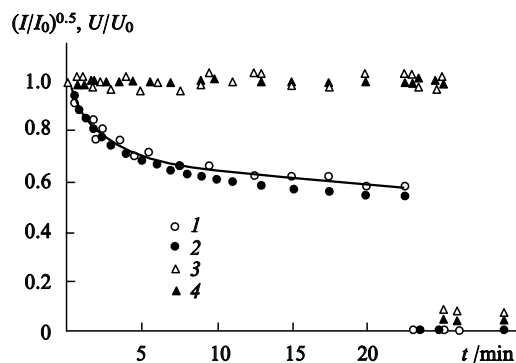


Figure 4. The kinetics of the decay of the second harmonic intensity and the surface potential. PVAC + 2 mass % of DO3 (1). PMMA + 5 mass % DO3 (2).

(1) second harmonic signal for PVAC + 2 mass % of DO3, keeping at 43 °C for 5 min, then charging by the corona discharge for 2 min at 23 °C; (2) surface potential for PMMA + 5 mass % DO3, charging by the corona discharge for 10 min at 23 °C, measurement at 23 °C; (3) second harmonic signal; (4) surface potential. the curve is plotted according to equation (19) with parameters $\varphi = 0.3$, $\tau_1 = 2.3$ min, $\tau_2 = 115$ min.

the electronic conductivity can not be assumed in the films. Even if we consider that the chromophores can serve as the electron-transport centres, their concentration (2 mass %–5 mass %) is definitely insufficient for the effective electron (or hole) transport through the film as the mean distance between neighbouring transport centres should not be exceeded ~ 15 Å.⁶⁷ In addition, penetration of ions into the bulk of the film should possibly be excluded. This is supported by the fact that after the polymer film treatment in the electrolyte solution the surface charges are practically completely removed (see Fig. 4).

The process of the surface potential decrease consisting of relatively fast (hundreds of seconds) and slow steps is well known. This was observed for different polymeric films without low-molecular-weight chromophores charged by the corona discharge (see Ref. 30 and references therein). For different polymers, the magnitude of the surface potential at the fast step varies from several to dozens percent relative to the initial value. It is assumed that the fast decay is connected with the drift of ions and their capture near the film surface by the polarisation and structural traps. The slow exponential decay seems to be related to the discharge of the captured charge because of the intrinsic bulk electric conductivity of the film. The rate of this decay is determined by the dielectric relaxation time (τ_M). Polymeric films always possess some ionic conductivity due to the residual solvent or ionic dissociation of the polar groups in macromolecules.^{30, 68} Thus, the decay of the surface potential is expressed by equation

$$U = U_0 \left[\varphi \exp\left(-\frac{t}{\tau}\right) + (1 - \varphi) \exp\left(-\frac{t}{\tau_M}\right) \right],$$

where $\tau = (v_t N \sigma)^{-1}$, $\tau_M = \varepsilon \varepsilon_0 / e n \mu$, v_t is the thermal velocity of ions, N is the concentration of the capture centres, σ is the charge capture cross-section, e is the electron charge, n and μ are the concentration and the mobility of the free charge carriers in the polymer bulk.

Retardation of the decay kinetics of $\chi^{(2)}$ upon physical ageing of a polymer can be explained by the decrease in the polymer free volume. The diffusion coefficient of molecules D in an amorphous phase at $T < T_g$ is linked to the free volume by Eqn (16). Taking into account the Einstein relation

$$\frac{\mu_d}{D} = \frac{e}{kT},$$

where μ_d is the mobility, we obtain that the decrease in $V_{fr}(T)$ leads to the increase in τ_M .

VII. The second harmonic electrooptical coefficient and nonlinear coefficient

The idea of using light for information transmission has become a reality after the invention in the 50–60s of coherent radiation sources in UV, visible, and IR ranges, as these allow one to increase substantially the capacity of the transmitting optical systems and to multiply the capacity of systems in the millimetre range. However, in addition to the coherent light sources it was necessary to develop transmitting media, active optical elements, materials for recording, storage and reproduction of optical information that would be cheap, technological, highly efficient, and compatible with modern microelectronic devices. Nowadays, organic polymeric materials of different chemical structure meet these requirements entirely. Polymeric nonlinear optical systems are promising for their utilisation as the light beam modulators, fibre optic switches, the laser radiation harmonic generators for enhanced capacity of recording, photorefractive media for the reversible recording of the holograms with the diffractive efficiency close to 100%, etc.^{69–71} The main parameter, which characterises an electrooptical material is the electrooptical coefficient r . For example, r is 1.43 pm V⁻¹ for AsGa, and 30 pm V⁻¹ for LiNbO₃, it increases considerably (up to 100 pm V⁻¹) for polymers.⁷⁰

On the one hand the electrooptical coefficient relates the change in the refractive index Δn of a polymer to the magnitude of the external electric field E : $\Delta n = -0.5n^3 r E$. On the other hand, the electrooptical coefficient is connected with the second-order susceptibility, which determines the intensity of the second harmonic

$$r = -\frac{2\chi^{(2)}}{n^2 \varepsilon}, \quad (20)$$

If r directly characterises the effects of modulation and switching of light fluxes and also the efficiency of the hologram recording on polymeric photorefractive materials, $\chi^{(2)}$ determines the efficiency of the laser radiation frequency transformation. Generally, the quantities r and $\chi^{(2)}$ are of equal value for the characterisation of the electrooptical properties of the material, however, in this review more numerous and detailed studies on the second harmonic generation are analysed. In addition, the relation of $\chi^{(2)}$ to the molecular motions in a polymeric matrix is direct and more obvious.

The steady-state values of the second harmonic nonlinear coefficient ($d_{33} = 0.5\chi_{zzz}^{(2)}$) measured (mainly at 20 °C) after the orientation of the chromophores in a constant electric field at the glass transition temperature for different polymeric systems are listed in Table 3. Despite different conditions corresponding to the measurement of this characteristic, some general features may be found. As is seen, the host–guest systems with small rotational diffusion times are characterised by low d_{33} values. The nonlinear coefficient in polyesters with chromophores in the pendent substituents (entries 17–19) is close to the d_{33} values in inorganic crystals and is increased markedly upon replacement of the stilbene-containing chromophores by the diazo groups. In the polymer 19 (where $-X=X-$ is $-N=N-$), the increase in the concentration of the chromophore groups first results in the increase of d_{33} , then it passes through a maximum (with one third of the repeating units containing the chromophores), and then gradually decreases. The decrease is related to the change in the polymer conformation at high chromophore content. The d_{33} values of polyimides (entry 24) with the high glass transition temperatures and, consequently, low polymeric chain mobility at room temperature exceeding remarkably those in inorganic crystals. Polyurethanes (entry 27), which acquire rigid structure after

the orientation due to the presence of intermolecular hydrogen bonds, possess the highest d_{33} values (≥ 200 pm V $^{-1}$).

Polyesters with the pendent chromophore groups that alternate with the cinnamate groups $-(CH=CH)-_n-R$ (R is alkyl), are used for the creation of a rigid polymeric matrix following UV radiation.⁹⁵ It is known that UV light induces $[2 + 2]$ -cycloaddition involving of the double bonds and results in cross-linking of the neighbouring side groups. The polymers 16b and 17 contain the epoxy groups which are cross-linked in the course of the orientation in the constant field at the temperature above 70°C. The absence of the effect of the epoxy groups (see entries 16a and 16b) is explained by the fact that the cross-linking proceeds faster than orientation, which becomes ineffective in the rigid cross-linked matrix. It should be added that in polydiacetylenes^{96,97} the stable oriented state is achieved even in the absence of the external electric field, namely, upon radiation-chemical or thermal synthesis from substituted diacetylene leading to the formation of a cross-linked three-dimensional structure. The polymer obtained in this synthesis had $d_{33} = 5.57$ pm V $^{-1}$.

All systems considered above contain chromophores with intramolecular electron transfer. Significant effects can be expected in polymeric systems with intermolecular donor-acceptor complexes. This followed from the fact that self-organised Langmuir–Blodgett films⁹⁴ consisting of centrosymmetrical molecules of 2,4-bis[4-(*N,N*-dibutylamino)-phenyl]squaraine $(C_4H_9)_2N-C_6H_4-C_4O_2-C_6H_4-N(C_4H_9)_2$ possessed high second-order susceptibility $\chi_{ef}^{(2)} = 250$ pm V $^{-1}$ ($d_{ef} = 125$, see Table 3, entry 28). The effect is due to the formation of the noncentrosymmetrical intermolecular donor-acceptor T-shape complexes, where the donor amino group of one molecule is oriented towards the central four-membered acceptor ring $-(C_4O_2-)$ of another molecule.

As regards practical application of polymeric materials with stable nonlinear second-order properties, for example, as optical switches or modulators, the absence of optical absorption at the wavelength of the second harmonic and photochemical stability of the chromophore groups and molecules with respect to the atmospheric oxygen are of significant importance.⁹⁸ The former demand can be met by the synthesis of appropriate chemical structures, and the latter is achieved by the introduction of oxygen acceptors into the working layer and the use of protective layers. In all cases, low electric conductivity of polymeric nonlinear optical systems is a must.

VIII. Conclusion

In polymeric host–guest NLO systems in ordinary conditions (room temperature or temperature up to T_g , the range of characteristic time from ~ 0.1 s to ∞) the decay kinetics of the SH intensity is determined entirely by the kinetics of the change in the surface potential. This phenomenon is explained by the fact that the characteristic times of the rotational diffusion of chromophores are shorter than the times of flight of the charged particles through the polymeric films. The reasons for the decrease in the surface potential and the features of this process are not sufficiently studied to date. In polymeric systems where chromophores are chemically linked to the polymer chain (pendent substituents) or they are the fragments of the main chain, at the temperatures below T_g the behaviour of the SH is determined by the dynamic characteristics of the polymeric matrix. For example, the formation of a polymeric network or strong intermolecular interaction due to the formation of the hydrogen bonds or the presence of the charged groups determine the SH stability with time, which is not connected with the presence of an external electric field.

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

Conjugated nitrosoalkenes[†]

I M Lyapkalo, S L Ioffe

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Abstract. Published data on the preparation, structure, physical and chemical properties, and reactivity of nitrosoalkenes are described systematically. The influence of the structure and stereoelectronic effects of substituents at the double bond on the stability of nitrosoalkenes is analysed. Primary attention is paid to concerted cycloaddition of nitrosoalkenes to miscellaneous multiple bonds, in particular, to the problems of regio-, stereo-, and enantioselectivity of [4 + 2]-cycloaddition of nitrosoalkenes to alkenes. The bibliography includes 183 references.

I. Introduction

The nitroso group is a powerful electron-withdrawing substituent; this has a crucial effect on the chemical properties of all conjugated systems containing this group. In particular, the nitroso group is known to promote efficiently nucleophilic substitution in benzene derivatives, and in some cases its activating influence is even more pronounced than that of the nitro group.^{1,2}

The main methods for synthesis, physical properties, structures, and reactivities of conjugated nitrosoalkenes are considered in only one review covering publications which appeared before 1983.³ However, more recently, some important aspects of the chemistry of these compounds have been further developed, most of all, owing to the efforts of the research groups headed by Reissig and Gilchrist. In the present review, we generalise and describe systematically the data published up to the end of 1997 including those concerning participation of nitrosoalkenes in concerted processes, primarily, in [4 + 2]-cycloaddition to alkenes.

The formation of nitrosoalkenes as reactive intermediates was hypothesised as early as 1898;⁴ however, it was not until 1960 that synthesis of the first stable compound of this type, trifluoronitrosoethylene, was reported.⁵ Since then, only a few stable nitrosoalkenes have been prepared; they usually contain bulky aryl, *tert*-alkyl, or halo substituents at the β -carbon atom. Nitrosoalkenes in which the β -carbon atom is included into a heterocyclic system can also be put into this group.

However, there is strong evidence indicating that many nitrosoalkenes can exist in solutions as unstable intermediates. They comprise a large number of β -alkyl- and β -aryl-substituted nitro-

soalkenes, several halo-substituted derivatives, and only few compounds containing OR or NR₂ groups at the β -position. Some of these intermediates have been identified by spectroscopy, while others have been detected on the basis of their characteristic blue colour. The lifetimes of these compounds vary a over wide range.

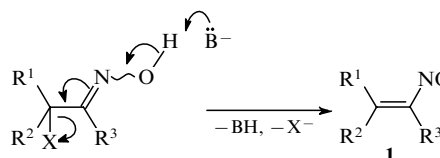
Finally, there exist nitrosoalkenes, which cannot be detected due to their instability. The formation of these compounds is judged based on experiments on their trapping. Thus all the known intermediates of the general formula CH₂=C(R)NO belong to this group. The properties of typical representatives of nitrosoalkenes **1** are listed below in Table 1.

This review consists of three parts. The first part is devoted to the methods for the synthesis of nitrosoalkenes, and the second one deals with their physical properties and structures. The third part describes chemical transformations of nitrosoalkenes, classified according to the type of reaction.

II. Methods for generation of nitrosoalkenes

1. 1,4-Elimination in α -substituted oximes under the action of bases

In recent years, the chemistry of nitrosoalkenes **1** (Table 1) has been developing especially successfully, mostly owing to the elaboration of a simple and reliable method for their generation from available precursors, α -substituted oximes.



This method has been used to prepare all the compounds listed in Table 1, except for trifluoronitrosoethylene **1a**. The chloride ion is the most frequently used leaving group; however, other halides are also suitable. Since nitrosoalkenes are sensitive to nucleophilic attacks, it is very important to choose appropriate conditions for their generation. The reaction should be carried out using weakly nucleophilic solvents and bases, except for those cases where they are used to trap nitrosoalkenes. Stable nitrosoalkenes have been synthesised using tertiary amines, Et₃N⁶ and 1,5-diazabi-

I M Lyapkalo, S L Ioffe N D Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (095) 135 53 29

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[†] The review is dedicated to Professor Seebach in connection with his 60th birthday.

Table 1. Typical representative nitrosoalkenes **1**.

Alkene 1	R ¹	R ²	R ³	Properties	Ref.
a	F	F	F	blue gas, stable up to 100 °C	5
b ^a	H	Mes	Me	blue crystals, m.p. 47–58 °C	6
c	Bu ^t	Bu ^t	H	blue crystals, m.p. 38 °C	7
d	Cl	Cl	Me	can be isolated at room temperature	8
e	Cl	Cl	CCl=CCl ₂	m. p. 44 °C at 0.02 mm Hg	9
f	H	–(CH ₂) ₄ –		blue crystals at –50 °C, decomp. above –30 °C	10
g ^a	H	Cl	Cl	long-lived in solution	8
h	Cl	Cl	H	the same	8
i ^a	H	Ph	Me	detected in solution (colour)	11
j ^a	Me	Mor ^b	Ac	the same	12
k	H	H	H	lifetime in the gas phase 30 s	13
l	H	H	Ph	the existence was confirmed by trapping and by kinetic studies	14, 15
m	H	H	Ac	detected only by cycloaddition	16
n	H	H	CF ₃	the same	17

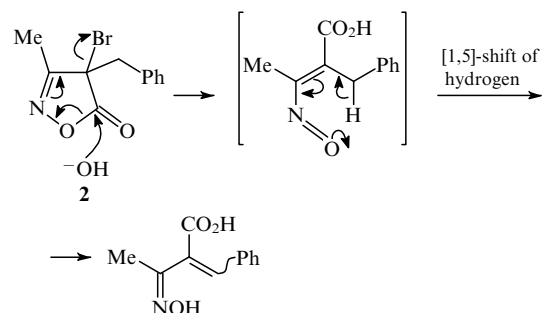
^a The stereochemistry at the C=C bond was not studied;

^b Mor = 

cyclo[4.3.0]non-5-ene (DBN).⁷ Unstable intermediates are better generated by treatment of α -halo oximes in non-nucleophilic organic solvents with insoluble inorganic bases such as Na₂CO₃^{17, 18} or Ca(OH)₂.¹⁰ These conditions ensure maintenance of a very low steady-state concentration of the highly reactive intermediates **1** and, as a consequence, suppression of the undesirable side processes involving more than one nitrosoalkene molecule, for example, polymerisation.

Denmark *et al.*^{19, 20} proposed a very interesting and useful modification of this method, namely, generation of nitrosoalkenes under 'neutral' conditions by treating *O*-trialkylsilyl derivatives of α -halo oximes with fluoride ions in weakly nucleophilic aprotic solvents. The best results were obtained with CsF and KF in MeCN;²⁰ however, AgF or Bu₄NF can also be used.

One of the synthetic modifications of the general method for the generation of the compounds **1** is rupture of the C–O bond in the isoxazoline ring of compound **2** as a result of deacetylation of the oxyimino group on treatment with a base and subsequent elimination of Br[–].²¹



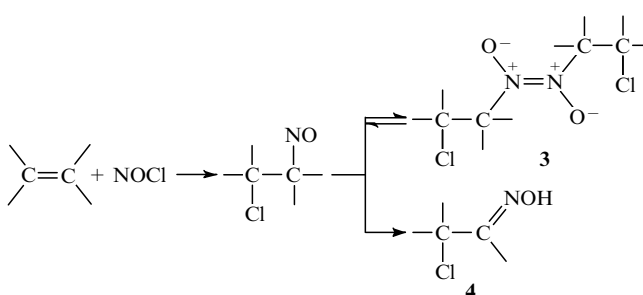
Since α -halo oximes are important precursors of nitrosoalkenes, we considered it pertinent to outline here the three main methods for the synthesis of these compounds.

The first method is based on the reaction of the corresponding halo ketones with hydroxylamine. In particular, α -chloro oximes are prepared from α -chloro ketones and hydroxylammonium chloride in protic solvents.¹⁹ To synthesise α -bromo oximes, hydroxylammonium sulfate is used in order to avoid halogen exchange.²² It is undesirable to use alcohols as solvents, because they can substitute the halogen if the reaction time is long.¹⁶ According to the Denmark modification,¹⁹ *O*-trialkylsilyl derivatives of α -chloro oximes are prepared by condensation of the corresponding chloro ketones with *O*-trialkylsilylhydroxylamine in CHCl₃ in the presence of 4 Å molecular sieves.

The second method includes interaction of nitro alkenes with SnCl₂²³ or TiCl₄.⁸ It is used to prepare some α -chloro oximes or α -chlorohydroxyiminoyl chlorides, respectively.

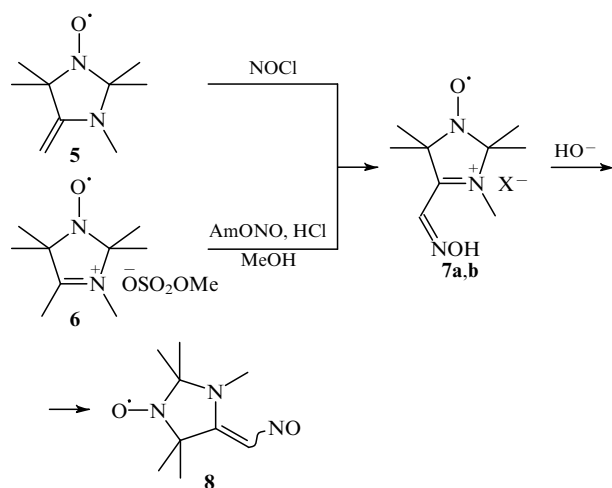
The third method is also applicable only to the synthesis of chloro oximes. It is based on the addition of nitrosyl chloride to alkenes,^{24–29} and was first proposed more than a hundred years ago²⁶ for the synthesis of crystalline derivatives of terpenes. In the 60s, this reaction was extended to a broad range of nucleophilic and electrophilic alkenes mostly in the studies by Ogloblin *et al.*^{27–29} It is a convenient pathway to chloro oximes of the type ClCH₂C(R)=NOH [R = C(O)H, Ac, C(O)Ph, and CN]. The reactions of alkenes with NOCl yield initially β -chloro nitroso-compounds, which can subsequently dimerise to give compound **3** and/or rearrange into α -chloro oximes **4**. The latter route is possible if the carbon atom bound to the nitroso group carries a hydrogen atom (Scheme 1).^{24, 25}

The reactions with ordinary alkenes can be classified as electrophilic substitution, and the adduct is formed in conformity with the Markovnikov rule.^{24, 25} The fact that nitrosyl chloride adds unexpectedly rapidly to some α,β -unsaturated carbonyl compounds^{27–29} might be due to preliminary coordination of the nitrosonium cation (NO⁺) to the oxygen atom of the carbonyl group.

Scheme 1

If there are substituents at the C=C bond of the substrate molecule, able to stabilise efficiently the carbocationic site resulting from the attack by the NO⁺ cation, the reaction product has an ionic structure. The reactions shown in Scheme 2 are interesting examples of the generation of ionic intermediates of this type.³⁰

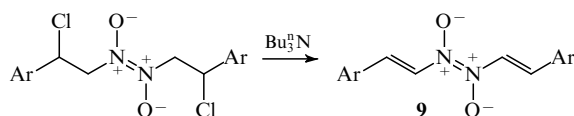
Scheme 2



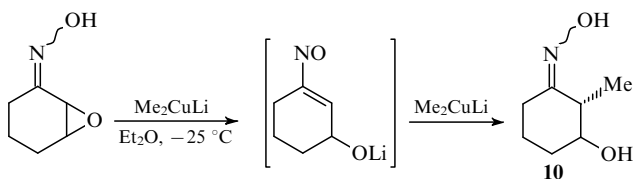
$\text{X} = \text{Cl}$ (**a**), OSO_2OMe (**b**).

The nitrosation of the double bond in compound **5** by nitrosyl chloride or the acid-catalysed reaction of alkyl nitrate with the immonium cation **6** give compounds **7a,b**. To prepare nitrosoalkene **8**, the nitrosation product is treated with a base. During the transformations presented in Scheme 2, the sterically hindered radical site remains intact.³⁰

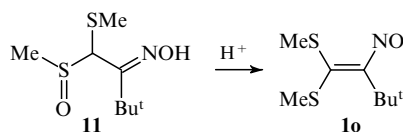
The type **3** dimers of β -chloro nitroso-compounds have also been used as precursors of some nitrosoalkenes.^{31–34} Thus the reaction of Bu_3N with dimers of chloro nitroso-compounds prepared from styrenes affords only orange dimers of β -nitroso styrenes **9**.³³



There are only few examples of generation of nitrosoalkenes from oximes with leaving groups other than halide ions. Thus products of the addition of nitrosyl sulfate ($\text{NO}^+\text{HSO}_4^-$) to alkenes have been used as the initial compounds for the preparation of nitrosoalkenes.³⁵ The nitrite ion can also serve as the leaving group.⁷ Yet another interesting variant of this approach is cleavage of the oxirane rings in α -epoxy ketoximes on treatment with the cuprate reagent to give compound **10**.³⁶



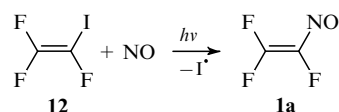
The acid-catalysed dehydration of sulfoxide **11** involves presumably the intermediate formation of the nitrosoalkene **10**.³⁷



However, as far as we know, the direct dehydration of α -hydroxy ketoximes has not been used as a method for generation of nitrosoalkenes.

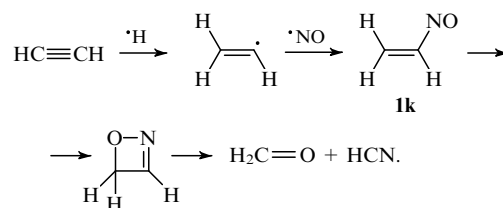
2. Reactions of nitrogen(II) oxide with vinylic radicals

Trifluoronitrosoethylene **1a** was obtained by photolysis of trifluoroiodoethylene **12** in the presence of nitrogen(II) oxide.⁵

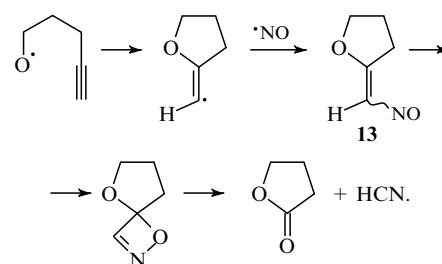


It has been assumed that the reaction product is formed upon recombination of trifluorovinyl radical with NO . To date, the compound **1a** is the only vinylic nitroso derivative prepared in a pure state using this type of reaction; however, in a number of other syntheses, nitrosoalkenes have been postulated as reaction intermediates.

Thus acetylene reacts with hydrogen atoms and NO to give HCN and formaldehyde resulting apparently from rearrangement and fragmentation of the intermediate nitroso ethylene **1k**.³⁸



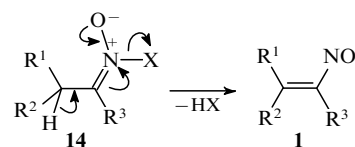
Several more reactions of this type have been reported.^{38,39} For example, nitrosoalkene **13** was postulated as an intermediate in the reaction presented below:³⁹



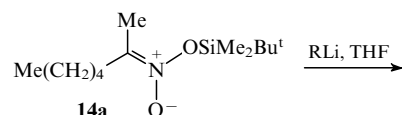
3. 1,3-N,C-elimination of trialkylsilanol from silyl nitronates

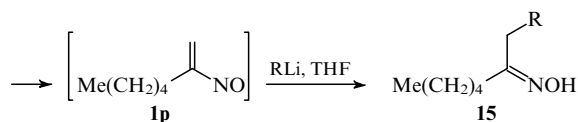
The reactions of 1,4-elimination of HX from α -substituted oximes under the action of bases is the most important and the most general method for the generation of nitrosoalkenes **1**.

It is curious to note, however, that the 'alternative' possibility of 1,3-elimination of HX from compounds like **14** as a route for generation of nitrosoalkenes has not been specially considered until recently.



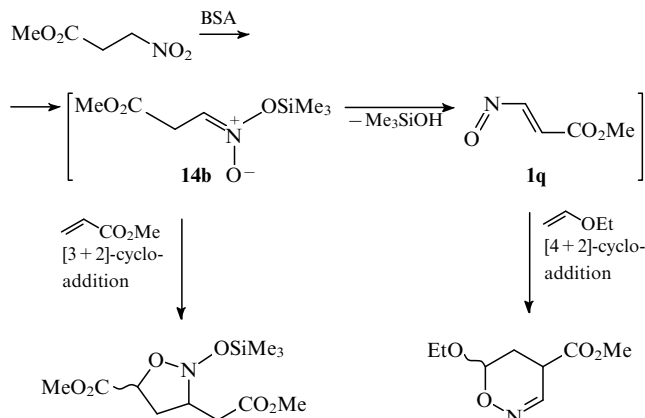
The possibility of this transformation was first hypothesised by Seebach *et al.*⁴⁰ They postulated 2-nitrosohept-1-ene **1p** as an intermediate in the reaction of *tert*-butyldimethylsilyl nitronate **14a** with excess organolithium reagent. The first equivalent of RLi reacts as a base facilitating the abstraction of *tert*-butyldimethylsilyl, and the second equivalent reacts with the resulting nitrosoalkene **1p** as a nucleophile, and this leads to the final reaction product, dialkyl ketoxime **15**.⁴⁰





Later, in studies by Ioffe *et al.*,^{41–44} β -functionally substituted nitrosoalkenes **1** have been considered as the most probable intermediates for trimethylsilylation of nitro compounds containing electron-withdrawing groups at the β -position (Scheme 3). In the authors' opinion, these substituents facilitate spontaneous fragmentation of the intermediate trimethylsilyl nitronates **14**. The fate of the resulting nitrosoalkenes **1** depends on their structure, in particular, on whether or not protons or electron-withdrawing groups are present at the γ -position of the initial nitro compound.⁴⁴ The final reaction products are either *O*-trimethylsilyl-derivatives of α,β -unsaturated oximes **16** [pathway (a)] or *N,N*-dialkenyl-*N*-trimethylsilyloxyamines **17** [pathway (b)]. The reaction follows pathway *a* if the molecule **1** contains two electron-withdrawing groups (R^2 , R^4) such as CN or COOMe. In the latter case [pathway (b)], silyl nitronates **14** not only serve as the source of nitrosoalkenes **1** but also react with them according to the pattern of 1,2-addition to the nitroso group.

Recently, the generation of silyl nitronates **14** and then of nitroso alkenes **1** during the formation of type **17** products was confirmed by selective trapping of these intermediates in the silylation of methyl 3-nitropropionate.⁴⁵

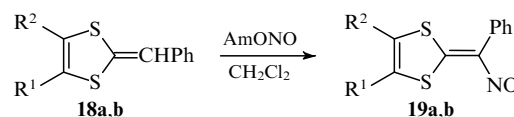


The above sequence of reactions confirms the possibility of generating nitrosoalkenes **1** from silyl nitronates **14**. This is

fundamentally important, since the compounds **14** are readily accessible and can prove to be convenient precursors of nitrosoalkenes, especially, of β -functionally substituted ones, which have scarcely been studied.

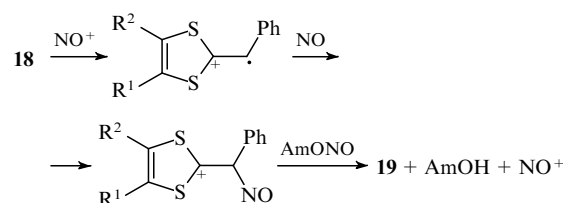
4. Nitrosation of C=C bonds enriched in electrons

When dithiafulvenes **18** are treated with amyl nitrite, nitroso-compounds of the type **19** are readily produced.⁴⁶

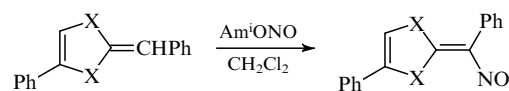


$\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$ (a); $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Me}$ (b).

The ease of nitrosation is due to the presence of the electron-donating heterocyclic fragment, which efficiently stabilises the positive charge on the endocyclic C(2) atom by means of aromatisation. The reaction is accelerated by catalytic amounts of acids and inhibited by tertiary amines; therefore, it is believed that at the first stage, the nitrosonium cation is generated. However, in the opinion of the researchers cited,⁴⁶ the electrophilicity of the NO^+ cation is insufficient to accomplish nitrosation by an electrophilic mechanism; therefore, as the most probable reaction route, they proposed a scheme involving single-electron transfer.



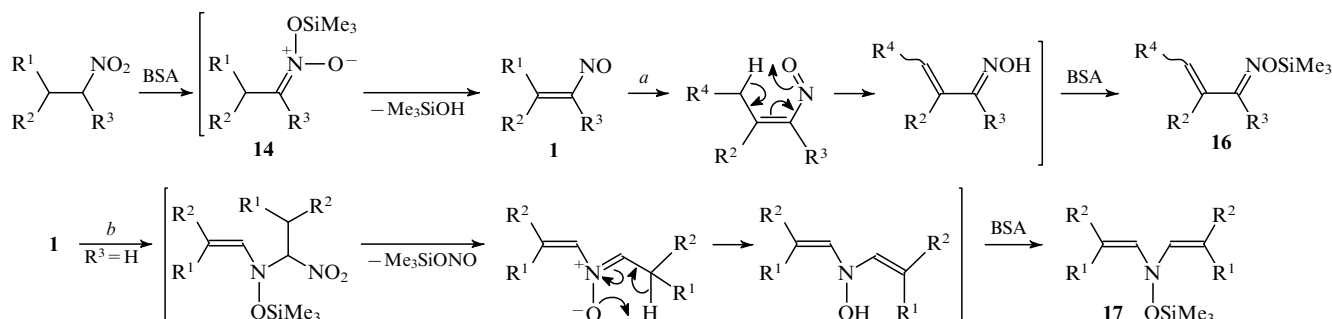
Selenium-⁴⁷ and tellurium-containing⁴⁸ analogues have been synthesised in a similar way.



$\text{X} = \text{Se}, \text{Te}$.

Nitration or nitrosation of trithiapentalene **20a** has given unsaturated nitroso-derivative **21a**, the first representative of 2,4-epidithio-1-nitrosobuta-1,3-dienes.⁴⁹

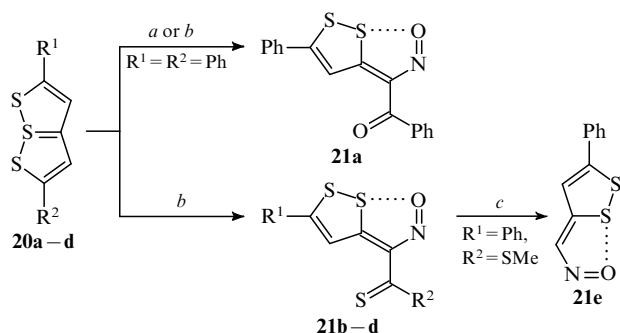
Scheme 3



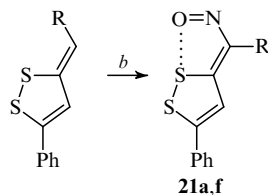
BSA is *N,O*-bis(trimethylsilyl)acetamide;

(a) $\text{R}^1 = \text{CH}_2\text{R}^4$; R^2 , R^4 are electron-withdrawing groups;

(b) 1,2-addition of **14**.



$R^1 = \text{Ph}; R^2 = \text{Ph}$ (**a**), SMe (**b**), NMe_2 (**c**); $R^1 = R^2 = \text{SMe}$ (**d**).



$R = \text{PhCO}$ (**a**), NO_2 (**f**);

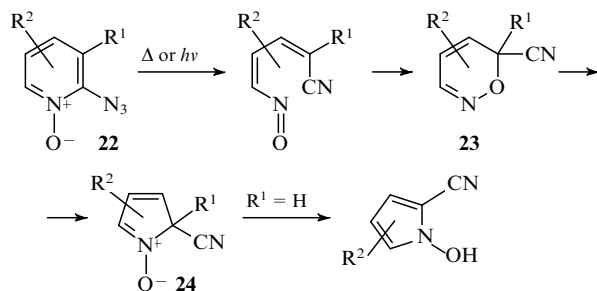
(**a**) $\text{HNO}_3 - \text{AcOH}$; (**b**) $[\text{HONO}]$; (**c**) $\text{Hg}(\text{OAc})_2$.

At $R^1 = R^2 = \text{Ph}$, the introduction of a nitroso group is accompanied by the transformation of the thiobenzoyl substituent into benzoyl (compound **21a**).⁴⁹ The formation of 2,4-epidithio-1-nitrosobuta-1,3-dienes **21b–d** from the corresponding trithiapentalenes **20b–d** occurs with retention of the thiocarbonyl fragment.^{49, 50} The CS_2Me group in the compound **21b** is removed on treatment with mercury(II) acetate.⁴⁹ The nitrosation of the corresponding 2,4-epidithiobuta-1,3-dienes yields the compounds **21a**⁴⁹ and **21f**.⁵¹

5. Other methods

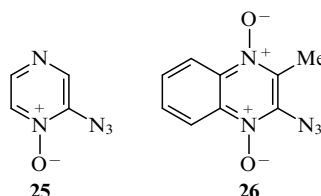
Other methods are as yet of limited utility. Examples of generation of nitrosoalkenes from substrates having some specific structural features have been reported; in some cases, the arguments for the intermediate formation of nitrosoalkenes are based on the analysis of the final reaction products and, hence, they are not always convincing.

For example, 2-azidopyridine *N*-oxides **22** have been shown to undergo a number of transformations on exposure to radiation or on heating above 85°C .^{52–54} It is assumed that upon ring opening and concerted elimination of N_2 , the compounds **22** can be converted into conjugated nitroso dienes, which then cyclise. When a substituent is present at the 3-position, two types of products can be formed, namely 6*H*-1,2-oxazines **23** and cyclic nitrones, 2*H*-pyrrole *N*-oxides **24**. When $R^1 = \text{Cl}$ or Br , the compounds **23** can undergo subsequent transformations in the presence of nucleophilic solvents.⁵³

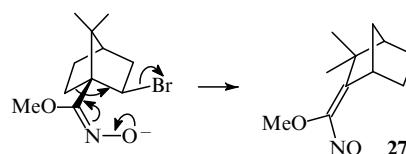


When $R^1 = \text{Me}$ or H , the oxazines **23** are kinetically controlled products, whereas the nitrones **24** are thermodynamically controlled products of cyclisation of the intermediate nitroso dienes.⁵⁴ Similar transformations have also been observed for azidopyrazine 1-oxides **25**⁵² and azidoquinoxaline

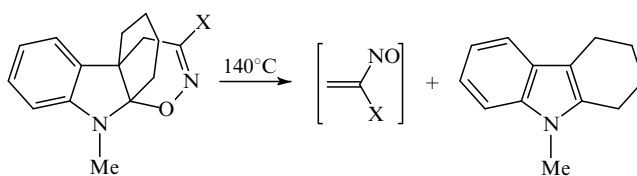
1,4-dioxides **26**.⁵⁵ In the opinion of Abramovich *et al.*,⁵⁴ in the latter case, a cyclic nitrone of type **24** is the kinetically controlled product, and 1,2-oxazine of type **23** is the thermodynamically controlled product.



The generation of nitrosoalkenes **27** is accompanied by isomerisation of the carbon skeleton of the substrate.⁵⁶

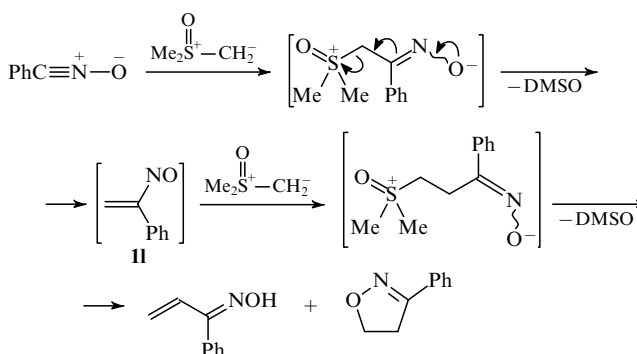


One more particular example of formation of nitrosoalkenes is retro-[2 + 4]-cycloaddition, which is facilitated by the formation of the stable aromatic structure of substituted indole.⁵⁷

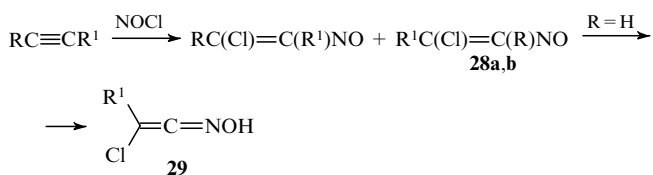


$X = \text{COMe}, \text{CO}_2\text{Et}$.

Apparently, the reactions of sulfonium ylides with nitrile oxides also proceed *via* nitrosoalkenes, which then react with nucleophilic ylides according to the addition–elimination reaction pattern or addition followed by cyclisation.^{34, 58–61} An example of this type of reaction is presented below:

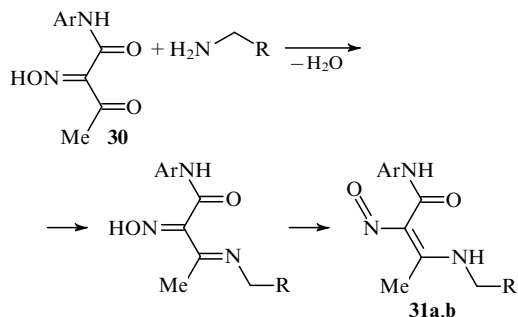


Indian researchers⁶² have shown that the addition of gaseous NOCl in CH_2Cl_2 at 0°C to the triple bonds in methyl alkynoates affords the corresponding β -chloro nitrosoalkenes. They found that nitrosoalkenes of type **28a** can isomerise to the corresponding chloro ketene oximes **29**. However, it should be mentioned that this isomerisation has never been observed for other nitrosoalkenes.



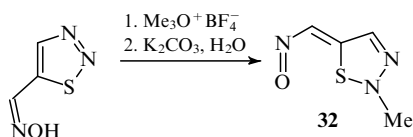
$R = \text{H}$ (**a**), Alk (**b**); $R^1 = (\text{CH}_2)_n\text{CO}_2\text{Me}$.

Condensation of oximes **30** with allylamine⁶³ or benzylamine⁶⁴ makes it possible to isolate moderately stable nitrosoalkenes **31** as highly coloured crystals. The structure of the compound **31a** was confirmed by X-ray diffraction analysis.⁶⁴

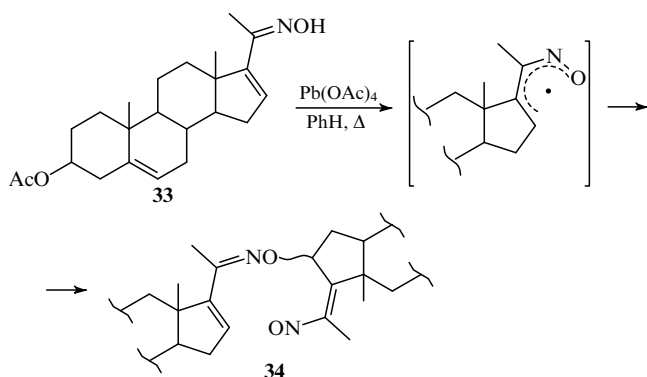


Ar = 4-ClC₆H₄; R = Ph (**a**), CH = CH₂ (**b**).

Methylation of 5-hydroxyiminomethyl-1,2,3-thiadiazole followed by treatment with a base affords a stable nitrosoalkene in a low yield.⁶⁵

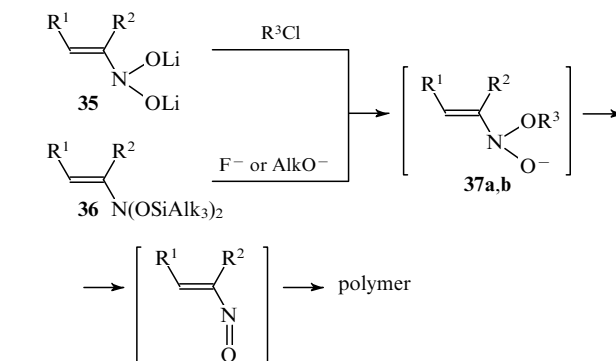


Oxidative dimerisation of α,β -unsaturated steroid oxime **33** gives rise to nitrosoalkene **34**, which is formed apparently by a radical mechanism.⁶⁶



Deoxygenation of perchloro-2-nitrobuta-1,3-diene upon treatment with R¹P(OR)₂ results in the formation of perchloro-2-nitrosobuta-1,3-diene **1e** (see Table 1). The yield of this product is not indicated in the study cited.⁹ Gas-phase thermolysis of nitroethylene on Fe or Ni at 883 K yields nitrosoethylene **1k**, together with MeCN.⁶⁷

There exist two groups of compounds that can serve as close precursors of nitrosoalkenes, owing to their structural features. The first group comprises *N,N*-bis(lithioxy)enamines **35**, which were first described by Seebach *et al.*,⁶⁸ and the second group includes *N,N*-bis(trialkylsilyloxy)enamines of type **36**. It was shown⁶⁸ that treatment with benzoyl chloride of 1-[*N,N*-bis(lithioxy)]amino-2-phenylethylene, the product of double deprotonation of 1-nitro-2-phenylethane, gives a polymer. This was explained by assuming the generation and subsequent polymerisation of β -nitrosostyrene under the reaction conditions. However, no additional evidence supporting this hypothesis was presented.⁶⁸ Moreover, β -nitrosostyrene had been described earlier³³ as a stable crystalline dimer.



R¹ = Ph, R² = H, R³ = PhCO (**37a**); SiAlk₃ (**37b**).

N,N-Bis(trialkylsilyloxy)enamines **36** were first described⁶⁹ as products of double silylation of aliphatic nitro compounds. The thermal instability of the compounds **36** (Alk = Me) observed in some cases was explained by possible easy elimination of (Me₃Si)₂O giving nitrosoalkenes, which then polymerise. However, the attempt to trap nitrosoethylene **1k** as the corresponding adduct with cyclopentadiene during decomposition of the enamine **36** (R¹ = R² = H, Alk = Me) failed.⁶⁹

Nevertheless, compounds **37** which have become quite available by now, are of interest as initial compounds for the generation of nitrosoalkenes *via* anionic intermediates of the semiacetal type by treatment with reagents possessing nucleophilic properties with respect to the trialkylsilyl group (see Scheme 3). Previously this route for the construction of a nitroso group has been realised during ring opening in *N*-trimethylsilyloxyisoxazolidines.^{41, 71}

III. Structure and physical properties of nitrosoalkenes

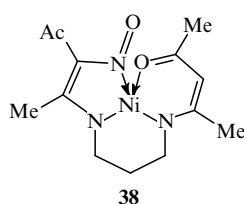
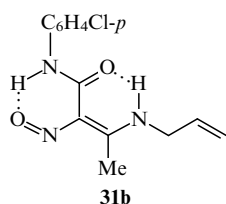
As was to be expected, stable nitrosoalkenes, the properties of which are listed in Table 1, have been characterised most comprehensively by spectroscopic data.

Spectroscopic characteristics of long-lived nitrosoalkenes have been described systematically.⁸ The blue colour of these compounds is due to absorption in the visible region (λ_{max} = 675–795 nm) with low extinction coefficients (ϵ = 20–60).¹⁹ Absorption is also observed between 250 and 350 nm (in some cases, two maxima can be distinguished).

IR spectra of nitrosoalkenes contain two absorption bands in the region 1420–1660 cm⁻¹. A band in the range 1420–1480 cm⁻¹ corresponds to the stretching vibrations of the N=O bond (for 2,2-di-*tert*-butylnitrosoethylene **1c**⁷ this band occurs at 1485 cm⁻¹). The same region contains the absorption bands for the N=O bonds in other monomeric nitroso compounds.⁷² The absorption at shorter wavelengths (1500–1600 cm⁻¹) was assigned to stretching vibrations of the C=C bond.⁸

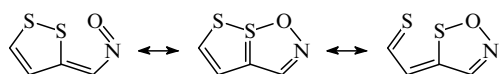
In the ¹H NMR spectra of the compounds **1b** and **1f** (see Table 1), the vinylic protons account for signals at δ 9.13 ppm⁶ and 8.68 ppm,¹⁰ respectively. In the case of the nitrosoalkene **1c**, the signal due to the proton at the carbon atom bound to the nitroso group manifests itself in a substantially higher field (δ 6.30 ppm).⁷ Thus, spectral data attest to the occurrence of appreciable π -conjugation between the C=C bond and the nitroso group.

The stability of nitrosoalkenes markedly increases in the presence of halogen atoms or bulky aryl or *tert*-alkyl groups (see Table 1), as well as upon formation of strong intramolecular hydrogen bonds (compound **31b**)⁶³ or complexes with transition metals (compound **38**).⁷³

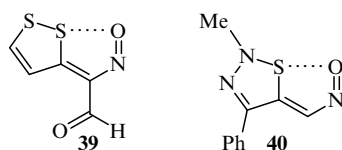


The high stability of 2,4-epidithio-1-nitrosobuta-1,3-dienes **21**, the nitroso compound **32**, the nitroso fulvenes **19**, and their selenium- and tellurium-containing analogues is due to the fact that the β -carbon atom of the nitrosoalkenyl fragment and the electron-donating substituents attached to it are incorporated into a common 6π -electron heterocyclic system.

The structure of the nitrosobutadienes **21a,f** was unambiguously determined based on X-ray diffraction analysis. It was found that the $S\cdots O$ interatomic distance is much shorter than that expected on the basis of the van der Waals radii of the S and O atoms.^{74–76} The abnormally short distance between the sulfur and oxygen in the nitrosobutadienes **21** is explained by the ability of the formally divalent sulfur atom to be involved into additional binding, which can be accomplished either with participation of the sulfur d orbitals or due to the formation of a three-centred electron-enriched $S-S-O$ bond.⁷⁵ It is noteworthy that, according to X-ray diffraction data, the $S\cdots O$ interatomic distance formed upon coordination of the nitroso group to sulfur is markedly shorter than that arising upon coordination to a carbonyl⁷⁶ or nitro group.⁷⁴ The configuration of the $C=C$ bond in the compounds **21** is determined by the fact that sulfur coordinates preferentially to the oxygen atom of the nitroso group rather than to other groups ($C=S$, $C=O$, or NO_2).⁵¹ In terms of the valence-bond method, the $S\cdots O$ binding can be represented by the following canonical structures:

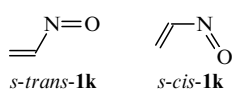


The CNDO/2-SCF-MO calculations⁷⁷ for a hypothetical structure of aldehyde **39** demonstrated the possibility of this binding. The X-ray diffraction⁷⁸ and ¹⁵N NMR spectroscopy⁷⁹ data for 1,2,3-thiadiazole **40** also imply a thiapentalene character of this structure.



Mass spectra of 2,4-epidithio-1-nitrosobuta-1,3-dienes **21b,e,f** have been studied.⁸⁰

Unstable nitrosoalkenes have scarcely been investigated by spectroscopy. The structure of the *s-trans*-rotamer of nitrosoethylene **1k** generated by pyrolysis of chloroacetaldoxime has been studied by microwave spectroscopy in the gas phase.¹³ The molecular orbitals of **1k** have been calculated by the Hückel⁵⁶ and CNDO⁸¹ methods. The optimised structures, bond orders, and electrostatic potentials for the compound **1k** and fluoronitrosoethylenes have been calculated by the *ab initio* (SCF-MO) method.⁸² It was found⁸¹ that the *s-trans*-rotamer of **1k** is somewhat more stable than the *s-cis*-rotamer.

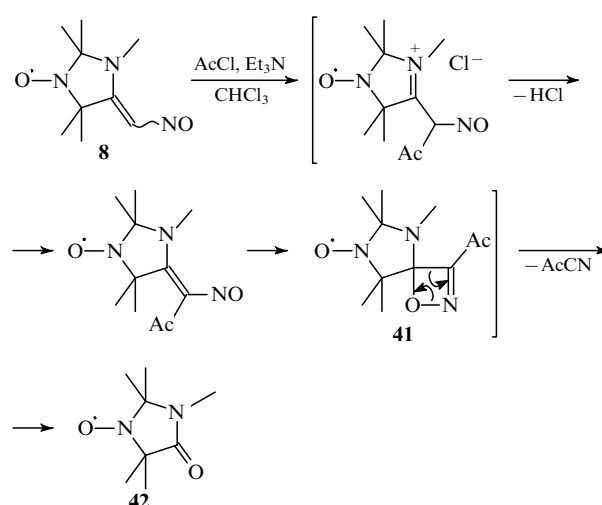


IV. Reactions of nitrosoalkenes

Due to the presence of the $C=C-N=O$ fragment, nitrosoalkenes are highly reactive compounds; they readily undergo intramolecular rearrangements, react with nucleophiles, and enter into concerted cycloaddition reactions.

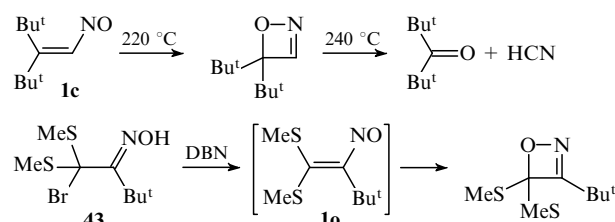
1. Unimolecular reactions

Two types of intramolecular rearrangements of nitrosoalkenes have already been mentioned here; these are cyclisation to 1,2-oxazetines followed by fragmentation (see Section II.2) and cyclisation of nitroso-dienes to 6*H*-1,2-oxazines and 2*H*-pyrrole *N*-oxides (see Section II.5). Taking into account the reaction conditions described in Ref. 30, the transformation of the nitrosoalkene **8** into the final product **42** upon treatment with acetyl chloride occurs most probably *via* an intermediate 1,2-oxazetene rather than according to the haloform decomposition pattern, as the authors cited³⁰ believe.



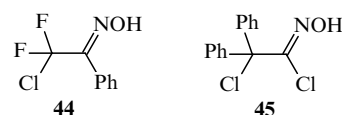
The intramolecular route of fragmentation of nitrosoethylene **1k** involving intermediate formation of 1,2-oxazetene was confirmed subsequently by *ab initio* (SCF-MO) calculations.⁸³

Oxazetines have also been isolated after thermal rearrangement of the nitrosoalkene **1c**⁷ and after the reaction of bromo oxime **43** with bases. In the latter case, the intermediate formation of the nitrosoalkene **1o** was assumed.³⁷

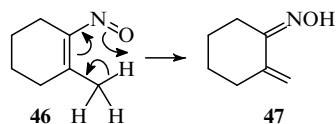


DBN is diazabicyclononane.

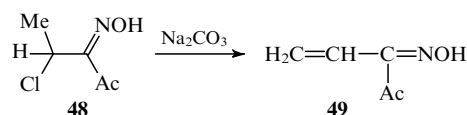
It has been suggested⁸ that cyclisation to 1,2-oxazetines followed by fragmentation is the main route of decomposition of many other nitrosoalkenes, which do not isomerise to unsaturated oximes without external nucleophiles. The examples of formation of PhCN and Ph₂CO upon treatment of oximes **44** and **45**, respectively, with Na₂CO₃ in CH₂Cl₂ were presented as evidence supporting this hypothesis.⁸



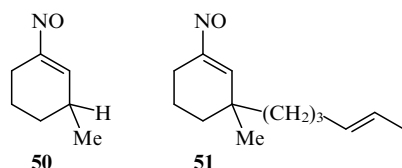
Yet another characteristic type of intramolecular rearrangements is [1,5]-shift of a hydrogen atom. This is the main route of transformation of internal nitrosoalkenes having allylic hydrogen atoms. This rearrangement results in the formation of the corresponding unsaturated oximes in 28%–72% yields.³¹ Thus it has been assumed³⁵ that the [1,5]-shift of hydrogen in 2-methyl-1-nitrosocyclohexene **46** gives unsaturated oxime, which has been identified³ as having the structure **47**. During the reaction, the blue colour, typical of solutions of the nitrosoalkene **46**, disappears.



When chlorinated oxime **48** is treated with Na_2CO_3 ,⁸⁴ [1,5]-shift of hydrogen results in the formation of unsaturated oxime **49**. The same compound is formed as a side product in cycloaddition reactions of the nitrosoalkene $\text{MeCH}=\text{C}(\text{Ac})\text{NO}$ ¹⁶ (see Section IV.3).



It has been found¹⁹ that the rearrangement giving unsaturated oximes can occur not only as an intramolecular transformation but also as a base-catalysed one. Thus nitrosoalkene **50** for which concerted hydrogen [1,5]-shift is impossible due to steric reasons, is much less stable than compound **51**, which contains no hydrogen atoms at C(3) (the half-life $\tau_{1/2}$ for the compound **50** in a dilute solution is 12 min, while that for the compound **51** is 900 min).¹⁹



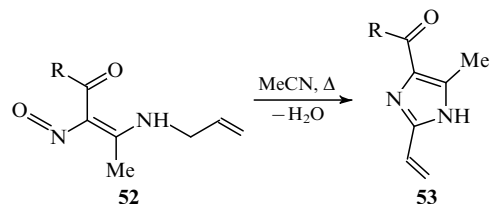
The scheme of transformation of the isoxazolinone **2** into the corresponding α,β -unsaturated oxime (see Section II.1)²¹ and the synthesis of *O*-trimethylsilyl derivatives of the α,β -unsaturated oximes **16** (see Scheme 3)⁴⁴ have also been assumed to include stages involving the [1,5]-shift of hydrogen.

2. Reactions with nucleophiles

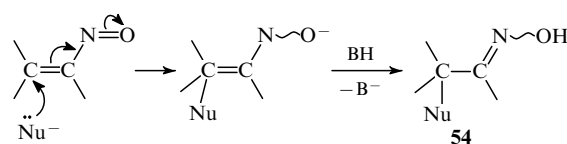
In the nitroso compounds **1**, the $\text{C}=\text{C}$ double bond is conjugated with the nitroso group and is thus activated. The reactivity of nitrosoalkenes obviously resembles those of other activated alkenes, for example, conjugated nitroalkenes. The presence of π -conjugation accounts for the high electrophilicity of the β -carbon atom in nitrosoalkenes; therefore, these compounds are especially prone to react with nucleophiles.

The reactions of nitrosoalkenes with nucleophiles can be conventionally divided into two groups: (1) 1,2-addition at the $\text{N}=\text{O}$ bond and (2) conjugate 1,4-addition.

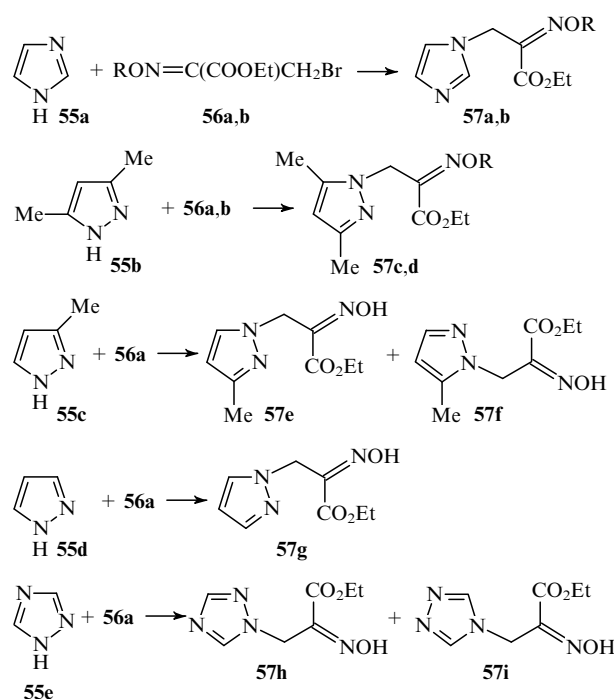
Only two examples of reactions of the former type are known. These are addition of silyl nitronates to the nitroso group in β -substituted vinyl nitroso compounds [see Scheme 3, pathway (*b*)] and intramolecular condensation of substituted nitrosoalkenes **52** to the corresponding vinylimidazoles **53**.⁶³



Conjugate 1,4-nucleophilic addition is much more typical of vinyl nitroso compounds and largely determines their synthetic value.



When α -halo oximes are used as synthetic precursors of the substituted oximes **54**, two routes are, in principle, possible: (1) 1,4-elimination–addition with intermediate formation of nitrosoalkenes and (2) direct substitution of the halogen by a nucleophile by the $\text{S}_{\text{N}}2$ mechanism. Is it possible to determine which of the mechanisms is realised in each particular case? This important question has been answered⁵⁵ based on a semiquantitative study of the rates of *N*-alkylation of azoles **55a–e** by model α -bromo oximes **56a,b**. The results of this study are presented in Table 2.



$\text{R} = \text{H}$ (**56a**, **57a**), CMe_2OMe (**56b**, **57b**).

It can be seen from the data of Table 2 that imidazole **55a** and 3,5-dimethylpyrazole **55b** react with α -bromo oxime **56a** much faster than their less basic analogues. On passing to the bromo oxime **56b**, the rate of the reaction with the compounds **55a,b**

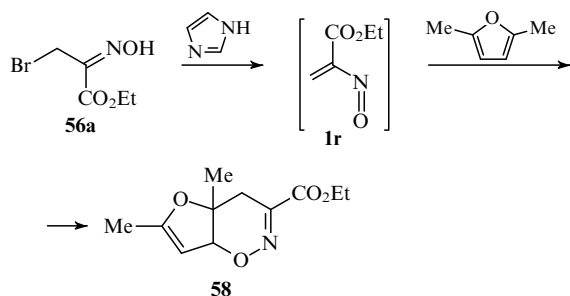
Table 2. Effect of the basicity of the azoles **55a–e** on the duration of *N*-alkylation with α -bromo oximes **56a,b**.

Substrate 55	$\text{pK}_{\text{a}}^{\text{a}}$	Duration of the reaction (h) with the oximes	
		56a	56b
a	7.10	0.2	24
b	4.12	0.5	48
c	3.32	24 ^b	—
d	2.52	72	—
e	2.27	72	—

Note. An azole (2.0 mmol) and a bromo oxime (1 mmol) in 25 ml of MeCN, 20 °C. ^aFor aqueous solutions of conjugated acids. ^bThe ratio **57e**:**57f** = 2 : 1.

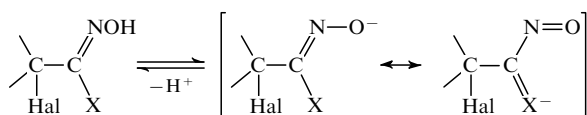
markedly decreases and becomes comparable with the rates of reactions of weakly basic azoles.

Evidently, the azoles **55a,b** are sufficiently basic to react with the oxime **56a** via the 1,4-elimination–addition pattern involving intermediate formation of the corresponding nitrosoalkene, acting simultaneously as bases and as nucleophiles. Bromo oxime **56b** cannot react according to the elimination–addition scheme. In this case, the reaction occurs as direct S_N2 substitution. The conclusion about the formation of ethyl α-nitrosoacrylate **1r** during this reaction was confirmed⁸⁵ by its trapping. The product of reaction of the nitrosoalkene **1r** with 2,5-dimethylfuran **58** was obtained in 50% yield.

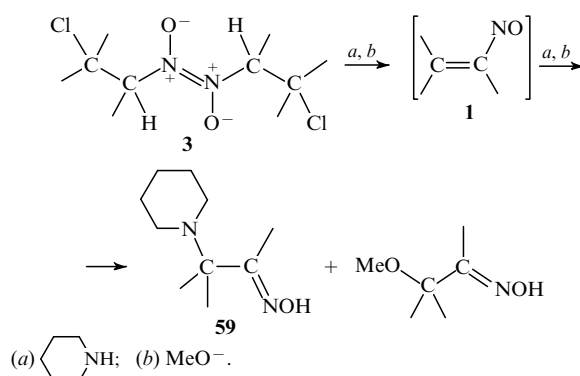


The reaction of the oxime **56a** with a weaker base, pyrazole **55d**, in the presence of 2,5-dimethylfuran yields only the corresponding *N*-alkylation product, cycloadduct of type **58** being totally missing. When Na₂CO₃ is added to a solution of pyrazole **55d** and bromo oxime **56a** under standard conditions, the reaction is completed over a period of 10 min giving the corresponding *N*-alkylation product in a high yield.⁸⁵ Based on these data, it was concluded that the reactions of the azoles **55c–e** with the oxime **56a** and of the compounds **55a,b** with the oxime **56b** occur as direct S_N2 substitution.

The facts presented in the study cited⁸⁵ to justify the assumption that the mechanism of *N*-alkylation changes upon a decrease in the azole basicity seem quite convincing. However, in our opinion, the reaction mechanism depends not only on the basicity of the nucleophile but also on the acidity of the preceding oxime, which varies as a function of the substituent X at the C=N bond.

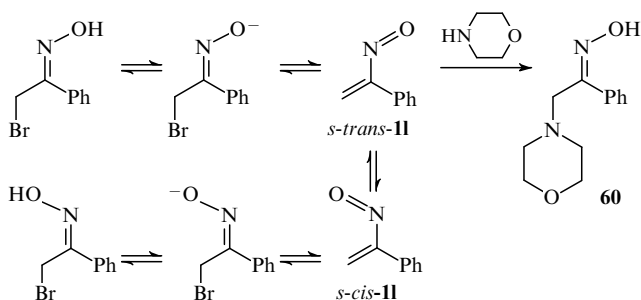


There are weighty arguments that the reactions of the dimers of β-chloro nitroso compounds **3** with nucleophilic bases occur by the elimination–addition mechanism. These compounds react with MeONa faster than with piperidine; however, when both bases are present, α-piperidino oximes **59** are the major reaction products.³³



The experimental results rule out the direct substitution mechanism. It is obvious that the ratio of the reaction products is determined by the fact that at a fast reaction step, piperidine which possesses stronger nucleophilic properties, adds preferentially to the nitrosoalkene **1**.

Study of the reactions of *syn*- and *anti*-α-bromoacetophenone oximes with morpholine in an aqueous buffer solution also points to the intermediate formation of 1-nitroso-1-phenylethylene **11**. Reactions with both bromo oximes give *anti*-α-morpholino oxime **60**.¹⁵



Presumably, bromo oximes undergo fast deprotonation and then eliminate Br[−] in the rate-determining step yielding the intermediate 1-nitroso-1-phenylethylene **11**. Morpholine adds to the nitrosoalkene **11**, which occurs in the transoid conformation.

In the majority of other cases, the mechanisms of reactions of nucleophiles with α-halo oximes and with dimers of β-chloro nitroso compounds have not been studied. Alkylation of the anions derived from 1,1-dinitroalkanes⁸⁶ or tertiary phosphines^{87,88} with α-halo oximes proceeds apparently as the direct S_N2 substitution of the halogen atom. In view of the relatively low basicity of these nucleophiles, the intermediate formation of nitrosoalkenes during their alkylation seems unlikely.

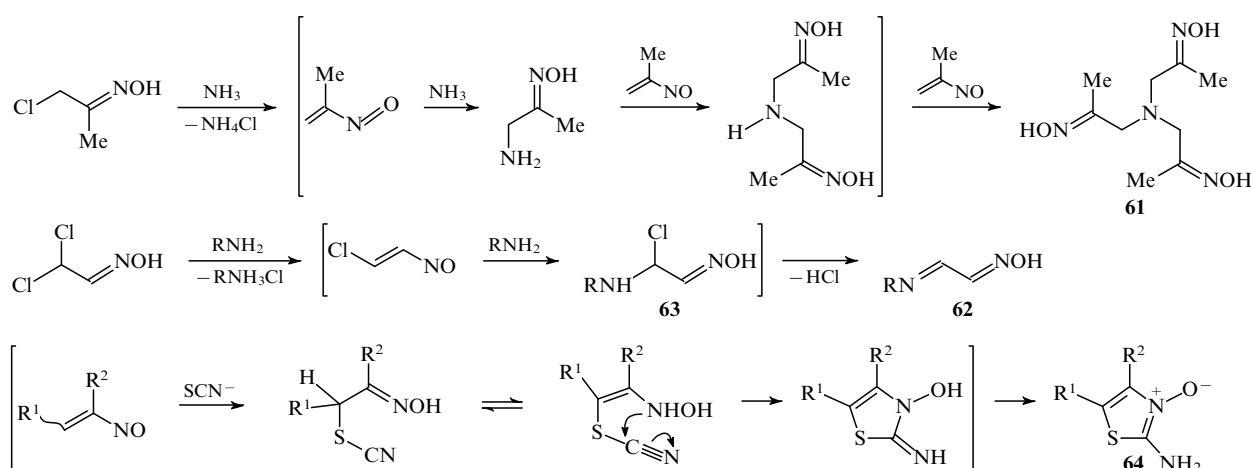
Below we discuss only those examples in which either the reaction conditions strongly imply the occurrence of the elimination–addition mechanism or independent evidence for the intermediate formation of nitrosoalkenes exists.

Examples of interaction of *N*-, *O*-, and *S*-nucleophiles with nitrosoalkenes are presented in Table 3.

Table 3. Addition of *N*-, *O*-, and *S*-nucleophiles with nitrosoalkenes.

Nitrosoalkenes	Types of nucleophiles	Ref.
CH ₂ =C(Me)NO	NH ₃ , R ₂ NH	4
CH ₂ =C(Pr)NO	RCH(NH ₂)CO ₂ Et	89
CH ₂ =C(Ph)NO (11)	NH ₃ R ₂ NH SCN [−]	90 15 91
CH ₂ =C(Ac)NO (1m)	(H ₂ N) ₂ CS, H ₂ NCH ₂ CN RCH(NH ₂)CO ₂ Et Me(CH ₂) ₄ OH	91 92 57
CH ₂ =C(CO ₂ Et)NO (1r)	ArSH	93
R ¹ R ² C=C(R ³)NO R ¹ = H, Alk; R ² , R ³ = Alk, cyclo-Alk	NH ₃ , RNH ₂ , R ₂ NH, NH ₂ OH, NO ₂ [−] , N ₃ [−] R ₂ NH, ROH, ArSH R ₃ N	94 31, 33, 35, 95 11
ClCH=CHNO	RNH ₂ , ArNH ₂	96
Cl ₂ C=CHNO (1h)	ArNH ₂	97
ArCH=C(R)NO	R ₂ NH, ROH, ArSH R ₃ N SCN [−] , EtOCS ₂ [−]	31, 33 11 98
CH ₂ =C(CF ₃)NO (1n)	Et ₂ NH, H ₂ O	17

Scheme 4

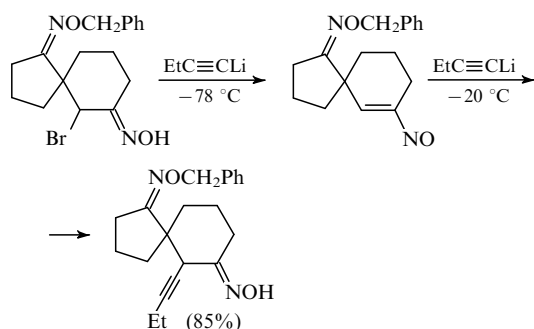


The reaction follows the general Scheme 4; however, the primary adducts often undergo subsequent transformations. For example, treatment of chloroacetone oxime with aqueous ammonia affords tertiary amine **61**.⁴ Reactions of this type have also been observed for 1-haloalkyl phenyl ketoximes.⁹⁰ The dichloroacetaldehyde oxime reacts with primary amines to give imines **62** resulting from elimination of HCl from the primary adduct **63**;⁹⁶ the chloral oxime reacts in a similar way.⁹⁶ The reactions with thiocyanate ions yield 2-aminithiazole *N*-oxides **64** formed upon cyclisation of the primary adducts.^{31, 91, 98}

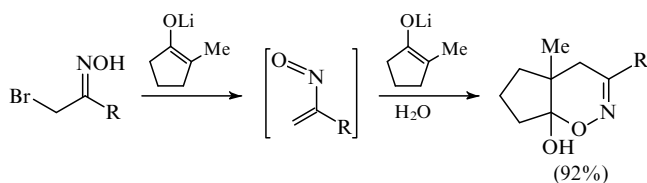
The interaction of nitrosoalkenes with enamines and other electron-donating alkenes will be considered in Section IV.3.b among cycloaddition reactions. In this section, we shall discuss reactions of nitrosoalkenes with carbanions and also electrophilic substitution in aromatic substrates.

Vinyl nitroso compounds are convenient reagents for alkylation of nucleophilic carbon atoms under mild conditions. Reactive carbanions or their equivalents serving as nucleophiles in these reactions are taken in a twofold (or larger) molar excess. The first mole of a nucleophilic compound reacts as a base with liberation of an intermediate nitrosoalkene, and the second mole acts as the nucleophile. A typical example of these reactions is the generation of nitrosoalkenes followed by nucleophilic addition of organometallic substrates to them, which gives rise to the compounds **10**³⁶ and **15**.⁴⁰

EtMgBr ,¹¹ PhMgBr ,⁹⁴ and $\text{EtC}\equiv\text{CLi}$ ⁹⁹ have also been used in similar reactions.



α -Bromo oximes have been used to alkylate lithium enolates prepared from substituted cyclopentanones.^{100, 101}

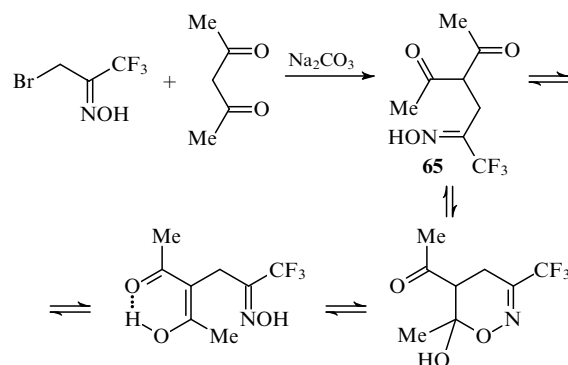


$\text{R} = (\text{CH}_2)_3\text{CH}=\text{CH}_2$.

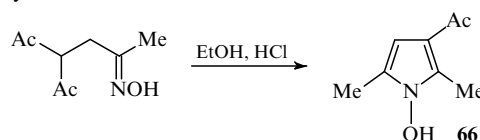
The reactions of nitrosoalkenes with other stabilised carbanions are presented in Table 4. In many cases, EtONa and EtOH are used as the base and the solvent, respectively; in some cases, Na_2CO_3 in CH_2Cl_2 ⁹³ or in Bu^tOMe ¹⁷ or piperidinium acetate in THF ⁹⁶ are also employed.

The reaction products are 1 : 1 adducts; they exist in solutions as mixtures of linear tautomers and five- or six-membered cyclic species, as for example, the adduct **65** (Scheme 5).¹⁷

Scheme 5



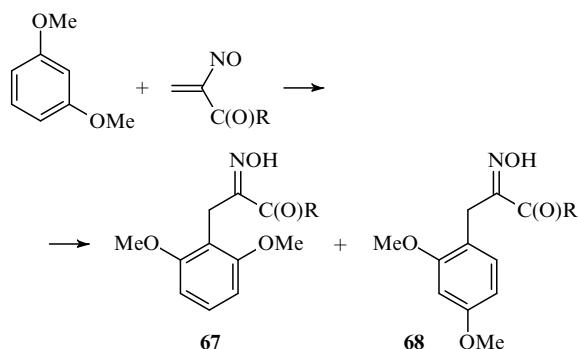
Some of the addition products can undergo subsequent transformations. Thus the adducts obtained from the nitrosoalkene $\text{ClCH}=\text{CHNO}$ eliminate HCl under the reaction conditions giving rise to α,β -unsaturated oximes $\text{R}^1\text{R}^2\text{C}=\text{CHCH}=\text{NOH}$.⁹⁶ Some of the adducts can be converted into the corresponding 1-hydropyrroles by treatment with an acid.^{102–105, 107} An example is provided by the formation of 3-acetyl-1-hydroxy-2,5-dimethylpyrrole **66** from the adduct of chloroacetone oxime and acetylacetone.¹⁰²



Reactions of sulfonium ylides yielding isoxazolines and α,β -unsaturated oximes have been described above (Section II.5).^{34, 58–61}

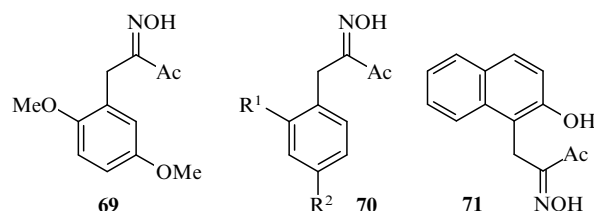
It seems very attractive to use nitrosoalkenes as electrophiles in aromatic substitution reactions, because they are generated under mild conditions in the absence of acids. This reaction would permit introduction of various functional groups. However, in practice, only highly electrophilic nitrosoalkenes in combination with highly nucleophilic aromatic and heteroaromatic systems are suitable for this purpose. Thus alkylation of 1,3-dimethoxybenzene with electrophilic nitrosoalkenes is one of the few

reported examples of this type of reaction.¹⁶ The ratio of the isomers **67** and **68** formed in this process is 1 : 4.



R	H	Me	OEt
Yield of 67 + 68 (%)	41	63	11

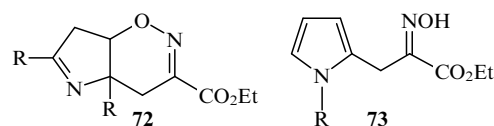
Alkylation of 1,4-dimethoxybenzene, *N,N*-dimethylaniline, and 2-naphthol with 3-nitrosobut-3-en-2-one **1m** gives the corresponding products **69–71** in low yields; less electrophilic ethyl α -nitrosoacrylate **1r** does not alkylate 2-naphthol.



R¹, R² = H, NMe₂.

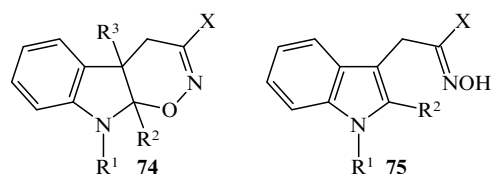
The reactions of nitrosoalkenes with heteroaromatic systems (furans, benzofurans, pyrroles, and indoles) are more general. In this review, we classify these reactions as electrophilic substitution. However, this classification is quite arbitrary (see, for example, Refs 16, 17, and 108), because for these heterocycles it is often difficult to decide between electrophilic substitution and [4 + 2]-cycloaddition reaction mechanisms.

The reactions of pyrroles with ethyl α -nitrosoacrylate **1r** involve only the 2-position.^{108, 109} The data about the formation of 3-substituted pyrroles^{3, 16} as side products have not been supported later.¹⁰⁸ Depending on the presence and the positions of substituents, pyrroles give 1 : 1 adducts of two types, **72** and **73**. This is apparently due to proton migrations in the adducts formed initially. Unfortunately, the attempt to involve ethyl α -nitrosoacrylate **1r** in the reaction with 1,2,5-trisubstituted pyrroles, which would rule out the possibility of these migrations, was unsuccessful. Ethyl α -nitrosoacrylate also did not react with less electron-donating *N*-(toluene-4-sulfonyl)pyrroles and pyrrole-2-carbaldehyde.¹⁰⁸

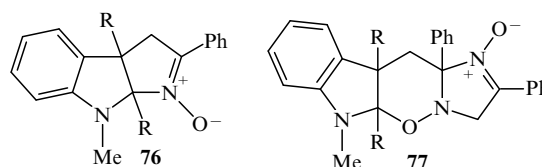


R = Me, Ph (**72**); R = H, Me (**73**).

Unlike pyrroles, indoles are alkylated by nitrosoalkenes; the reaction involves the 3-position and yields two types of adducts, **74** and **75**, depending on whether or not this position contains substituent.



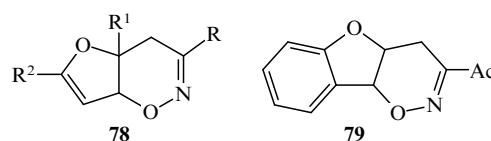
In the case of electron-deficient nitrosoalkenes — CH₂=C(CO₂Et)NO (**1r**),^{16, 93, 110} CH₂=C(Ac)NO (**1m**),¹⁶ and CH₂=C(CF₃)NO (**1n**)¹⁷ — the corresponding adducts are formed in high yields (65%–88%) even from equimolar amounts of bromo oxime and indole.¹⁶ However, at elevated temperatures, the yields decrease, because the reaction becomes noticeably reversible.⁵⁷ When 1-nitroso-1-phenylethylene **1l** reacts with *N*-methyltetrahydrocarbazole, cyclic nitron **76** and 2 : 1 adduct **77** are formed together with the main product **74**.⁵⁷



R, R = (CH₂)₄.

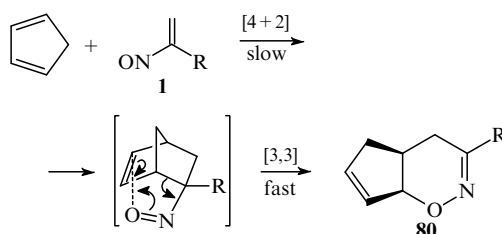
Alkylation of 2-substituted indoles by the nitrosoalkene CH₂=C(CO₂Et)NO (**1r**) is the key stage in the synthesis of several tryptophan derivatives.^{111, 112} A series of studies^{113–115} have been devoted to alkylation of 3-substituted indoles with ethyl α -nitrosoacrylate aimed at the synthesis of biologically active tryptophan derivatives. In some cases, the primary adducts were found to be unstable and to rearrange readily.^{113–115}

The reactions with less aromatic substrates such as furan,^{16, 18, 93} 2-methyl-,¹¹⁶ 2,5-dimethyl-,^{16, 18, 116, 117} and benzofuran¹⁶ always afford cycloadducts **78** and **79**, which readily undergo selective cleavage on treatment with acids^{16, 118} or bases¹¹⁶ to give either products of oxazine ring opening or products of more extensive transformations.^{116, 118}



3. Cycloaddition reactions

Nitrosoalkenes can participate in cycloaddition reactions either as 2 π -electron systems (the reaction involves the nitroso group) or as 4 π -electron conjugated heterodienes (1,2-dihetero-1,3-diene systems). No examples of reactions involving only the C=C bond have been found yet. However, some researchers^{119, 120} have suggested that nitrosoalkenes enter into [4 + 2]-cycloaddition reactions with 1,3-dienes as 2 $\pi_{C=C}$ components, which are followed by fast [3,3]-sigmatropic rearrangement of the resulting adducts into the final products. For example, cycloaddition of nitrosoalkenes to cyclopentadiene to give adduct **80** can be considered within the framework of this hypotheses; however, no facts supporting it have been obtained.



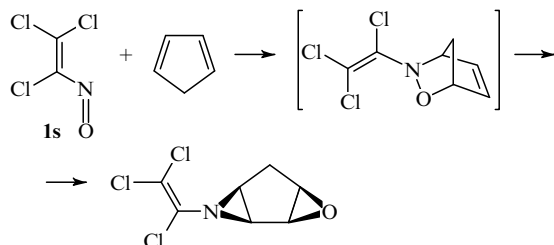
R = Ar, C(O)R.

a. Nitrosoalkenes as 2 π systems in cycloaddition reactions

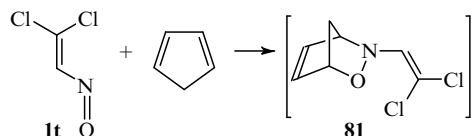
Cycloaddition to a nitroso group acting as a 2 π -electron system is typical of nitroso compounds of many classes.^{121–123} In the case of nitrosoalkenes, this type of reaction is limited to β,β -dihalo- and β -halo- β -alkyl-derivatives.⁸ For example, trichloronitrosoethylene **1s** reacts as heterodienophile with various cyclic and

acyclic nucleophilic dienes including butadiene,⁸ 1-methoxybutadiene,⁸ cyclopentadiene,⁸ cyclohexadiene,⁸ and benzene oxide.¹²⁴

Adducts formed from cyclic dienes are thermally unstable and readily rearrange at room temperature to epoxyaziridines, similarly to the [4 + 2]-cycloadducts of 1,3-dienes with singlet oxygen, which are converted into 1,3-diepoxydes.^{125, 126}



The structure of the adduct derived from β,β -dichloronitrosoethylene **1t** and cyclopentadiene **81** was confirmed by recording its low-temperature NMR spectrum.¹²⁷

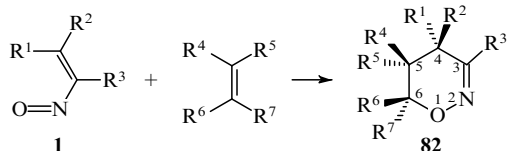


It should be emphasised that the rearrangement to epoxyaziridines is typical only of adducts of halo-substituted nitrosoalkenes with cyclic dienes. Cycloadducts of nitrosoalkenes with acyclic dienes,⁸ as well as the products of [4 + 2]-cycloaddition of cyclic 1,3-dienes to the nitroso groups of other types of nitroso compounds,^{121, 127} do not undergo this rearrangement. This regularity has not been explained yet.

It has been shown that tetrafluoroethylene and chlorotrifluoroethylene add to the nitroso group of trifluoronitrosoethylene **1a** according to the [2 + 2]-cycloaddition pattern to give 1,2-oxazetidines.⁵

b. Nitrosoalkenes as conjugated heterodienes in the cycloaddition to C = C bonds

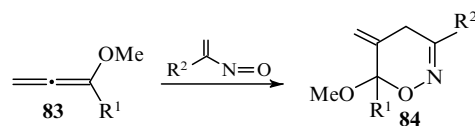
The [4 + 2]-cycloaddition to alkenes is perhaps the most important reaction of nitrosoalkenes, which has mainly determined the vigorous development of the chemistry of these compounds in the last decade. In this reaction, nitrosoalkenes **1** act as electron-withdrawing 4π -components (conjugated heterodienes) and give rise to 5,6-dihydro-4*H*-1,2-oxazines **82**, which are valuable intermediate compounds in the synthesis of various cyclic and linear polyfunctional compounds.



This type of addition was observed for the first time in the reaction of cyclopentadiene¹⁸ with 1-nitroso-1-phenylethylene **11**. Later, this reaction route has been extended to other alkenes and nitrosoalkenes; as a rule, the latter contain unsubstituted β -carbon atoms ($R^1 = R^2 = H$).^{8, 14, 16} although this type of cycloaddition is also possible^{8, 16, 45, 128} for some β -substituted nitrosoalkenes, for instance, $\text{MeCH}=\text{C}(\text{Ac})\text{N}=\text{O}$ (**1u**)¹⁶ and $\text{MeO}_2\text{CCH}=\text{CHN}=\text{O}$ (**1q**).⁴⁵

The reaction is highly regio- and stereoselective; in the adducts of type **80** derived from cyclopentadiene, the oxygen atom of the nitroso group is always attached to the allylic carbon atom of the cyclopentene fragment. Other linear and cyclic conjugated dienes add to nitrosoalkenes of the general type $\text{CH}_2=\text{C}(\text{R})\text{NO}$ in a similar way.^{8, 14, 18, 120, 129}

Another type of nucleophilic dienes, methoxyallenes **83**, readily react with nitrosoalkenes to give 6-methoxy-substituted cycloadducts **84** with high regioselectivity.^{130, 131} The successful synthesis of these compounds opened up new opportunities for using the oxazine ring in various transformations.^{132–136}



Unfortunately, the attempt to extend cycloaddition to allene, phenylallene, and trimethylsilyllallene was unsuccessful, indicating that the electronic requirements to allenes are stricter than those to alkenes.¹³¹

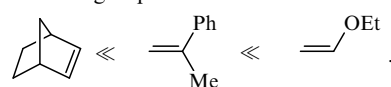
Electron-deficient alkenes, diethyl fumarate,¹⁶ *trans*-1,2-dichloroethylene,¹⁶ and maleic anhydride¹³⁷ do not form [4 + 2]-cycloaddition products with nitrosoalkenes.

Simple alkenes, oct-1-ene,^{14, 16} *cis*-cyclooctene,^{16, 138} and cyclohexene,¹⁶ react only with highly electrophilic nitrosoalkenes **1** ($R^1 = R^2 = H$), containing substituents such as Ac, CHO, or 4- $\text{NO}_2\text{C}_6\text{H}_4$ at the α -position; these reactions can give mixtures of regioisomers. Thus 1-nitroso-1-(4-nitrophenyl)ethylene **1v** reacts with oct-1-ene giving rise to a mixture of 6- and 5-*n*-hexyl-substituted 1,2-oxazines **82** in a ratio of 85:15.¹⁴ However, the reactions of nitrosoalkenes with conjugated terminal mono- and disubstituted alkenes result in the formation of only 6-mono- and 6,6-disubstituted regioisomers **82** ($R^4 = R^5 = H$; $R^6 = \text{NR}_2$, OR or Ar; $R^7 = H$, Alk, or Ar).^{14, 18, 120} The interaction with 1,2-disubstituted alkenes follows a more complex route. Thus the reaction of *trans*-1-phenylpropene with nitrosoalkenes affords both regioisomers with low regioselectivity. The introduction of an electron-donating methoxy group into the *para*-position of *trans*-1-phenylpropene markedly increases the regioselectivity of this reaction; in this case, regioisomers containing the aryl group at the 6-position are formed predominantly.¹⁴

The cycloaddition of nitrosoalkenes to 1,2-disubstituted alkenes, containing an OR or NR_2 group as one of the substituents at the C = C bond, always yields 6-alkoxy(or silyloxy-) or 6-dialkylamino(or disilylamino)-substituted 1,2-oxazines, respectively.^{117, 120, 139–144} The versatility and high regioselectivity of the cycloaddition of nitrosoalkenes to vinyl ethers or enamines have stimulated investigations of the synthetic potential of the reaction products, namely, 5,6-dihydro-4*H*-1,2-oxazines containing OR or NR_2 groups at the 6-position.^{93, 107, 117, 118, 138–140, 145–152}

It is noteworthy that allylsilanes proved to be convenient ene components for [4 + 2]-cycloaddition to nitrosoalkenes (triallylbutylstannane reacts in a similar way¹²⁰). The reaction is highly regioselective and results in the formation of 6-(1-trimethylsilylalkyl)-1,2-oxazines,^{120, 151, 152} which can be converted into valuable compounds by modification of the oxazine ring¹⁵⁵ and also proved to be convenient starting compounds for the synthesis of γ,δ -unsaturated ketones and amines.^{120, 153–155}

Using the method of competing reactions, it has been found¹⁶ that the rate of [4 + 2]-cycloaddition of alkenes to 3-nitrosobut-3-en-2-one **1m** increases with increase in the electron-donating capacity of the substituents at the C = C bond in the alkenes; in terms of the reaction rate, the alkenes studied can be arranged in the following sequence:



Reissig *et al.*¹²⁸ studied the relative reactivities of various alkenes in more detail. They used mainly trimethylsilyl ethers of enols and chose 1-nitroso-1-phenylethylene **11** as the model nitrosoalkene.¹²⁸ The following relative rate constants (*k*) were obtained for cycloaddition of various alkenes to 1-nitroso-1-phenylethylene:^{128, 156}

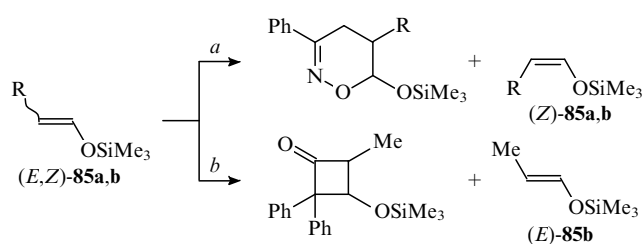
Alkene	<i>k</i>	Alkene	<i>k</i>
	17		0.33
	11.5		0.2
	8.5		0.19
	3.5		0.13
	2.2		0.11
	1.2		0.09
	1.0		0.09
	0.95		< 0.01
	0.6		< 0.01
		(R = Pr ⁱ , Ph, Bu ^t)	

The rate constant (*k*) values presented above indicate that the EtO group possesses higher activating ability than the Me₃SiO group. It is also noteworthy that the reactivity of 1,1-disubstituted trimethylsilyl enol ethers is much lower than that of 1,2-disubstituted derivatives. For example, the relative reactivity of *E*-(1-trimethylsilyloxy)propene is ~100 times higher than that of (2-trimethylsilyloxy)propene, and the enol silyl ethers containing Prⁱ, Ph, or Bu^t groups at the α-position do not react with the nitrosoalkene **11** at all. The absence of the reaction in the latter case is due to the steric influence of substituents and, hence, it confirms indirectly the concerted mechanism of [4 + 2]-cycloaddition of nitrosoalkene. If the reaction occurred by a stepwise mechanism, these substituents would efficiently stabilise the positive charge or the radical site in an intermediate.¹²⁸

The substantially higher reactivity of the *E*-isomers of vinyl ethers compared to that of the *Z*-isomers also deserves attention.¹²⁸ The ratios of the reaction rates for *E*- and *Z*-isomers [*k*(*E*)/*k*(*Z*)] are the following:

Compound	The <i>k</i> (<i>E</i>)/ <i>k</i> (<i>Z</i>) ratio
MeCH=CHOSiMe ₃	26
Pr ⁱ CH=CHOSiMe ₃	25
PhCH=CHOSiMe ₃	> 50
Me ₃ SiOCH=CHOSiMe ₃	> 50
MeCH=CHOEt	6

This relationship has found application in the development of an elegant method for the kinetic resolution of mixtures of the *E*- and *Z*-isomers of trimethylsilyl vinyl ethers,¹⁵⁷ based on the difference between the rates of their cycloaddition to 1-nitroso-1-phenylethylene **11** and diphenyl ketene.¹⁵⁷ 1-Nitroso-1-phenyl-



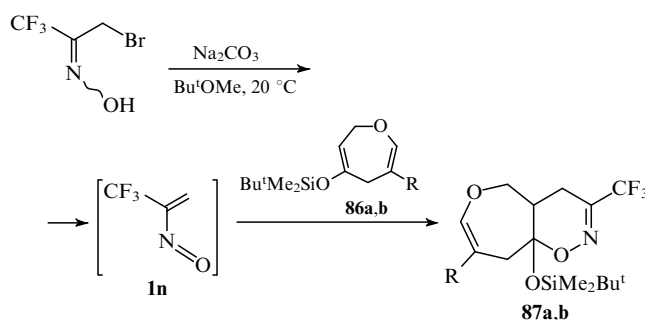
R = Me (a), Ph (b);

(a) $\text{Ph}-\text{CH}=\text{NOH}$, Na_2CO_3 , Et_2O ; (b) $\text{Ph}_2\text{C}=\text{C}=\text{O}$.

Compound	(<i>E</i>)- 85a	(<i>Z</i>)- 85a	(<i>Z</i>)- 85b
Yield (%)	66	43	99
Degree of enrichment (%)	> 98	> 99	> 99

ethylene **11** generated *in situ* reacts selectively with the *E*-isomers of the silyl ethers **85a,b**, whereas diphenyl ketene reacts with the *Z*-isomers; as a consequence, the initial mixtures of trimethylsilyl enolates become enriched in the less reactive isomers.

Although alkyl ethers of enols are generally more reactive towards nitrosoalkenes than silyl ethers,¹²⁸ the reaction of dihydrooxepines **86a,b** with the nitrosoalkene **1n** gives fused 1,2-oxazines **87a,b** as the only reaction products. This unexpected result has been explained by assuming that specific conformational features of the dihydrooxepine ring prevent the lone electron pair of the endocyclic oxygen atom from overlapping efficiently with the C(5)=C(6) double bond, and hence, the C(2)=C(3) bond becomes more reactive.¹⁵⁸



R = H (a), R = Me (b).

The high stereospecificity of cycloaddition confirms its concerted mechanism. It has been established reliably that the formation of mixtures of *cis*- and *trans*-1,2-oxazines from *cis*-alkenes, observed in some cases, is due to some amounts of *trans*-isomers present in the initial alkenes. Since the rate of cycloaddition of nitrosoalkenes to *trans*-alkenes is markedly higher, and the typical experimental procedure involves the use of a large excess of the alkene, the content of *trans*-substituted 1,2-oxazines in the reaction products can be quite noticeable.^{14, 16, 17, 128}

The nitrosoalkenes **1** with R¹ = R² = H are extremely unstable (see Table 1); therefore, their relative reactivities can hardly be estimated. Nevertheless, some qualitative conclusions have been drawn.

For example, the yields of cycloaddition products obtained from 1-nitroso-1-(4-nitrophenyl)ethylene **1v** were generally higher than those obtained from 1-nitroso-1-phenylethylene **11**. Therefore, it was concluded that the former is more reactive.¹⁴ 3-Nitrosobut-3-en-2-one **1m**, which is more reactive, forms adducts with cyclohexene and benzofuran, whereas ethyl α-nitrosoacrylate **1r** does not react with these substrates. This reflects the general tendency of the reactivity to decrease upon replacement of the acetyl group by CO₂Et.¹⁶ As noted above, sterically hindered alkenes like CH₂=C(R)OSiMe₃ (R = Prⁱ, Ph, Bu^t) do not react with 1-nitroso-1-phenylethylene **11** or ethyl α-nitrosoacrylate;^{120, 128} however, more reactive 1,1,1-trifluoro-2-nitrosopropene **1n** does form cycloadducts with these alkenes, although in low yields.¹⁷ The higher reactivity of the nitrosoalkene **1n** compared to 1-nitroso-1-phenylethylene **11** was also confirmed by MNDO calculations.¹⁷

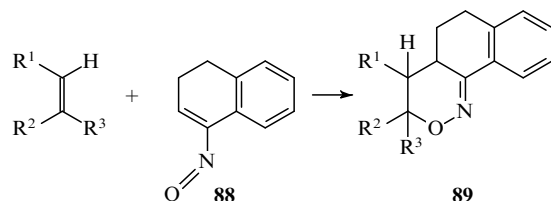
Nitrosoethylene,¹⁸ 2-nitrosopropene,^{8, 120} and some other 1-alkylnitrosoethylenes¹²⁰ form cycloadducts in extremely low yields or do not react at all even with the most reactive dienophiles, cyclopentadiene and ethyl vinyl ether.

Recently, calculations have been carried out for some cycloaddition reactions of nitroso ketene¹⁵⁹ and nitrosoethylene.^{160, 161}

It is of interest that trichloronitrosoethylene **1s** readily reacts with various alkenes as a conjugated heterodiene,¹⁶² although as has been noted above, it behaves as a typical dienophile towards conjugated dienes.

The reactions of 1-nitroso-1-phenylethylene **11** with norbornene and norbornadiene yield mainly *exo*-adducts.¹²⁰

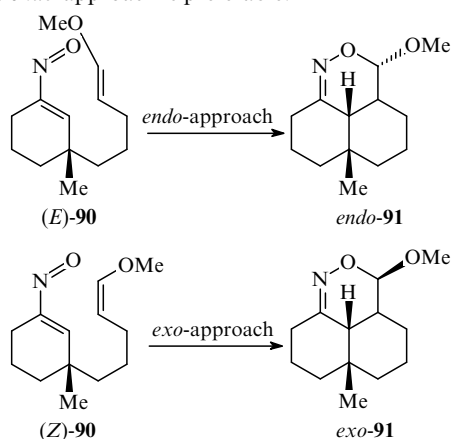
The diastereoselectivity of cycloaddition of alkenes to 3,4-dihydro-1-nitrosonaphthalene **88** has been studied.¹²⁸



Ratio <i>exo</i> - 89 : <i>endo</i> - 89	R ¹	R ²	R ³
> 97 : 3	H	H	OSiMe ₃
64 : 36	Me	H	OSiMe ₃
18 : 82	(CH ₂) ₃		OSiMe ₃
1 : 1	H	H	CH ₂ SiMe ₃

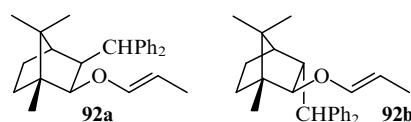
It was found that trimethylsilyloxyethylene affords almost exclusively the *exo*-adduct. When there are one or two alkyl substituents at the double bond, the proportion of the *endo*-adduct increases. In the case of 1-trimethylsilyloxycyclopentene, the *endo*-adduct **89** predominates among the reaction products. Evidently, in this case, the *exo*-approach in the transition state is sterically hindered. For methoxyallene, the steric obstacles to the *exo*-approach prove to be insignificant, and consequently, this alkene, like trimethylsilyloxyethylene, forms predominantly the *exo*-adduct (the *exo* : *endo* ratio is 92 : 8).¹³¹ The fact that the reaction of 1-nitroso-3,4-dihydronaphthalene **88** with allyltrimethylsilane is less diastereoselective than its reaction with trimethylsilyloxyethylene has been explained¹²⁸ by different reactive conformations of these molecules.

Intramolecular [4 + 2]-cycloaddition of the nitroso-alkene fragment to the vinyl-ether fragment in compound **90** has been studied.²⁰ An equimolar mixture of the *E*- and *Z*-isomers of **90** was converted into a mixture of *endo*- and *exo*-adducts **91** in a ratio of 3.4 : 1 (total yield 35%). Based on these data, it was concluded that the *endo*-approach is preferable.

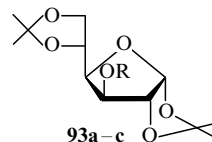


However, in our opinion, this selectivity is actually due to the fact that the *Z*-alkene fragment is much less reactive than the *E*-fragment.

Arnold and Reissig¹⁶³ were the first to use nitrosoalkenes in enantioselective synthesis. They studied [4 + 2]-cycloaddition to optically active vinyl ethers with various optically active fragments and alkenyl residues. The highest diastereoisomeric excess (up to 90%) was observed for the reaction of 1-nitroso-1-phenylethylene **11** with isomeric bulky norbornane derivatives **92a,b**.¹⁶³



Further studies along this line have shown¹⁶⁴ that readily available diacetone glucosyl is the most versatile optically active fragment. Compounds with the general formula **93**, where R are various alkenyl groups (including the allenyl group) ensure high diastereoisomeric yields in [4 + 2]-cycloaddition to terminal nitrosoalkenes.



R = CH = CHMe (*E*, *Z*) (**a**); CH = CMe₂ (**b**); CH = C = CH₂ (**c**).

The above characteristic features of the cycloaddition of nitrosoalkenes to alkenes lead to the clear idea that this is a concerted Diels–Alder reaction with inverse electron demand.^{165–168} The concept of this reaction, first proposed by Gilchrist,^{3,14} is based on interaction of the lowest unoccupied molecular orbital (LUMO) of nitrosoalkene, acting as an electron-withdrawing conjugated heterodiene, with the highest occupied molecular orbital (HOMO) of the alkene, which serves as the electron-donating dienophile. The regioselectivity of this reaction is determined by the HOMO coefficients of the atoms in the alkene (the greatest coefficient characterises the β-C atom) and the LUMO coefficients of the atoms in the nitrosoalkene (the greatest coefficient belongs again to the β-C atom) (Fig. 1); the greater these coefficients, the higher the cycloaddition rate.

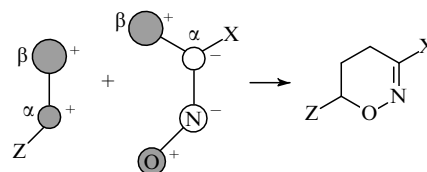


Figure 1. Reaction of nitrosoalkenes with alkenes in terms of the MO LCAO method.^{3,14}

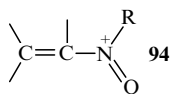
It should be emphasised that no examples of participation of nitrosoalkenes in any Diels–Alder reactions of the standard type have been found so far. The attempts to carry out their cycloaddition to alkenes with electron-withdrawing substituents^{16,137} failed.

It would be expedient to systematise the available arguments supporting the concerted mechanism of cycloaddition of nitrosoalkenes to alkenes:

- (1) there are no indications of formation of any long-lived dipolar¹⁴ or diradical¹²⁸ intermediates;
- (2) the process is highly stereospecific;
- (3) the relative rate constants for the cycloaddition of *E*- and *Z*-isomers of alkenes are substantially different;
- (4) the rates of cycloaddition substantially decrease on passing to alkenes like CH₂ = C(R)OSiMe₃;
- (5) there are no rearrangements during cycloaddition to strained alkenes: norbornadiene,¹²⁰ norbornene,^{120,128,156} and benzvalene.^{128,156}

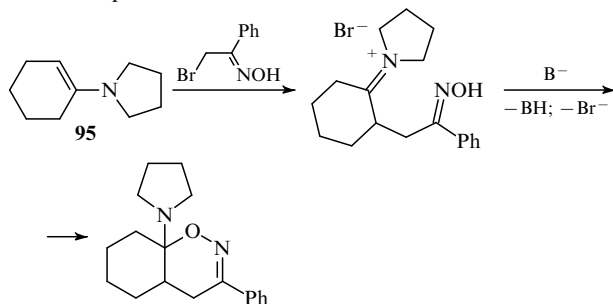
In a more detailed investigation of the reaction mechanism, it was noted¹²⁸ that, despite the concerted character of the reaction, the transition state can be asymmetrical; in particular, the formation of the C–O bond can lag behind the formation of the C–C bond. This assumption was confirmed by PM3 calculations. It has also been suggested¹³¹ that in special cases, this reaction can follow a two-step mechanism involving formation of 1,6-zwitterion intermediates. This occurs, for instance, when 1-nitroso-1-phenylethylene **11** adds to highly sterically strained 1-(hydroxydi-phenylmethyl)-1-methoxypropa-1,2-diene.¹³¹

The closest analogues of nitrosoalkenes in [4 + 2]-cycloaddition reactions are vinylnitrosonium cations **94**^{169–172} and conjugated nitro alkenes.^{173–177}

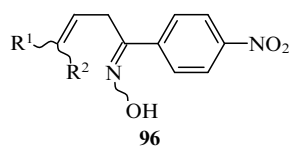


Apparently, the range of cycloaddition reactions of nitrosoalkenes to C = C bonds is not exhausted by the data presented above. Thus Gilchrist *et al.*^{18,93} believe that the reaction of α -halo oximes with enamines in the presence of Na₂CO₃ involves generation and subsequent [4 + 2]-cycloaddition of nitrosoalkenes to electron-rich C = C bonds.^{18,93}

However, the alkylation of enamines with α -bromo oximes^{152,153} in the absence of bases should apparently be regarded as direct S_N2 substitution of bromine, because the intermediate immonium salts can be isolated. The structures of these intermediates have been established by IR, UV, and ¹H NMR spectroscopy.¹⁵¹ It was found that on treatment with bases, the immonium salts cyclise to 6-(*N,N*-dialkylamino)-5,6-dihydro-4*H*-1,2-oxazines. This sequence of reactions is considered below in relation to the alkylation of 1-pyrrolidincyclohexene **95** with α -bromoacetophenone oxime.¹⁵¹



[4 + 2]-Cycloaddition of nitrosoalkenes can be accompanied by the formation of side products. Thus the reactions of 1-nitroso-1-(*p*-nitrophenyl)ethylene with styrene, α -methylstyrene, and α -phenylstyrene, in addition to 1,2-oxazines, affords β,γ -unsaturated oximes **96**¹⁴ (the formation of similar products has also been reported in another study¹⁵²).



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

c. [3 + 2]-cycloaddition of nitrosoalkenes to alkenes

[4 + 2]-Cycloaddition of 1-nitroso-1-phenylethylene **11** and 1-nitroso-1-(4-nitrophenyl)ethylene **1v** to 2-methoxypropene giving rise to the corresponding 1,2-oxazines is accompanied by [3 + 2]-cycloaddition, which yields cyclic nitrones **97** as minor products¹⁴ (see also Section IV.2, compound **76**). It was shown in special experiments that the ratio of the [4 + 2]- to [3 + 2]-cycloadducts does not depend on the *E*- or *Z*-configuration of the α -bromo oximes, precursors of nitrosoalkenes.¹⁴

In Gilchrist's opinion,³ for concerted [3 + 2]-cycloaddition to occur, the nitrosoalkene molecule should assume a reactive conformation in which the lone electron pair of the nitroso-group nitrogen atom lies in a plane parallel to the plane of the $\pi_{C=C}$ bond, according to the 1,3-dipole type (Fig. 2).

At the same time, it was noted¹⁴ that the minor products **96** and **97** are formed in those cases where the possible dipolar intermediates are efficiently stabilised. However, in both cases, the product ratio proved to be insensitive to an increase in the polarity of the solvent.¹⁴

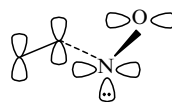
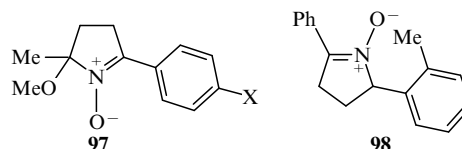


Figure 2. Conformation of nitrosoalkene during [3 + 2]-cycloaddition.

The [3 + 2]-cycloaddition of 1-nitroso-1-phenylethylene **11** to *o*-methylstyrene gives nitrone **98**.¹⁷⁸

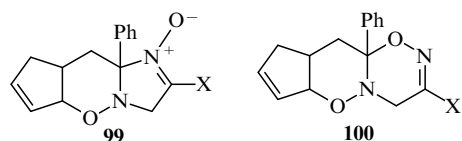


X = H, NO₂.

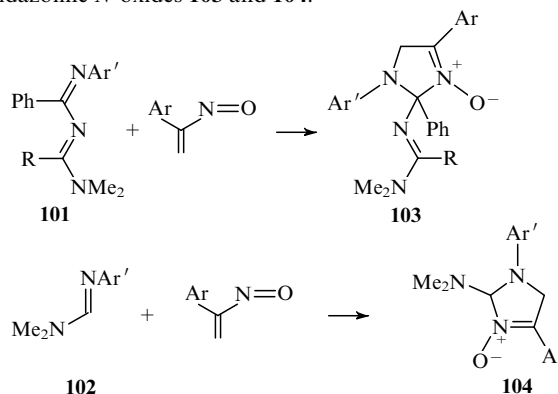
The reaction of nitrosoalkenes considered in this Section resembles the known [3 + 2]-cycloaddition of azines to multiple bonds.¹⁷⁹

d. Nitrosoalkenes in cycloaddition to C = N, C = S, and C $\equiv$ C bonds

[4 + 2]-Cycloaddition of nitrosoalkenes is a general method for functionalisation of alkenes. However, cycloaddition to nitrosoalkenes is not restricted to the reactions with carbon-carbon double bonds. Nitrosoalkenes are able to add to C = N bonds in some cyclic 1,2-oxazines to give nitrones **99**^{119,180} (see also Section IV.2, compound **77**) and fused 1,2,5-oxadiazines **100**,¹⁸¹ their yields ranging from low to moderate. This reaction is not a general transformation of the oximine fragment.¹⁸⁰

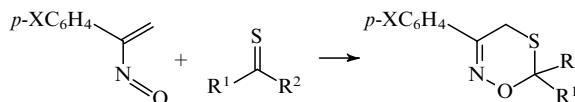


Recently, it has been shown that nitrosoalkenes react smoothly with amidines of type **101** and **102** according to the [3 + 2]-cycloaddition fashion giving rise to the corresponding imidazoline *N*-oxides **103** and **104**.¹⁸²



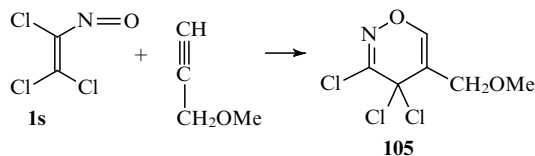
This reaction is general and, in the opinion of the researchers cited,¹⁸¹ occurs *via* formation of a stabilised dipolar intermediate.

The use of the C = S bonds of thiocarbonyl compounds as a heterodienophilic 2 π -component in [4 + 2]-cycloaddition to substituted α -nitrostyrenes has been reported.¹⁸² The reaction of trichloronitrosoethylene **1s** with Ph₂C = S is an example.¹⁶²



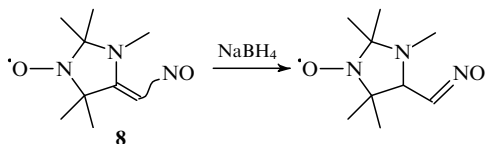
X = H, OMe, NO₂; R¹, R² = Ar, PhS, R₃Si.

Trichloronitrosoethylene is capable of reacting with methyl propargyl ether to afford 4*H*-1,2-oxazine **105**;¹⁶² however, the attempts to involve various alkynes in cycloaddition to nitrosoalkynes of the type $\text{CH}_2=\text{C}(\text{R})\text{NO}$ were unsuccessful.^{3, 17, 120}

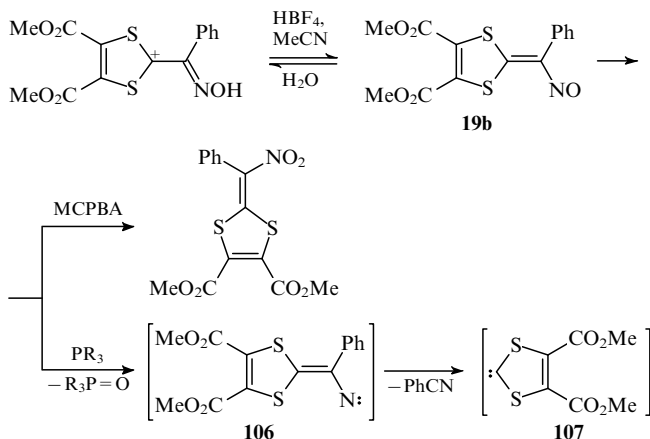


e. Other reactions

The known chemistry of nitrosoalkenes is virtually exhausted by the information presented here. At present, there are no reliable data concerning radical addition or ene reactions of these compounds, although these are typical reactions of other types of nitroso derivatives. It can only be added that 1-nitrosocyclohexene **1f**¹⁰ and trifluoronitrosoethylene **1a**⁵ can undergo electrophilic addition. The addition of HCl to some nitrosoalkenes has been reported.¹⁰ Trifluoronitrosoethylene **1a** is able to polymerise by a radical mechanism in solution.⁵ The reduction of the nitrosoalkene **8** with NaBH_4 gives rise to the corresponding oxime.



Several reactions have been reported for the nitrosofulvene **19b**, namely, reversible *O*-protonation, oxidation to nitrofulvene by *m*-chloroperbenzoic acid, and deoxygenation by tertiary phosphines followed by fast fragmentation of the intermediate nitrene **106**, resulting in the generation of carbene **107**.⁴⁶



MCPBA = 3-ClC₆H₄COOOH.

Nitrosoalkenes (nitrosodithiofulvenes and nitrosodiselenofulvenes) form coordination compounds with PdCl_2 .¹⁸³

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Palladium carbonyl complexes[†]

T A Stromnova, I I Moiseev

Contents

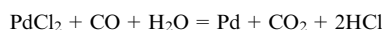
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Abstract. Data on palladium carbonyl complexes are described systematically and subjected to a critical analysis. The methods of synthesis and data on the structures and chemical properties of mono- and poly-nuclear carbonyl-containing palladium complexes in which the formal oxidation state of the metal varies from 0 to +2 are discussed. Virtually all the publications on this question up to 1997 are examined. The bibliography includes 241 references.

I. Introduction

The interest in the chemistry of palladium carbonyl complexes is to a large extent determined by the activity of palladium and its compounds in the catalysis of reactions involving CO. Such reactions include in the first place the catalytic oxidation of CO to CO₂, the synthesis of alkyl oxalates and alkyl carbonates, reactions involving the carbonylation of alcohols, saturated hydrocarbons, and aromatic nitro-compounds, *etc.*¹ The study of the properties and reactivities of carbon-containing palladium complexes is an essential stage in the investigation of the mechanisms of the reactions occurring with participation of palladium catalysts.² The carbonyl complexes of palladium and other platinum metals are of undoubted interest from the standpoint of the theory of coordination compounds, especially the nature of the bond in complex many centre systems of clusters containing the metal in the lowest oxidation states.

The susceptibility of PdCl₂ to reduce by carbon monoxide to the metal, *i.e.*



was observed more than 100 years ago.^{3–5} Palladium carbonyl chlorides were among the first platinum metal carbonyl complexes synthesised.⁶ However, owing to their higher reactivity compared

with other platinum metal carbonyls, they remained for a long time represented by a few poorly characterised compounds. The available information about their structures and reactivities was based solely on indirect data (mainly by analogy with compounds of other platinum metals).

Data on the chemistry of palladium carbonyl complexes have been partly surveyed in a monograph⁷ in which none of the compounds of this class have been reliably characterised. A review⁸ presents the structural characteristics of two palladium carbonyl complexes — [Pd(dam)Cl]₂CO,^{9,10} where dam = bis(di-phenylarsino)methane, and Pd₄(CO)₄(OAc)₄.^{11,12} Since the end of the 1970s, the number of studies on palladium carbonyls has increased sharply.

The classification of the compounds constituting the subject of the present review is based on the formal oxidation state (FOS) of palladium. The formal oxidation state of the metal atom in a complex is defined as the average charge of the metal atoms which they possess after the removal of the ligands.^{13,14} It is assumed that in the leaving ligands (for example, such as H[–], Cl[–], O^{2–}, OH[–], NH₂[–], NR₂[–], PR₂[–], SnCl₃[–], and CH₃[–]) the electron shell of the atom linked to the metal corresponds to the shell of the nearest inert gas atom; the ligands are removed in the form of neutral molecules (CO, NO, N₂, CO₂, C₂H₂, C₂H₄, *etc.*). As regards certain π -linked organic groups (allyl C₃H₅, cyclopentadienyl C₅H₅), they are regarded as anions, like the σ -linked C₃H₅[–] and C₅H₅[–] groups.

Mainly mononuclear compounds are considered in classical coordination chemistry. The stable oxidation states 0 and +2 are attributed to palladium. However, the study of polynuclear, mainly cluster, compounds has shown that many of them have an oxidation state of +1; there are also compounds in which the formal charge per metal atom is nonintegral. Palladium carbonyl hydride complexes, for which the exact stoichiometry of the polyhydrides can be established in by no means all cases which precludes in its turn the determination of the FOS of the metal, constitute a separate group. A separate Section has been devoted to the palladium carbonyls isolated in zeolite cells, which may function as polyanions.

T A Stromnova, I I Moiseev N S Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, Leninskii prosp. 31, 117907 Moscow, Russian Federation. Fax (7-095) 954 12 79. Tel. (7-095) 952 12 03 (T A Stromnova)

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[†]Commemorating Professor Peter M Maitlis on the occasion of his 65th birthday.

A systematic treatment of heteronuclear, palladium-containing complexes in accordance with the above principles is in many cases difficult. The FOS of palladium can be comparatively readily inferred, provided that the structure of the heterometal-containing species forming part of the complex remains unchanged on formation of the compound.

For example, the reaction^{15, 16} of the benzonitrilepalladium(+2) complex $\text{PdCl}_2(\text{NCPh})_2$ with $\text{Na}[\text{Co}(\text{CO})_4]$ affords, after the substitution of Cl^- by $[\text{Co}(\text{CO})_4]^-$, the trinuclear cluster $\text{Pd}[\text{Co}(\text{CO})_4]_2(\text{NCPh})_2$, in which the palladium atom is believed to retain a FOS of +2. However, on interaction of this cluster with dppm [dppm = bis(diphenylphosphino)methane], which leads to $\text{PdCo}_2(\text{CO})_5(\mu\text{-dppm})_2$, not only are the benzonitrile ligands displaced but also three carbonyl groups are lost by the two anionic carbonylmetallates $[\text{Co}(\text{CO})_4]^-$. The CO-containing complexes formed ultimately have to analogues in classical coordination chemistry and this hinders the overall classification.

The present review deals with individual heteronuclear palladium-containing complexes, the assignment of which to a particular Section of the review is not open to doubt.

Since the aim of the present review is the analysis of the methods of synthesis and the characteristics of the structures and reactivities of molecular palladium complexes with carbonyl ligands, we shall deal only briefly with data on the palladium carbonyls formed on the surface of oxide carriers.

II. Activation of carbon monoxide in the coordination sphere of the transition metal and the strength of the M–CO bond

In the complexes of transition metals carbon monoxide effectively stabilises their lowest oxidation states. The carbonyl complexes of each metal from the first series of transition elements have been well characterised.¹⁷ The composition of the compounds obeys the '18 electron' rule, which predicts monomeric compounds for Group IV metals, for example, $\text{Cr}(\text{CO})_6$, $\text{Fe}(\text{CO})_5$, and $\text{Ni}(\text{CO})_4$. The metals in odd Groups form paramagnetic $[\text{V}(\text{CO})_6]$ or dimeric $[\text{Mn}_2(\text{CO})_{10}]$ or $[\text{Co}_2(\text{CO})_8]$ carbonyls. Mononuclear complexes are not very characteristic of transition metals in the second and third series. These metals afford preferentially compounds in which the number of metal atoms is from 2 or 3 to several hundreds.^{18–21} From a formal point of view, features, structure and chemical properties) common to mononuclear carbonyls and a metallic surface coated by adsorbed CO molecules are characteristic of these clusters.²²

A considerable number of communications (see, for example, Refs 23–27) have been devoted to the question of the stability of monomeric transition metal, especially palladium, carbonyls. It has been established on the basis of quantum-chemical calculations that, among the transition metal carbonyls $\text{M}(\text{CO})_6$ (M = Cr, Mo, W), $\text{M}(\text{CO})_5$ (M = Fe, Ru, Os), and $\text{M}(\text{CO})_4$ (M = Ni, Pd, Pt), the metal–carbonyl bond energy and the dissociation energy of the first carbonyl ligand are a minimum for $\text{Pd}(\text{CO})_4$. Calculations led to the conclusion that the π -back-donation from the ligand to the metal makes a much greater contribution in the stable $\text{M}(\text{CO})_m$ systems than the σ -donor bond.

Thus the results of quantum-chemical calculations have shown the palladium carbonyls should have a minimum thermal stability and a maximum kinetic lability among transition metal carbonyls. These properties of the Pd–CO bond have probably in fact been responsible for the activity of palladium and its compounds in the catalysis of processes occurring with participation of carbon monoxide. However, the same properties have apparently 'inhibited' the development of the chemistry of palladium carbonyl complexes compared with other transition metal complexes.

The catalytic activation of carbon monoxide entails a change in the molecular orbitals of this ligand due to coordination to the metal atom. Carbon monoxide is a weak σ -donor ligand, but it

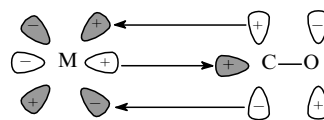


Figure 1. Schematic illustration of the bonds between carbon monoxide and a metal atom.

can bind fairly strongly to the metal atom. The overall mechanism of the binding of carbon monoxide to a metal atom is presented in Fig. 1.

According to this scheme, apart from the ligand–metal interaction determined by the σ -donor properties of the ligand, the back-donation from the occupied d orbitals of the metal to the occupied antibonding π orbitals of the ligand takes place. Evidently, these two bonding modes should lead to opposite effects in the resulting transfer of electron density between the metal and the ligand.²⁸ Until recently the view that the π -acceptor properties of the ligand predominate in the formation of the metal–carbonyl bond was dominant. This was used to account for the weakening of the C–O bond in the carbonyl ligand itself, observed on coordination of CO to metals in the lowest oxidation states, and hence for the appreciable decrease in the ν_{CO} stretching vibrational frequencies in the IR spectra of the compounds.

However, on coordination of CO to metals in high oxidation states, for example on formation of $\text{Pd}(+2)$ carbonyls, the predominance of the σ -donor properties of the ligand over their π -acceptor properties was noted, which leads in its turn to an increase in ν_{CO} to values equal to and even exceeding the stretching vibrational frequencies of CO in free carbon monoxide.²⁹

III. Palladium(0) carbonyl complexes

All the Pd(0) complexes described hitherto have been described by convention in two groups — binary carbonyls (compounds containing only CO molecules as the ligands) and complexes with additional stabilising ligands (as a rule N- or P-donor ligands).

1. The binary carbonyls

The binary carbonyls are characteristic of many Group VIII metals and are readily formed even at room temperature when the metal interacts with carbon monoxide. In contrast to these metals, palladium does not form binary carbonyls on direct interaction with CO at room or elevated temperature.

The binary palladium carbonyls began to be synthesised simultaneously by two groups of investigators.^{30–34} The method involving the joint condensation of metal vapour and CO at 4.2–27 K with isolation of the carbonyl in a crystalline argon or CO matrix was employed. At 4.2–10 K and for a CO content in the gas phase ranging from 100% to 10%, $\text{Pd}(\text{CO})_4$ was obtained. On raising the temperature and on reducing the partial pressure of CO, the formation of $\text{Pd}(\text{CO})_3$, $\text{Pd}(\text{CO})_2$, and $\text{Pd}(\text{CO})$ was observed.

All the conclusions concerning the structure of the binary palladium carbonyls are based on the results of the study of their vibrational spectra. Analysis of the Raman and IR spectra of carbonyl molecules containing isotope-substituted CO fragments ($^{12}\text{C}^{16}\text{O}$, $^{13}\text{C}^{16}\text{O}$, $^{12}\text{C}^{18}\text{O}$) showed that the $\text{Pd}(\text{CO})_4$ molecule is tetrahedral like $\text{Ni}(\text{CO})_4$ (T_d symmetry).³³ The frequency of the stretching vibration active in these spectra (the T_2 band) is 2066 cm^{-1} ; the frequency of the A_1 vibration, active in the Raman spectrum, is 2122 cm^{-1} and the force constant $k_{\text{CO}} = 17.48\text{ mdyn \AA}^{-1}$ in the Cotton–Kraihanzel approximation. It is of interest that the force constant k_{CO} for the more stable $\text{Ni}(\text{CO})_4$ molecule is virtually the same ($17.23\text{ mdyn \AA}^{-1}$). The M–C stretching vibrational frequency and force constant are more sensitive to the nature of the central atom. The $\nu_{\text{M-C}} = 258\text{ cm}^{-1}$ for palladium tetracarbonyl, whereas the

corresponding band has been observed at 435 cm^{-1} for nickel tetracarbonyl.³⁴

Spectroscopic data have led to the conclusion that the $\text{Pd}(\text{CO})_3$ molecule is planar (D_{3h} symmetry), while the $\text{Pd}(\text{CO})_2$ (D_h symmetry) and $\text{Pd}(\text{CO})$ (C_v symmetry) molecules are linear. The frequencies of the IR-active vibration are respectively 2060, 2044, and 2050 cm^{-1} for these molecules, but the force constant k_{CO} varies from 17.35 to $16.96\text{ m dyn } \text{\AA}^{-1}$.³² The decrease in the force constant is correlated with the decrease in the stability of the carbonyls in the sequence $\text{Pd}(\text{CO})_4 > \text{Pd}(\text{CO})_3 > \text{Pd}(\text{CO})_2 > \text{Pd}(\text{CO})$.³³ Apparently the palladium mono-, di-, and tri-carbonyls are mononuclear, the CO groups are terminal, and there is no metal–metal interaction.^{31,33} The stretching vibrational frequency of the terminal CO group in the mononuclear complexes is in the range $2050\text{--}2066\text{ cm}^{-1}$.

The formation of binary carbonyls stable at temperatures up to 190 K has been noted in the deposition of palladium from a gas phase containing carbon monoxide onto an Al_2O_3 surface.³⁵ These carbonyl compounds have been characterised under high vacuum conditions by thermal desorption spectroscopy (TDS), diffraction of slow electrons (LEED), UV photoelectron spectroscopy (UPS), and X-ray electron spectroscopy (ESCA).

Another type of binary palladium carbonyls — the cationic complexes $[\text{Pd}(\text{CO})_4]^{2+}$ — is considered below.

2. Palladium(0) carbonyl complexes containing stabilising ligands

The binary $\text{Pd}(0)$ carbonyls are extremely unstable and decompose at a temperature above 20 K. The insertion into the coordination sphere of palladium of additional ligands having low-lying unoccupied orbitals capable of accepting the d electrons of the central atom (for example, N- and P-donor bases) made it possible to obtain relatively thermally stable $\text{Pd}(0)$ complexes.

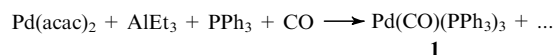
Carbonyl-containing $\text{Pd}(0)$ complexes are synthesised mainly by three methods: by the reduction of $\text{Pd}(+2)$ complexes under a CO atmosphere; by the substitution of ligands by carbon monoxide in preformed $\text{Pd}(0)$ complexes; by the mild oxidation of coordinated ligands (for example, by the oxidation of phosphines to phosphine oxides, which leads to the ‘liberation’ of coordination sites and hence the formation of clusters with a greater nuclearity).

Only the first method or the first method combined with the third have been used to obtain $\text{Pd}(0)$ carbonyl complexes. When the first method was used, carbon monoxide served only in rare instances both as a reductant and as a stabilising ligand. As a rule, more vigorous reductants have been used in the reduction of $\text{Pd}(+2)$ to $\text{Pd}(0)$; the products of such reduction were small clusters. In order to obtain clusters with a greater nuclearity (Pd_{10} and above), ‘mild’ oxidation (*i.e.* oxidation of only some of the isotypical ligands) has been used, leading to the liberation of coordination sites and the formation of new metal–metal bonds. Mainly $\text{Pd}(+2)$ and $\text{Me}_3\text{N}^+\text{O}^-$ have been used as the oxidants in this instance.

a. Mononuclear palladium(0) complexes

The reduction of $\text{Pd}(+2)$ in the presence of carbon monoxide and additional stabilising ligands leads as a rule to di- and poly-nuclear complexes; the number of isolated and reliably characterised mononuclear $\text{Pd}(0)$ complexes is extremely small (Table 1).

The first mononuclear $\text{Pd}(0)$ complex was obtained by the reduction of palladium acetylacetonate with triethylaluminium in toluene at 223 K.³⁶



Together with mononuclear complexes, the formation of the polynuclear complexes $\text{Pd}_3(\text{CO})_3(\text{PPh}_3)_3$ **2** and $\text{Pd}_3(\text{CO})_3(\text{PPh}_3)_4$ **3** has been observed.

Table 1. Mononuclear palladium(0) complexes.

Complex	Physical methods used to characterise the substance	$\nu_{\text{CO}}/\text{cm}^{-1}$	Ref.
$\text{Pd}(\text{CO})(\text{PPh}_3)_3$	elemental analysis, IR spectroscopy	1955	36–38, 40, 41
$\text{Pd}(\text{CO})(\text{NP}_3)^a$	elemental analysis, IR spectroscopy, $^{31}\text{P}\{^1\text{H}\}$ NMR	1930	42
$\text{Pd}(\text{CO})[\text{MeC}(\text{CH}_2\text{PPh}_2)_3]$	elemental analysis, IR spectroscopy, XRD	1919	44
$\text{Ba}[\text{Pd}(\text{CN})(\text{CO})]_2$	elemental analysis, IR spectroscopy	1780, 1720	45
$[\text{RPh}_3\text{P}]^+[\text{Pd}(\text{CN})(\text{CO})]_2^-$	the same	1790	45

^a $\text{NP}_3 = \text{tris}(2\text{-diphenylphosphinoethyl})\text{amine } \text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3$.

Complex **1** has also been obtained by the reduction of the phosphinepalladium(+ 2) chloride complex in methanol at 228 K by the reaction.³⁷



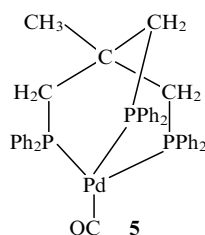
The interaction of $\text{PdCl}_2(\text{PPh}_3)_2$ and CO in a mixture of methanol with primary or secondary alkylamine also results in the formation of complexes **1** and **3**.³⁸ However, one cannot rule out the possibility that in this instance the amine itself exhibits reducing properties. When a primary or secondary amine is replaced by a tertiary amine, a methoxycarbonyl derivative of divalent palladium, $(\text{PPh}_3)_2\text{PdCl}(\text{COOMe})$, is formed.³⁸ This complex has also been synthesised by Zhir-Lebed' *et al.*³⁹

The formation of complex **1** has been noted in the carbonylation of $[(\eta^3\text{-allyl})\text{PdCl}]_2$ in the presence of PPh_3 in solution in methanol or ethanol ($P_{\text{CO}} = 4\text{ atm}$; 293 K).⁴⁰

The divalent palladium acetate complex $(\text{PPh}_3)_2\text{Pd}(\text{OAc})_2$ is not reduced by carbon monoxide in methanol under mild conditions.⁴¹ Only at 323 K and a CO pressure of 20–50 atm is $\text{Pd}(+2)$ reduced to $\text{Pd}(0)$ with formation of a mixture of complexes **1** and **3**.

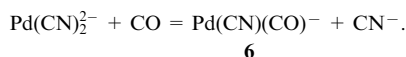
In all the studies described, complex **1** was characterised solely by elemental analysis and IR spectroscopic data. The stretching vibration frequency of the carbonyl group is fairly low (1955 cm^{-1}), which precludes an unambiguous determination of the mode of coordination of this ligand (bridging or terminal carbonyl) and it is therefore impossible to estimate the reliability of the conclusion that this compound is mononuclear. However, later investigations of the complexes $\text{Pd}(\text{CO})\text{L}_3$ made it possible to regard complex **1** as mononuclear with a terminal carbonyl ligand.

Thus, when carbon monoxide is passed through a benzene solution of $\text{Pd}(\text{NP}_3)$ [$\text{NP}_3 = \text{tris}(2\text{-diphenylphosphinoethyl})\text{-amine } \text{N}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3$], $\text{Pd}(\text{NP}_3)\text{CO}$ **4** was obtained.⁴² Complex **4** is stable only under a CO atmosphere. Its IR spectrum contains an intense band at 1930 cm^{-1} . The presence of a band at 2820 cm^{-1} , assigned to the stretching vibrations of the CH–N bond, showed that the nitrogen atom is not linked to the metal atom. The $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum indicated the equivalence of all the phosphorus atoms. On the basis of the entire set of data obtained and comparison with the data for the analogous nickel complex characterised by X-ray diffraction,⁴³ the structure assigned to compound **4** consists of a tetrahedron in the centre of which is the palladium atom and whose vertices are occupied by the carbon atom of the carbonyl ligand and the three phosphorus atoms of tris(phosphino) amine. The complex $\text{Pd}[\text{MeC}(\text{CH}_2\text{PPh}_2)_3](\text{CO})$ **5**, obtained later and characterised by X-ray diffraction, has precisely this structure.⁴⁴



Complex **5** is formed on interaction of Pd(DBA) (DBA = dibenzylideneacetone) and the triphosphine ligand MeC(CH₂PPh₂)₃ in toluene under a CO atmosphere. It has been isolated in the form of yellow needles and characterised by IR spectroscopy ($\nu_{\text{CO}} = 1919 \text{ cm}^{-1}$) and X-ray diffraction. In the molecule of compound **5**, the palladium atom is linked to the carbon atom of the terminal CO group and the phosphorus atom of the triphosphine, forming a trigonal pyramid.

Carbon monoxide is capable of substituting CN^- in $\text{Pd}(\text{CN})_2^{2-}$, obtained by the reduction of $\text{Pd}(\text{CN})_4^{2-}$.⁴⁵ On treatment with oxygen-free dry CO in liquid ammonia (196 K), the following reaction takes place:



Complex **6** has been isolated⁴⁵ in the form of a salt with PRPh_3^+ (R = Me or Ph) and also in the form of a barium salt and has been characterised by elemental analysis and IR spectroscopy. The stretching vibrational frequencies, which are extremely low for a terminal carbonyl ligand ($\nu_{\text{CO}} = 1790 \text{ cm}^{-1}$ for the phosphonium salts and $\nu_{\text{CO}} = 1780$ and 1720 cm^{-1} for the barium salt), provide grounds for the assumption that in these compounds the CO group is a bridging structure between two or three metal atoms and the compounds themselves are at least dinuclear.

The ability of carbon monoxide to reduce Pd(+2) in aqueous solutions has been used to obtain carbonyl complexes stabilised by 1,10-phenanthroline (Phen) or α, α' -bipyridyl (Bipy).⁴⁶ When a solution of PdCl_2 containing Phen or Bipy is treated with CO containing 5% of O₂, a bright-red solution is obtained, from which the substance (L)Pd(CO)·4H₂O (L = Phen or Bipy) was isolated on treatment with acetone. Certain properties of this complex (good solubility in water, inability to dissolve in organic solvents resistance to the action of oxygen, etc.) provide grounds for the assumption that it contains ionogenic groups and that the oxidation state of palladium is greater than zero.

b. Polynuclear palladium(0) complexes

Polynuclear (cluster) Pd(0) complexes consist mainly of compounds containing carbonyl and phosphine ligands. Clusters comprising metals having a large number of valence electrons (nickel, palladium, and platinum) are capable of coordinating a smaller number of ligands than clusters of the preceding transition metals, which leads to the instability of their carbonyl derivatives.⁵⁰ The coordination of tertiary amines, which produce the same number of valence electrons as carbon monoxide but ensure, by virtue of steric factors, more effective shielding of the surface of the metal core, leads to the formation of fairly stable compounds. The methods of synthesis structures and reactivities of phosphine palladium carbonyl clusters are considered below.

The formation of the dinuclear $\text{Pd}_2(\text{dppm})_2(\text{CO})$ is described in a communication⁴⁷ devoted to the synthesis of catalysts for the hydrogenation of carbon dioxide. The complex, believed to contain a bridging carbonyl group, was obtained by the reduction of $\text{PdCl}_2(\text{dppm})_2$ with sodium tetrahydroborate in ethanol under a CO atmosphere. There are only elemental analytical and IR spectroscopic data ($\nu_{\text{CO}} = 1820 \text{ cm}^{-1}$) and the conclusions concerning its structure are therefore insufficiently reliable.

Complexes which are at least dinuclear and contain sulfide ligands in addition to the carbonyl group have been obtained.^{48,49}

The reduction of palladium acetate with carbon monoxide in an aqueous solution of trifluoroacetic acid in the presence of an

excess of dialkyl sulfides R_2S (R = Me, Et, Prⁿ, Buⁿ) afforded complexes with the overall composition $\text{Pd}(\text{R}_2\text{S})_3(\text{CO})$.⁴⁸ The band at $1828 - 1838 \text{ cm}^{-1}$ (ν_{CO}) in the IR spectra of the complexes indicates the bridging coordination of the carbonyl ligand and hence the di- or poly-nuclearity of the complexes.

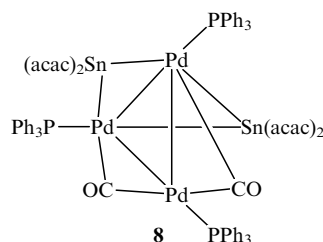
Compounds with the overall composition $\{\text{Pd}_2[\text{RS}(\text{CH}_2)_m\text{SR}]_2(\text{CO})(\text{HOAc})_m\}$ have been obtained similarly from palladium acetate in the presence of sulfides having the general formula $\text{RS}(\text{CH}_2)_m\text{SR}$, where $m = 1, 2$, or 3 and R = C₃H₇, C₇H₁₅, Ph, or Ph-CH₂.⁴⁹ The IR spectra of all the complexes isolated contain an intense band in the region of 1800 cm^{-1} , which has been assigned to the stretching vibrations of the bridging carbonyl ligand. Measurements of the molecular masses of the complexes, whose solubility is low, did not allow a choice to be made between dinuclear and tetranuclear complexes.

3. The trinuclear complexes $\text{Pd}_3(\text{CO})_3\text{L}_3$ and $\text{Pd}_3(\text{CO})_3\text{L}_4$

Clusters with the composition $\text{Pd}_3(\text{CO})_3\text{L}_3$ are known only for very bulky ligands (L = PBu_3 , PBu_3^tPh). Such clusters were obtained by the interaction of coordinatively unsaturated complexes PdL_2 and carbon monoxide.⁵¹ An X-ray diffraction analysis has been carried out only for the platinum analogue $\text{Pt}_3(\text{CO})_3[\text{P}(\text{cyclo-C}_6\text{H}_{11})_3]$.⁵² It has been established that the cluster has a metal core shaped as an equilateral triangle (in which the Pt-Pt bond length is $2.665 \text{ \AA}$), to the sides of which the bridging CO groups are coordinated. All the phosphorus atoms of the terminal phosphine ligands, one of which is coordinated to each metal atom, lie in the Pt_3 plane.

The interaction of $\text{M}[\text{M}'(\text{NR}_2)_2]_3$ and CO afforded⁵³ the heteronuclear clusters $\text{M}_3[\mu\text{-M}'(\text{NR}_2)_2]_3(\text{CO})_3$ **7** (M = Pd or Pt, M' = Ge or Sn, R = SiMe₃), which were characterised by IR spectroscopy and NMR involving various nuclei. X-Ray diffraction study of the structure of complex **7** with M = Pd and M' = Sn showed that it has a planar metal core, whose base consists of the Pd_3 triangle. The bridging $\text{Sn}(\text{NR}_2)_2$ ligands are coordinated symmetrically to the sides of the triangle. The carbonyl groups are terminal ($\nu_{\text{CO}} = 2038 \text{ cm}^{-1}$), one being coordinated to each palladium atom.

Heteronuclear clusters of another type, $\text{Pd}_3\text{Sn}_2(\eta^2\text{-acac})_4(-\text{CO})_2(\text{PR}_3)_3$ **8** (R = Ph, Et), was obtained by the interaction of the clusters $\text{Pd}_4(\mu\text{-CO})_5(\text{PR}_3)_4$ and $\text{Sn}(\text{acac})_2$ in a hydrocarbon solution.^{54,55}



Compounds **8** are sensitive to moisture and are unstable in solution. In the region of the vibrational frequencies of the carbonyl groups, their IR spectra contain only bands due to the bridging CO groups in the range $1770 - 1890 \text{ cm}^{-1}$. According to X-ray diffraction data, the palladium atoms in clusters **8** (R = Ph) form an isosceles triangle, the sides of which are spanned by bridging CO groups, while the base is coordinated to two $\text{Sn}(\eta^2\text{-acac})_2$ bridging ligands. One phosphine ligand is linked to each palladium atom. In principle, the Pd_3Sn_2 metal core may be regarded as a 'propeller' with a Pd-Pd axis and triangular wings made up from a Pd atom and two Sn atoms.

The trinuclear clusters $\text{Pd}_3(\text{CO})_3\text{L}_4$ are obtained by reducing PdCl_2L_2 (L = PPh_3)³⁶ or palladium acetate with carbon monoxide in the presence of NaOAc and two equivalents of the phosphine ligand (L = PPh_3 , $\text{P}(\text{C}_6\text{H}_4\text{OMe-}p)_3$).⁵⁶ The structure of clusters of this type has been established in relation to $\text{Pd}_3(\text{CO})_3(\text{PPh}_3)_4$.⁵⁷ The molecule of the cluster consists of an isosceles triangle, to the sides of which $\mu\text{-CO}$ groups are coordi-

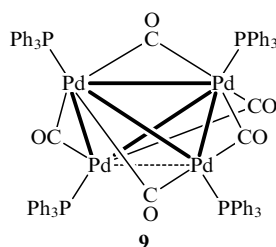
nated. Each metal atom in the base of the triangle is linked to one phosphorus atom, while the atom at the apex of the triangle is linked to two phosphorus atoms of the phosphine ligands. Such coordination of the phosphines leads to the nonequivalence of the carbonyl groups, which is reflected in the IR spectra: two intense bands are observed in the region of the stretching vibrations of the CO groups ($1820-1880\text{ cm}^{-1}$).

4. The tetranuclear clusters $\text{Pd}_4(\text{CO})_5\text{L}_4$ and $\text{Pd}_4(\text{CO})_6\text{L}_4$

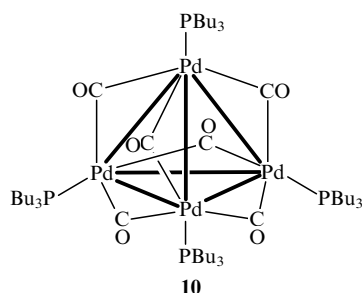
It was noted above that the coprecipitation of Pd and CO *in vacuo* at low temperatures leads to mononuclear complexes which decompose even on a slight increase in temperature. On the other hand, if hexafluorobut-2-yne $\text{F}_3\text{CC}\equiv\text{CCF}_3$ (HFB) is added to Pd and CO, then precipitation *in vacuo* at -196°C results in the formation⁵⁸ of a volatile substance having the tentative composition $\text{Pd}(\text{CO})_2(\text{HFB})$, which is converted into the cluster $\text{Pd}_4(\text{CO})_4(\text{HFB})_3$ on slow heating. The substance has been characterised by osmometric data obtained in acetone (molecular mass), IR spectroscopy ($\nu_{\text{CO}} = 2138$ and 2122 cm^{-1}), and ^{19}F NMR spectroscopy.

$\text{Pd}(\text{OAc})_2$ is usually employed for the synthesis of tetranuclear carbonyl clusters with phosphine ligands, but the conditions used in the preparation of compounds with aliphatic and aromatic phosphines are different.

The tetranuclear cluster $\text{Pd}_4(\text{CO})_5(\text{PPh}_2\text{Me})_4$ was obtained⁵⁸ by reducing $\text{Pd}(\text{NO}_2)_2(\text{PPh}_2\text{Me})_2$ with carbon monoxide in methylene chloride. The cluster $\text{Pd}_4(\text{CO})_5(\text{PPh}_3)_4$ **9** was obtained later in a similar reaction.⁵⁹ X-Ray diffraction analysis of $\text{Pd}_4(\text{CO})_5(\text{PPh}_2\text{Me})_4$ ⁵⁸ and compound **9**⁵⁹ showed that the metal cores in both clusters have the form of a tetrahedron with one elongated edge ('open' tetrahedron or 'butterfly'). All the carbonyl groups are involved in μ -type coordination on the edges, each metal atom being linked to one phosphorus atom of the phosphorus ligand. The IR spectra of the complexes in the region of the stretching vibration of the CO groups are characterised by one intense band.

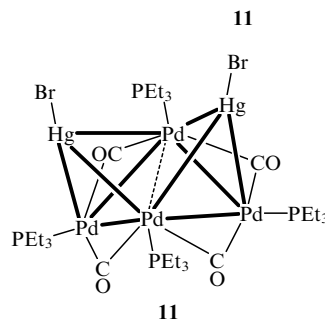
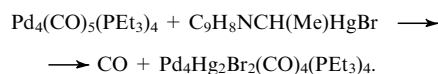


The $\text{Pd}_4(\text{CO})_5\text{L}_4$ clusters are not very stable in solution and are capable of adding additional ligands. Thus, slow crystallisation of $\text{Pd}_4(\text{CO})_5(\text{PBu}_3)_4$ under a CO atmosphere results in the addition of another CO molecule with formation of $\text{Pd}_4(\text{CO})_6(\text{PBu}_3)_4$ **10**.⁶⁰ According to X-ray diffraction data, the cluster has a tetrahedral metal core, to which bridging CO groups are coordinated along all the edges and each palladium atom is linked to one terminal phosphine ligand.



The interaction of the $\text{Pd}_4(\text{CO})_5\text{L}_4$ clusters with organomercury compounds takes place virtually without change in the metal core. Thus 8-(α -bromomercurioethyl) quinoline, both parts of the

molecule of which may assume the role of an additional ligand (substituted quinoline as a N,C-chelating ligand and mercury as a metalloligand) reacts with the $\text{Pd}_4(\text{CO})_5(\text{PEt}_3)_4$ cluster to form a heteronuclear compound.⁶¹

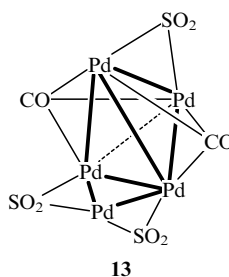


There is no information about the 'fate' of the quinoline component of the molecule. Formally, the two HgBr species generated as a result of the homolytic dissociation of the C–Hg bond, substitute one carbonyl group. However the coordination modes of CO and HgBr are different. According to X-ray diffraction data, the metal core is retained in cluster **11** in the form of an 'open' tetrahedron or a 'butterfly', to which external triangular faces the HgBr ligands are coordinated.

5. Pentanuclear palladium clusters

The pentanuclear carbonyl-containing platinum clusters are fairly numerous (see, for example, the review of Eremenko *et al.*⁵⁰). The methods of their synthesis include either the reductive carbonylation of platinum(+2) compounds or the interaction of platinum dicarbonyl with phosphines. Similar approaches have proved ineffective for the carbonyl-containing palladium clusters. Compounds of this group were obtained⁶² as a result of ligand substitutions in the presynthesised pentanuclear cluster $\text{Pd}_5(\mu\text{-SO}_2)_2(\mu_3\text{-SO}_2)(\text{PR}_3)_5$ **12**.⁶³

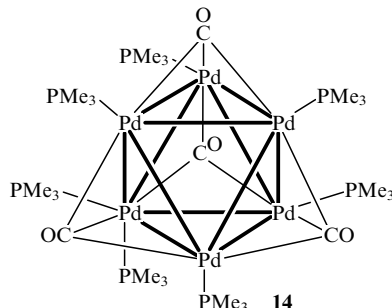
Thus, when CO was passed through a solution of compound **12** ($\text{R} = \text{Ph}$ or $\text{C}_6\text{H}_4\text{OMe-}p$) in dichloromethane, the corresponding complexes having the general formula $\text{Pd}_5(\text{SO}_2)_2(\text{CO})_2(\text{PR}_3)_5$ were obtained. They were characterised by ^{31}P NMR and mass spectrometry (fast atom bombardment method, FAB). If the initial complex contained another phosphine ligand, for example $\text{PR}_3 = \text{PMe}_2\text{Ph}$, the analogous reaction led to the complex $\text{Pd}_5(\text{SO}_2)_3(\text{CO})_2(\text{PMe}_2\text{Ph})_5$ **13**, characterised by X-ray diffraction data. The metal core of compound **13** consists of a tetrahedron, to one edge of which a fifth palladium atom ($\text{Pd}_{\text{bridge}}$) is μ -coordinated. The Pd–Pd distances are in the range from 2.73 to 2.97 Å.



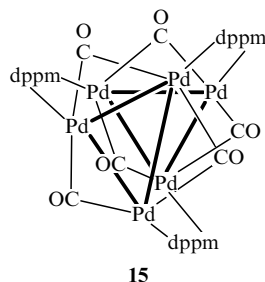
The bridging SO_2 groups are coordinated to two $\text{Pd}_{\text{bridge}}-\text{Pd}$ bonds and to the edge of the tetrahedron most remote from $\text{Pd}_{\text{bridge}}$. The carbonyl ligands are coordinated on the opposite faces of the tetrahedron and their coordination may be regarded as highly distorted μ_3 -coordination.

6. Hexanuclear palladium clusters

The first cluster containing six palladium atoms with the composition $\text{Pd}_6(\mu_3\text{-CO})_4(\text{PMe}_3)_7$ **14**, was obtained by the interaction of $\text{Pd}(\text{PMe}_3)_4$ and carbon monoxide ($P_{\text{CO}} = 1$ atm) at 323 K.⁶⁴ The cluster has a distorted octahedral metal core, on whose faces four carbonyl ligands are μ_3 -coordinated. The even phosphine ligands are linked to each of the palladium atoms.



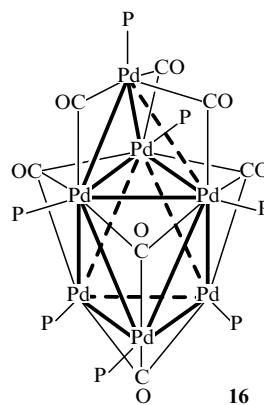
The reduction of potassium hexachloropalladate K_2PdCl_6 with sodium tetrahydroborate in the presence of dppm under a CO atmosphere in a toluene–ethanol mixture afforded the complexes $\text{Pd}_2(\mu\text{-CO})(\mu\text{-dppm})_2\text{Cl}_2$, $[\text{Pd}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3\text{Cl}] \cdot \text{Cl}$, $\text{Pd}_2(\mu\text{-dppm})_3$, and $\text{Pd}_6(\mu\text{-CO})_6(\mu\text{-dppm})_3$ **15**. The IR spectrum of the last compound contains bands characteristic of the stretching vibrations of the bridging CO groups ($\nu_{\text{CO}} = 1818\text{--}1884\text{ cm}^{-1}$).



According to X-ray diffraction data,⁶⁵ the palladium atoms in cluster **15** form two almost equilateral triangles in which the length of one side is 2.658–2.714 Å. The triangles are linked by three bridging diphosphine ligands. One carbonyl group is coordinated to each side of each triangle. The coordination of the diphosphine ligands is such that they form almost planar trimeric $\text{Pd}_3(\mu\text{-CO})_3\text{P}_3$ species, which are linked by the $-\text{CH}_2-$ bridges belonging to the dppm ligand. The Pd_3 triangles are almost parallel and have rotated relative to one another by 10° . Thus the metal core of the cluster can be regarded as a slightly distorted trigonal prism, the distances between the bases of which (along the Pd–Pd edges) are 3.030, 3.010, and 2.948 Å.

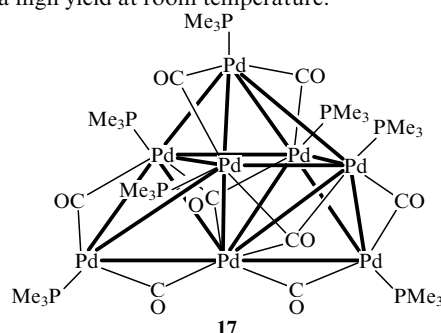
7. The heptanuclear $\text{Pd}_7(\mu_3\text{-CO})_4(\mu\text{-CO})_3(\text{PMe}_3)_7$ cluster

The heptanuclear $\text{Pd}_7(\mu_3\text{-CO})_4(\mu\text{-CO})_3(\text{PMe}_3)_7$ **16** cluster has been obtained by the reduction of the complex $\text{Pd}(\eta^1, \eta^3\text{-C}_8\text{H}_{12})(\text{PMe}_3)$ with carbon monoxide and is the only example of palladium clusters with the above degree of nuclearity.⁶⁶ The IR spectrum of the complex contains absorption bands in the region characteristic of the stretching vibrations of the bridging CO group ($1685\text{--}1825\text{ cm}^{-1}$). The structure of the cluster has been established by X-ray diffraction. The metal core consists of an octahedron with one ‘capping’ palladium atom. The additional palladium atom is located asymmetrically above the face of the octahedron: one of the interatomic ‘nonbonding’ $\text{Pd}_{\text{cap}}\text{--Pd}_{\text{octahedron}}$ (3.17 Å) is appreciably longer than the other two bonds (2.73 Å). The metal–metal bond lengths in the octahedron are 2.75–2.81 Å; these are typical values for distances over which direct metal–metal interaction usually takes place.



8. The octanuclear $\text{Pd}_8(\mu_3\text{-CO})_2(\mu\text{-CO})_6(\text{PMe}_3)_7$ cluster

The syntheses of phosphinepalladium(0) carbonyl are carried out under similar conditions. The formation of clusters with different nuclearities can be accounted for by the extreme sensitivity of the process leading to the formation of the cluster metal core to the nature of the reaction medium and the source of the palladium atoms. Thus, when a solution of $\text{Pd}(\text{DBA})_2$ (DBA = dibenzylideneacetone) was treated with carbon monoxide ($P_{\text{CO}} = 1$ atm) in dry CH_2Cl_2 containing PMe_3 , $\text{Pd}_8(\text{CO})_8(\text{PMe}_3)_7$ **17** was obtained in a high yield at room temperature.



The cluster was isolated in the form of dark reddish-black plates and was characterised by IR spectroscopy ($\nu_{\text{CO}} = 1763\text{--}1878\text{ cm}^{-1}$) and X-ray diffraction data.⁶⁷ According to the X-ray diffraction data, six of the eight palladium atoms in the cluster form a regular octahedron. The remaining two palladium atoms behave as ‘caps’ on two opposite faces of the octahedron and are linked to the same apical palladium atom not joined to the terminal phosphine ligand.

9. The decanuclear clusters $\text{Pd}_{10}(\text{CO})_{12}\text{L}_6$ and $\text{Pd}_{10}(\text{CO})_{14}\text{L}_4$

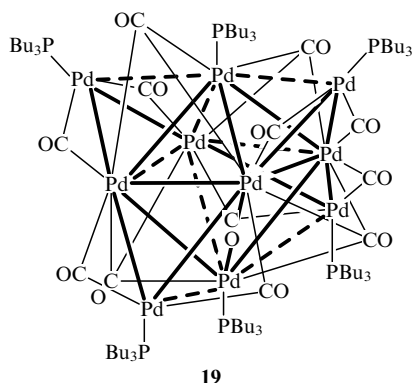
a. Clusters with aliphatic phosphines

The synthesis of palladium clusters with aliphatic phosphines has been studied in greatest detail. The compounds are formed on reduction of palladium acetate by carbon monoxide in the presence of CF_3COOH . In these syntheses, the acid generates the optimum equilibrium concentration of the free phosphine, the excess of which is bound in the phosphine salt $[\text{HPAlk}_3]^+[\text{CF}_3\text{COO}]^-$.^{60,68,69} Superstoichiometric amounts of PAlk_3 and the presence of a strong acid are necessary in the syntheses of the complexes $\text{Pd}_{10}(\text{CO})_{12}(\text{PEt}_3)_6$ **18**, $\text{Pd}_{10}(\text{CO})_{12}(\text{PBu}_3)_6$ **19**, and $\text{Pd}_{10}(\text{CO})_{14}(\text{PBu}_3)_4$ **20**. On the other hand, in weakly acid and neutral media, it is necessary to reduce the concentration of PAlk_3 to give stoichiometric ratios.⁶⁸ The compounds which could be isolated at a low PAlk_3 concentration in a neutral medium proved to be noncrystalline.

Clusters **18–20** were characterised by IR spectroscopic data (the bands in the range $1810\text{--}1920\text{ cm}^{-1}$ were assigned to the stretching vibrations of the bridging CO groups) and ^{31}P NMR

spectroscopic data.^{60,68–71} The ^{31}P NMR spectra of clusters **18** and **19** are characterised by two signals with an intensity ratio of 2:1 and $\delta = -11.0$ and -3.1 ppm for cluster **18** and $\delta = -4.0$ and $+3.3$ ppm for cluster **19**. The ^{31}P NMR spectrum of cluster **20** contains one singlet at $\delta = -5.0$ ppm.^{69,70}

The spectroscopic data are consistent with the structure of the clusters determined by X-ray diffraction analysis. Thus cluster **19** is an octahedron, over all the nonadjacent faces of which ‘capping’ palladium atoms are located.⁶⁹



The palladium atoms of the metalpolyhedron can be subdivided into equatorial, apical (in the octahedron), and ‘capping’. Since the $\text{Pd}_{\text{cap}}-\text{P}_{\text{eq}}$ distance (2.694–2.722 Å) is much shorter than the $\text{Pd}_{\text{cap}}-\text{Pd}_{\text{apic}}$ distance (3.301–3.421 Å), it would be more logical to regard the ‘capping’ atoms not as atoms μ_3 -linked to the Pd_3 face of the octahedron but as bridging atoms on the $\text{Pd}_{\text{eq}}-\text{Pd}_{\text{eq}}$ edges. The Pd–Pd distances in the inner octahedron are in the range from 2.791 to 2.851 Å. Eight $\mu\text{-CO}$ groups behave as bridges on the $\text{Pd}_{\text{cap}}-\text{Pd}_{\text{eq}}$ edges and four CO groups are μ -coordinated to the four free faces of the octahedron. The coordination of these CO groups is also asymmetric, but, in contrast to the ‘capping’ metal atoms, the carbon atoms of the $\mu_3\text{-CO}$ groups are displaced towards the apical palladium atoms. The six phosphorus atoms of the tributylphosphine ligands are bound to four capping and two apical palladium atoms.

Treatment of complex **18** with the isocyanide XylNC ($\text{Xyl} = \text{C}_6\text{H}_3\text{Me}_2\text{-2,6}$) leads to the displacement of some of the coordinated CO groups and the formation of the cluster $\text{Pd}_{10}(\mu\text{-CO})_6(\mu_3\text{CO})_2(\mu\text{-CNXyl})_2(\text{PET}_3)_6$ **21**. According to X-ray diffraction data⁷² cluster **21** retains the same metal core as cluster **18**.

b. Clusters with aromatic phosphines

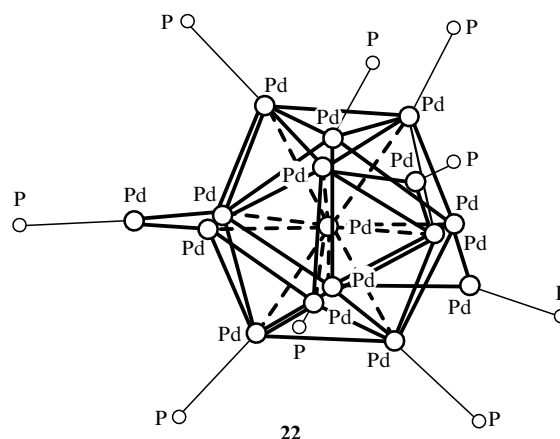
Aromatic phosphines [for example, PPh_3 , PMePh_2 , and P(OMe)Ph_2] are very weak bases and a very high content of hydrogen ions is required to regulate their concentration.

Attempts have been made^{69–71} to synthesise these compounds under neutral conditions with vigorous control of the concentration of the initial phosphine. The clusters $\text{Pd}_{10}(\text{CO})_{12}\text{L}_6$ [$\text{L} = \text{PPh}_3$, PMePh_2 , and P(OMe)Ph_2] were isolated in the solid state and identified by elemental analysis and IR spectroscopy.

10. The hexadecanuclear cluster $\text{Pd}_{16}(\text{CO})_{13}\text{L}_9$

The use of the traditional procedure — oxidation of CO by trimethylamine *N*-oxide⁷³ — made it possible to obtain⁷⁴ the 16-nuclear cluster $\text{Pd}_{16}(\text{CO})_{13}(\text{PET}_3)_6$ **22** by the reaction of $\text{Pd}_4(\text{CO})_5(\text{PET}_3)_4$ and $\text{Pd}_{10}(\text{CO})_{12}(\text{PET}_3)_6$. X-Ray diffraction study demonstrated the presence in this cluster of the centred icosahedron $\text{Pd}_{13}(\mu_3\text{-CO})_7(\text{PET}_3)_6$, overlaid by three bridging $\text{Pd}(\mu\text{-CO})_2\text{L}$ fragments. These fragments impart chirality to the centred icosahedral metal core of the cluster, reducing its idealised symmetry I_h to D_3 . The centrosymmetric racemic crystals of the clusters contain equal numbers of the optically active isomeric molecules.

Compound **22** is the first example of a polynuclear palladium complex with icosahedral packing of the metal atoms.



11. Tricosahedral clusters

The use of $\text{Pd}(\text{OAc})_2$ as a mild acceptor of phosphine ligands made it possible to convert decanuclear carbonyl–phosphine clusters into the compounds with a high nuclearity. Thus the interaction of $\text{Pd}_{10}(\text{CO})_{12}(\text{PET}_3)_6$ and $\text{Pd}(\text{OAc})_2$ (molar ratio 1:1) in benzene at 293 K for 24 h and subsequent addition of heptane afforded the cluster $\text{Pd}_{23}(\text{CO})_{22}(\text{PET}_3)_{10}$ **23**.⁷⁵ A slight change in the conditions of the synthesis (molar ratio $\text{Pd}:\text{Pd} = 1:1.5$; methanol–ether mixture, 303 K, 2.5 h) leads⁷⁶ to another 23-nuclear cluster having the composition $\text{Pd}_{23}(\text{CO})_{20}(\text{PET}_3)_8$ **24**. Both clusters have been characterised by X-ray diffraction data (Fig. 2a).

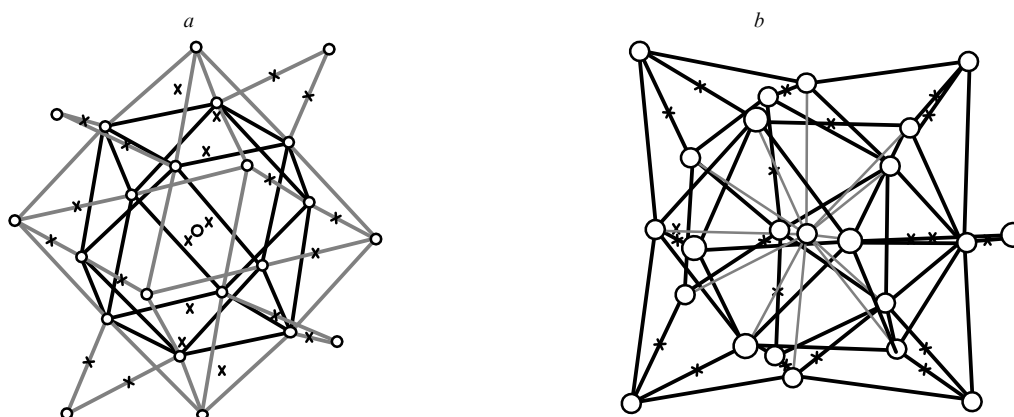


Figure 2. The structure of the metal cores of the $\text{Pd}_{23}(\text{CO})_{22}(\text{PET}_3)_{10}$ (a) and $\text{Pd}_{23}(\text{CO})_{20}(\text{PET}_3)_8$ (b) clusters according to X-ray diffraction data.^{75,76} The crosses designate the positions of the carbon atoms of carbonyl ligands.

The metal core of the centrosymmetric molecule of cluster **23** can be regarded as a cubooctahedron (designated by thickened lines in Fig. 2a) with one metal atom at the centre. This cubooctahedron has an idealised O_h symmetry. Six 'capping' palladium atoms are μ^4 -coordinated to each square face of the cubooctahedron while the remaining four metal atoms are symmetrically μ -coordinated to the four edges of the cubooctahedron. The metal–metal distances between the central and peripheral metal atoms (on average 2.847 Å) and between pairs of peripheral metal atoms (2.849 Å) in the cubooctahedron are virtually equal. All the other metal–metal distance in the metallopolyhedron are in the range from 2.720 to 2.920 Å.

Clusters **23** and **24** have a 22-atomic metallopolyhedron and one endopolyhedral metal atom. However, in contrast to complex **23**, containing a fragment with cubic close packing of metal atoms, the metallopolyhedron in complex **24** has a different structure. In the immediate environment of the endopolyhedral palladium atom, there are not 12, as in complex **23**, but 14 metal atoms; the average Pd–Pd distance (2.918 Å) exceeds by almost 0.17 Å the metal–metal distance in metallic palladium. The central palladium atom with metal atoms in its immediate vicinity is approximately regarded as a fragment with body-centred cubic packing (BCC), although the appreciable distortions of the idealised BCC packing observed in complex **24** are more likely to indicate that the polyhedron is not so regular in its shape. This polyhedron, made up of 15 metal atoms, is overlaid by eight 'caps' comprising palladium atoms, which are also coordinated to eight terminal phosphine ligands. The composition of the coordination sphere also includes three μ_3 -CO and seventeen μ -CO ligands.

12. The cluster $\text{Pd}_{34}(\text{CO})_{24}(\text{PET}_3)_{12}$

The 34-nuclear cluster $\text{Pd}_{34}(\mu\text{-CO})_{20}(\mu_3\text{-CO})_4(\text{PET}_3)_{12}$ **25** has been obtained as a by-product of the elimination of phosphine ligands from the decanuclear clusters $\text{Pd}_{10}(\text{CO})_{12}(\text{PET}_3)_6$ and $\text{Pd}_{10}(\text{CO})_{14}(\text{PET}_3)_4$, leading to the formation of a 38-nuclear cluster with 'irregular' packing of atoms in the quasi-spherical metal polyhedron (see below). According to X-ray diffraction data,⁷⁷ the metal polyhedron of the cluster contains four inner palladium atoms located at the apices of a distorted octahedron. Each of these atoms has a distorted icosahedral environment comprising 12 palladium atoms. This environment does not occur in the crystal lattice of the bulk metal but is encountered in the metal cores of cluster with finite dimensions. The observed metal–metal distances in the metal core of cluster **25** indicate unambiguously an icosahedral type of packing of the metal atoms (Fig. 3). Histograms of the metal–metal distances in large palladium clusters based on X-ray diffraction data have been compared with atomic radial distribution curves calculated from EXAFS data (Fig. 4).⁷⁸

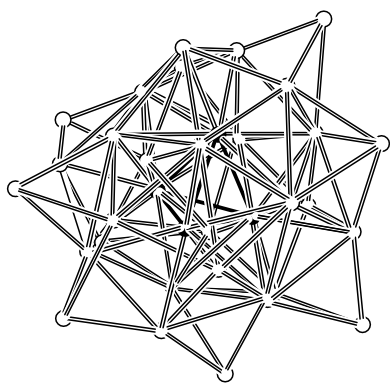


Figure 3. The structure of the metal core of the cluster $\text{Pd}_{34}(\mu\text{-CO})_{20}(\mu_3\text{-CO})_4(\text{PET}_3)_{12}$ according to X-ray diffraction data (the dark lines designate the inner metal tetrahedron).⁷⁷

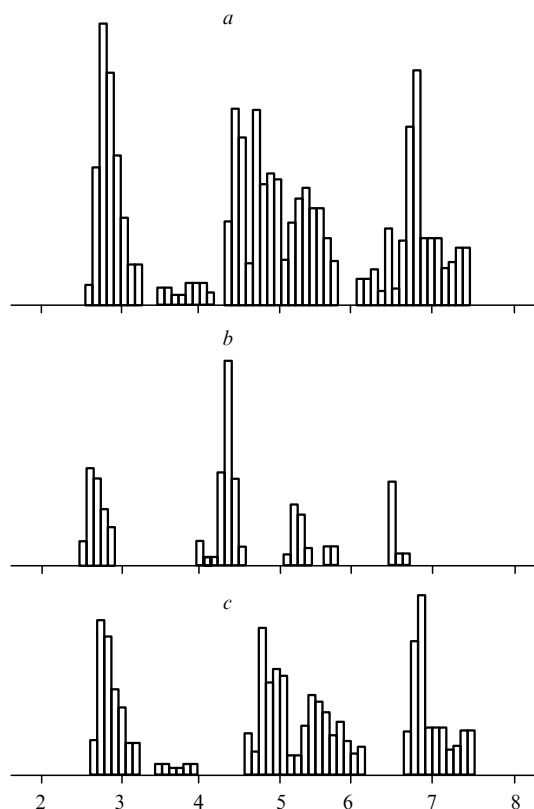


Figure 4. Histograms of the distribution of interatomic distances in the Pd_{34} metal core of the cluster $\text{Pd}_{34}(\mu\text{-CO})_{20}(\mu_3\text{-CO})_4(\text{PET}_3)_{12}$ with participation of only four intracluster atoms (a) with participation of all the remaining distances in the Pd_{30} metal 'shell' (b), and the theoretical distribution for the standard (idealised) icosahedral packing of the metal (c).

13. The cluster $\text{Pd}_{38}(\text{CO})_{28}(\text{PET})_{12} \cdot \text{Me}_2\text{CO}$

The cluster $\text{Pd}_{38}(\text{CO})_{28}(\text{PET})_{12} \cdot \text{Me}_2\text{CO}$ **26** was obtained, like the 23-nuclear clusters, by the reaction of the $\text{Pd}_{10}(\text{CO})_{12}(\text{PET}_3)_6$ with $\text{Pd}(\text{OAc})_2$ (molar ratio 1 : 2) in acetone in an argon atmosphere. The complex was isolated in the form of crystals sensitive to atmospheric oxygen and characterised by X-ray diffraction data (Fig. 5).⁷⁹

The cluster metal core has an incompletely regular structure with noncrystallographic symmetry close to D_2 . The flattened inner Pd_4 tetrahedron with two long (2.958 and 2.970 Å) and four short (2.539, 2.610, 2.603, and 2.514 Å) Pd–Pd bonds is surrounded by twenty metal atoms, located in four approximately parallel layers, and two metal atoms located outside these layers. All this corresponds to the 4 : 8 : 2 : 8 : 4 configuration. The 26-

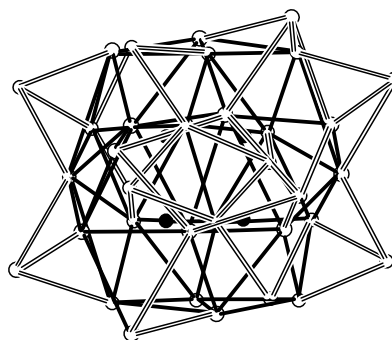


Figure 5. The structure of the metal core of the cluster $\text{Pd}_{38}(\text{CO})_{28}(\text{PET})_{12}$ (the filled circles identify the inner metal atoms).⁷⁹

nuclear metal core thus obtained is linked to twelve ‘capping’ palladium atoms, while each ‘capping’ metal atom is linked to the phosphorus atom of the terminal phosphine ligand. The average Pd–Pd distance for 118 metal–metal bonds is 2.775 Å. Among the 28 carbonyl groups, four are μ_3 -coordinated, whilst the others are μ -coordinated.

Analysis of the structures of the polynuclear phosphinepalladium(0) carbonyl complexes showed that the ‘tendency’ to form a spherical metallopolyhedron, leading to the minimisation of the surface of the molecule, is characteristic for these compounds, as in the case of the platinum and nickel clusters (Table 2). The structures of clusters **24–26** provide a good illustration of the characteristic feature of the structure of the entire class of large clusters: the possibility of the rearrangement of the metallopolyhedron following a change in the ligand environment and the ‘tendency’ to achieve close packing of the metal atoms.

In order to investigate the structure and nature of the chemical bonding in the palladium(0) carbonyl clusters, an attempt has been made⁸⁰ to apply an incorporation method as the basic procedure for the ‘construction’ of large clusters by the addition of ‘caps’ to the triangular and/or rectangular faces of the metallopolyhedron. The method is based on the graph theory. Thus the structures of clusters **16**, **17**, **19**, and **20** are produced by the addition of one, two, three, and four palladium ‘caps’ respectively to the central Pd₆ octahedron. However, for the description of the Pd₂₃ and Pd₃₈ clusters, this approach requires the introduction of additional concepts and appears somewhat artificial.

The results of the determination of the metal–metal bond length in a series of phosphinepalladium(0) carbonyl complexes from X-ray diffraction and EXAFS data agree well.⁷⁸ This gives rise to the hope for a wider application of the EXAFS method in the study of the structures of cluster compounds.

14. Infrared spectra of palladium(0) carbonyl complexes

Analysis of the IR spectra (Table 2) of structurally characterised carbonylphosphine clusters^{81,82} permitted the conclusion that the characteristic differences in the region of the stretching vibrations of the carbonyl group are observed only as the coordination mode of the carbonyl ligands is varied. Thus the vibrations of the terminal CO groups are manifested in the short-wavelength region (2000–2050 cm^{−1}), those of the μ -CO groups are in the middle region ($\sim$ 1850–1950 cm^{−1}), and those of the μ_3 -groups are shown in the longest-wavelength part of the spectrum. The regions corresponding to absorption by the last two types of CO ligands overlap appreciably. Complexes of different nuclearity, containing the same type of CO ligand, have no stable distinctive features in the IR spectra.

On the other hand, the presence at one metal atom of only one terminal group and three *n*-donor atoms {for example, in the complexes Pd(CO)(PPh₃)₃, Pd(CO)(NP₃) and Pd(CO)[MeC(CH₂PPh₂)₃], see Table 1} leads to a decrease in ν_{CO} to values characteristic of the stretching vibrations of the bridging CO groups, *i.e.* the region of the stretching vibrations of the bridging and terminal carbonyl groups overlap. It is noteworthy that in all other complexes where the number of *n*-donor atoms at each metal atom is smaller (for example, two or one phosphorus atoms), the stretching vibrational frequencies of the terminal CO group lie above 2000 cm^{−1}.

IV. Palladium(+1) carbonyl complexes

The coordination compounds in which palladium is present in the formal oxidation state +1 have been frequently postulated as active intermediates in palladium-catalysed reactions.^{84–86} This applies to a considerable extent to reactions occurring with participation of carbon monoxide. Palladium(+1) intermediate

Table 2. Characteristics of the polynuclear palladium(0) complexes containing carbonyl ligands.

Compound	Coordination of CO	$\nu_{\text{CO}}/\text{cm}^{-1}$	Metal core	Pd–Pd /Å	Ref.
Pd ₃ Sn ₂ (η^2 -acac) ₄ (CO) ₂ (PPh ₃) ₃	μ	1890–1770	equilateral Pd ₃ triangle	2.71–2.80	54, 55
Pd ₃ (CO) ₃ (PPh ₃) ₄	μ	1820–1880	the same	2.670, 2.741 2.777	57
Pd ₄ (μ -CO) ₅ (PPh ₂ Me) ₄	μ	1840, 1820	‘open’ Pd ₄ tetrahedron (‘butterfly’)	2.74–2.77 3.20	58
Pd ₄ (μ -CO) ₅ (PPh ₃) ₄	μ	1858	the same	2.74–2.78 3.19	59
Pd ₄ (μ -CO) ₆ (PBu ₃) ₄	μ		tetrahedron	2.77–2.79	60
Pd ₄ Hg ₂ Br ₂ (CO) ₄ (PEt ₃) ₄	μ	1897, 1855	‘open’ tetrahedron (‘butterfly’)	2.69–3.01 3.43	61
Pd ₅ (SO ₂) ₃ (CO) ₂ (PMe ₂ Ph) ₅	μ	1908	tetrahedron with one Pd bridge	2.73–2.97	62
Pd ₆ (μ_3 -CO) ₄ (PMe ₃) ₇	μ_3	1730, 1708	distorted octahedron	2.705–2.806	64
Pd ₆ (μ -CO) ₆ (μ -dppm) ₃	μ	1884, 1876, 1841, 1826, 1818	distorted trigonal prism	2.658–2.724	65
Pd ₇ (μ_3 -CO) ₄ (μ -CO) ₃ (PMe ₃) ₇	μ , μ_3	1825, 1800, 1785, 1770, 1750, 1685	octahedron with one Pd cap	2.75–2.81	66
Pd ₈ (CO) ₈ (PMe ₃) ₇	μ , μ_3	1878, 1843, 1810, 1803, 1775, 1763	octahedron with two Pd caps	2.73–2.87	67
Pd ₁₀ (CO) ₁₂ (PBu ₃) ₆	μ , μ_3	1920–1810	octahedron with four Pd caps	—	69
Pd ₁₆ (CO) ₁₃ (PEt ₃) ₉	μ , μ_3		centred icosahedron with three Pd caps	—	74
Pd ₂₃ (CO) ₂₂ (PEt ₃) ₁₀	μ , μ_3	1863, 1847, 1823	centred cubooctahedron with six μ_4 -coordinated and four μ -coordinated Pd caps	2.720–2.920	75
Pd ₂₃ (CO) ₂₀ (PEt ₃) ₈	μ , μ_3	1865, 1839, 1815	fragment of the BCC structure with eight Pd caps	2.819 ^a	76
Pd ₃₄ (μ -CO) ₂₀ (μ_3 -CO) ₄ (PEt ₃) ₁₂	μ , μ_3	1892, 1865, 1837, 1809	fragment of the icosahedral type of packing		77, 78
Pd ₃₈ (CO) ₂₈ (PEt ₃) ₁₂	μ , μ_3	1899, 1885, 1849, 1842, 1817, 1778	a not very regular structure with noncrystallographic symmetry	2.775 ^a	79, 83

^a Average distance.

complexes could arise either in the reduction of Pd(+2) by carbon monoxide or in the oxidation of Pd(0), for example, during oxidative addition in a medium containing CO as the stabilising ligand. These postulates constitute the basis of the syntheses of palladium(+1) carbonyl complexes, although other products of the oxidation–reduction reactions [except Pd(+1)] have by no means been characterised in any way and discussed in all cases.

The first among palladium(+1) carbonyl complexes was the carbonyl chloride Pd(CO)Cl obtained in 1926.⁸⁷ The structure of this complex and in the first place the coordination mode of the carbonyl group remained obscure for many years. It was not until more than half a century later that X-ray diffraction studies on the structures of palladium carbonyl complexes were published. [Pd(μ -dam)Cl]₂(μ -CO)^{9,10} and Pd₄(μ -CO)₄(μ -OAc)₄^{11,12} were investigated. X-Ray diffraction data with IR spectroscopic data provided answers to a number of questions concerning the structure of palladium carbonyl chloride, its analogues, and derivatives.

1. The syntheses and structures of palladium(+1) carbonyl complexes

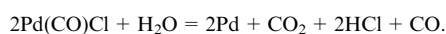
a. Palladium(+1) carbonyl halides and their anionic derivatives

The carbonyl chloride Pd(CO)Cl was first obtained by the reaction of solid PdCl₂ with carbon monoxide saturated with methanol vapour at 0 °C and atmospheric pressure.⁸⁷ A more convenient method of synthesis of the carbonyl halides involved the reaction of PdX₂ (X = Cl, Br) with CO at atmospheric pressure in a concentrated aqueous solution of the corresponding hydrogen halides. The formation of diamagnetic powdered Pd(CO)Cl and Pd(CO)Br deposits was observed when an aqueous solution of the corresponding palladium salt was treated with carbon monoxide or after treatment with formic acid.⁸⁸ Palladium carbonyl chloride has also been obtained by carbonylation of a suspension of PdCl₂ in the presence of acetyl chloride⁸⁹ or small amounts of H₂O^{90,91} and also by the reaction of PdCl₂ and allyl chloride with CO at both atmospheric and elevated pressures.^{91,92} The benzonitrile complex (PhCN)₂ · PdCl₂ — a convenient reagent which has proved very useful in the preparation of alkene palladium π -complexes⁹⁴ — has been employed as the starting material for the synthesis of Pd(CO)Cl.^{91,93}

The carbonyl chloride Pd(CO)Cl (ν_{CO} = 1975 cm⁻¹) has also been obtained⁹⁵ by treating the palladium(+2) carbonyl complex Pd₂(CO)₂Cl₄ with carbon monoxide (Ac₂O, 25 °C, 24 h, P_{CO} = 1 atm).

In contrast to the binary palladium(0) carbonyl compounds, which are not formed from metallic palladium at temperatures above 323 °C, the palladium(+1) carbonyl chloride can be produced from powdered palladium at a CO pressure of 170 atm and 190 °C in a phosgene-containing solution in *o*-dichlorobenzene.⁹¹ The palladium(+1) carbonyl fluoride or carbonyl iodide could not be obtained by any of the methods indicated above.

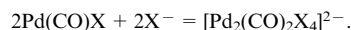
The elemental composition of palladium(+1) carbonyl chloride specimens obtained by different methods^{88–93} as a rule corresponds to the formula Pd(CO)Cl: the IR spectra of three specimens agree satisfactorily. A powdered amorphous or very fine-crystalline substance, which does not dissolve in organic solvents and is thermally stable up to 60 °C but readily decomposes on treatment with water or even atmospheric moisture, was obtained in all cases.



The reaction is strongly inhibited by H⁺ or Cl⁻ ions, as a result of which the carbonyl chloride dissolves almost without decomposition and is stable in concentrated hydrochloric acid. The properties of the thermally more stable (T_{decomp} = 120 °C) carbonyl bromide Pd(CO)Br are similar. This too is stable in concentrated aqueous HBr solution.⁸⁸ Both palladium(+1) carbonyl halides are relatively stable in air in the absence of H₂O.

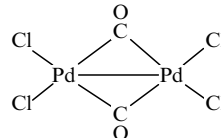
Thermolysis of the carbonyl halides leads to the elimination of CO and the formation of palladium metal. Probably as a result of slight decomposition the colour of the Pd(CO)X specimens obtained by different workers varies from yellow-green to dark-violet. The stretching vibrational frequency of the CO groups in these compounds varies in the range from 1850 to 2000 cm⁻¹.^{96,97}

It was postulated in early investigations that the compounds Pd(CO)X are polymers with halide⁸⁸ or carbonyl⁹⁸ bridges. On dissolution in the corresponding hydrogen halide solution, depolymerisation takes place with formation of mono- or di-nuclear anions, for example:



The crystalline substance with the composition (NH₄)₂[Cl₂Pd(CO)]₂ has been isolated from a solution of (NH₄)₂PdCl₄ in concentrated HCl, treated with carbon monoxide for several days, while in the presence of enH₂²⁺ and [Pt(NH₃)₄]²⁺ cations the crystalline salts of the latter with the [Pd₂(CO)₂Cl₄]²⁻ anion were obtained. It was assumed that the anion contains Pd(+3) atoms linked by bridging CO groups to form a dimer.⁹⁹ Without going into the question of the electronic structure of the anion, we may note that, since the CO group is electrically neutral, the formal oxidation state of palladium is in this instance +1. One cannot rule out the possibility that a metal–metal bond is present in the dimeric anion. The diamagnetism of the cesium rubidium, and tetraalkylammonium salts of the anions [Pd₂(CO)₂Cl₄]²⁻ and [Pd₂(CO)₂Br₄]²⁻ obtained by a similar method^{88,98} agrees with this hypothesis. Treatment of the complex Pd(CO)Cl with an equimolar amount of NH₂Et₂Cl afforded the anionic complex [NH₂Et₂]₂[Pd₂(CO)₂Cl₄], characterised by elemental analysis and IR spectroscopy (ν_{CO} = 1916 cm⁻¹).⁹⁵

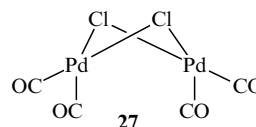
The structure of the anionic carbonyl halide complex [Bu₄N]₂[Pd₂(CO)₂Cl₄], synthesised by Goggin and Mink,⁹⁸ has been investigated by X-ray diffraction.¹⁰⁰ The 1966 and 1906 cm⁻¹ frequencies correspond to the stretching vibrations of the CO groups in the complex in solution in CH₂Cl₂. The palladium atoms in the anion of the complex are linked by two carbonyl bridges, each metal atom being bound to two terminal chloride ligands.



The metal–metal distance (2.697 Å) indicates the presence of the Pd–Pd single bond. Each palladium atom has a highly distorted tetrahedral environment, the PdCl₂ plane making a dihedral angle of 8–10° with the Pd₂(μ -C)₂ plane.

The planar configuration of the Pd₂(μ -C)₂ species agrees well with the IR spectrum of the solid complexes (the spectrum contains only the ν_{CO} = 1903 cm⁻¹ band due to the asymmetric vibrations). The presence in the spectrum of the solution in CH₂Cl₂ of a band at 1966 cm⁻¹ assigned to the symmetrical vibrations of the CO group, indicates the distortion of the planar configuration of the Pd₂(μ -C)₂ species in solution.

Thus the carbonyl ligand in virtually all the reliably characterised neutral and anionic palladium(+1) carbonyl halide complexes is a bridge between two metal atoms. The only exception is the complex [Pd(CO)₂(μ -Cl)]₂ **27** obtained when CO is passed (6 h, 60 °C) through a reaction mixture containing PdCl₂ and NaHCO₃ in anhydrous methanol in the presence of 2-(1,5-dimethylhex-4-enyl)-3-hydroxy-5-methyl-1,4-benzoquinone.¹⁰¹



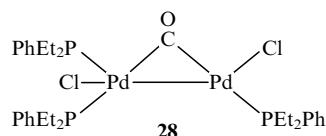
Complex **27** has been isolated from *n*-hexane in the form of crystals stable in air. Unfortunately, the very brief relevant publication¹⁰¹ contains no comments whatsoever concerning the fairly unexpected choice of reagents and the role of sodium bicarbonate or the substituted benzoquinone. The IR spectrum of the complex contains bands characteristic of terminal CO groups (2103, 2082, 2024, and 1997 cm⁻¹). According to X-ray diffraction data, the two palladium atoms of the complex, at a distance of 3.114 Å, are joined by two chloride bridges *cis*-posed relative to the Pd...Pd axis (the dihedral angle of the Pd...Cl triangle is 124°). Each metal atom is also joined to two terminal CO groups, which builds up their environment to a distorted planar square.

b. Palladium (+1) carbonyl halides containing *n*-donor stabilising ligands

Neutral molecules containing an element E (E = N, P, As, Sb), which is capable of donating an unshared electron pair, are usually employed as additional stabilising ligands. In the chemistry of carbonyl-containing palladium(+1) compounds, nitrogen-containing ligands are relatively rare, whilst phosphorus-containing ones (mono- and di-phosphines) are very common.

The complexes [(PdXL)₂CO]_n, where X = Cl, Br, or I and L = PPh₃, PPh(*p*-MeOC₆H₄)₂, PPh₂(C₆H₄COOH), PPh₂(C₆H₄F), PPh₂(C₆H₄Cl) or PPh₂(C₆H₄Me), have been obtained by the reactions of the corresponding phosphine with a solution of H₂Pd₂(CO)₂Cl₄ in concentrated HCl.¹⁰² The IR spectra of the solid complexes contain two bands in the range 1860–1962 cm⁻¹, which have been assigned to the stretching vibrations of the bridging CO groups. On the other hand, if a solution of H₂Pd₂(CO)₂Cl₄ in concentrated HCl is acted upon initially by a solution of SnCl₂ and then triphenylphosphine in concentrated HCl, all the acido-ligands are displaced from the initial carbonyl chloride and [Pd₂(PPh₃)₂(SnCl₃)₂]CO (*ν*_{CO} = 1800–2000 cm⁻¹) is formed.¹⁰³ The complexes [(PdXL)₂CO]_n, containing stabilising ligands of the type of arsine (L = AsPh₃) or stibine (L = SbPh₃) have been obtained on partial substitution of carbonyl and acido-ligands in palladium(+1) carbonyl halides and carbonyl acetate complexes by organoelement ligands.¹⁰⁴ The complexes have been characterised by elemental analysis, ESCA, and IR spectroscopy. Judging from the *ν* = 1710–1890 cm⁻¹ region, the carbonyl group in these compounds is involved in bridging coordination.

The dinuclear complex Pd₂(CO)Cl₂L₃ (L = PEt₂Ph) **28** has been obtained⁵⁹ in a fairly high yield (49%) yield by the reaction of CO with Pd(NO₂)₂L₂ in dichloromethane (293 K, *P*_{CO} = 1 atm, 48 h) and subsequent precipitation of the compound formed on treatment with CO-saturated hexane at 273 K. In the formation of compound **28**, the source of chloride ligands could be dichloromethane itself, although the authors did not rule out also the possibility of the interaction of the initial Pd(NO₂)₂L₂ and HCl or Cl₂, present in the solvent, with formation of PdCl(NO₂)L₂. In order to confirm this hypothesis, *trans*-PdCl(NO₂)L₂ was obtained. Its treatment with CO also affords the dimer **28**.



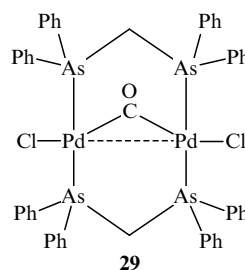
According to X-ray diffraction data, the two palladium atoms in the molecule of compound **28** (the Pd–Pd distance is 2.652 Å) are linked asymmetrically by the coordinated semibridging carbonyl ligand (the Pd–C distances are 1.874 and 2.110 Å, while the Pd–C–Pd angle is 83.3°).¹⁰⁵ They have nonequivalent environments. The palladium atom involved in the shorter bond with the carbonyl group is also linked to the second metal atom, one chloride ligand, and one phosphine ligand. It has a highly distorted 4-coordinated environment. There are five atoms in the

environment of the second palladium atom: one Cl atom, two phosphorus atoms of the phosphine ligands, palladium, and a somewhat remote carbon atom of the carbonyl ligand.

Unfortunately the authors do not quote spectroscopic data for complex **28**.

Complexes containing the Pd₂(μ-Q)₂ moiety, where Q = diphosphine or diarsine ligands having the composition R₂E(CH₂)_nER₂ (E = P or As, *n* = 1–3), constitute a special group. As a rule, such complexes are formed by the insertion of CO in the metal–metal bond in the dinuclear palladium(+1) complexes Pd₂(μ-Q)₂X₂ (X = Cl, Br, I), which are formed in their turn in the reaction of the polymeric [Pd(CO)X]_n (or its anionic derivatives) with the bidentate ligand Q. In the interaction of [Pd(CO)X]_n and dppm, the coordinated CO group is fully displaced with formation of the complexes [Pd(dppm)X]₂.⁸⁸ In the case of dam, the reaction product depends on the nature of the halogen: if X is chlorine or bromine, [Pd(μ-dam)X]₂(μ-CO) **29** is formed, whereas in the case where it is iodine the product is [Pd(μ-dam)I]₂.^{9, 10, 105}

In complex **29** (X = Cl) palladium atoms are bound to two dam molecules and the carbonyl bridge.



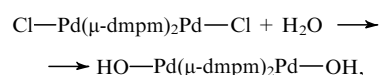
The Pd–Pd distance (3.274 Å) exceeds twice the covalent radius. Nevertheless, the compound is diamagnetic, so that the spins are apparently paired via the carbonyl bridge, which in this case is fairly unusual: the Pd–C–Pd angle is 119° and not 85–89° as in the majority of transition metal carbonyl complexes.

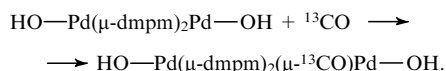
When [Pd(μ-dppm)X]₂ (X = Cl, Br) is treated with CO in dichloromethane, [Pd(μ-dppm)X]₂(μ-CO) (*ν*_{CO} = 1704 cm⁻¹) is formed;¹⁰⁶ it liberates CO reversibly on heating in solution in dichloromethane. The complex Pd₂(μ-CO)(μ-dppm)₂Cl₂ has been obtained as a result of the addition of oxalyl chloride ClC(=O)C(=O)Cl to Pd₂(dppm)₃ in dichloromethane.¹⁰⁷

The kinetics of the reversible insertion of carbon monoxide in the Pd–Pd bond of the complex Pd₂(dppm)₂X₂ with formation of Pd₂(μ-CO)(μ-dppm)₂X₂ have been investigated spectrophoto-metrically.¹⁰⁸ It was established that the reaction obeys a first-order equation with respect to both the metal and carbon monoxide.

The reaction of the polymer [Pd(CO)Cl]_n with dmpm (dmpm = bis(dimethylphosphino)methane) in dichloromethane at 198 K leads to the formation of Pd₂Cl₂(dmpm)₂ **30**. Treatment of compound **30** with carbon monoxide results in the formation of [PdCl(μ-dmpm)]₂(μ-CO) **31** with a bridging carbonyl ligand (*ν*_{CO} = 1710 cm⁻¹). According to X-ray diffraction data, the distance between the metal atoms in the molecule of compound **31** (the Pd–Pd distance is 3.169 Å) exceeds the sum of the covalent radii of palladium and the environment of each metal atom consists of an almost planar square.^{109, 110}

In contrast to analogues containing dppm, an unusually high solubility and stability in aqueous solution were characteristic of complex **31**. On the basis of IR, Raman, and NMR spectroscopy involving different nuclei and electrical conductivity data, it has been shown that the following reactions take place readily in water:



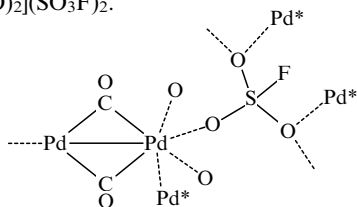


The interaction of $[\text{Pd}(\mu\text{-dppm})\text{X}]_2$ and SnCl_2 followed by treatment of the resulting solution with carbon monoxide afforded ¹¹¹ *in situ* the complex $\text{Pd}_2(\mu\text{-dppm})_2\text{Cl}(\text{SnCl}_3)(\mu\text{-CO})$ ($\nu_{\text{CO}} = 1688 \text{ cm}^{-1}$).

The principal characteristic feature of the reaction involving the insertion of small molecules in the Pd–Pd bond is the increase in the metal–metal distance on the formation of bridges. Despite the fact that the palladium–palladium distance increases to a value greatly exceeding the sum of the covalent radii, the compounds containing palladium in the formal +1 oxidation state remain diamagnetic. The probable causes of the diamagnetism of these compounds will be discussed below.

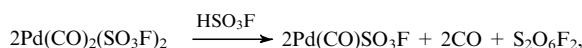
c. The binary palladium(+1) carbonyl

The only compound in which the Pd(+1) atom is linked to carbonyl groups only is the cationic complex $[\text{Pd}_2(\mu\text{-CO})_2](\text{SO}_3\text{F})_2$.

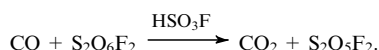


The reductive decomposition of the divalent palladium carbonyl $\text{Pd}(\text{CO})_2(\text{SO}_3\text{F})_2$ in solution in fluorosulfonic acid HSO_3F at 298 K leads to the formation (according to IR spectroscopic data) of a mixture of complexes containing both bridging and terminal CO groups.¹¹² Slow crystallisation (for about three weeks) of the mixture from fluorosulfonic acid leads to the precipitation of needle-like crystals.

It has been suggested that the reduction of Pd(+2) to Pd(+1) includes the elimination of the $\text{SO}_3\text{F}^\cdot$ radicals and their dimerisation to $\text{S}_2\text{O}_6\text{F}_2$ with simultaneous liberation of one mole of CO in accordance with the equation



which is probably followed by the oxidation of CO to CO_2 :



The formation of $\text{S}_2\text{O}_5\text{F}_2$ in the reaction mixture has been confirmed by ^{19}F NMR (signal at $\delta = 47.5 \text{ ppm}$).

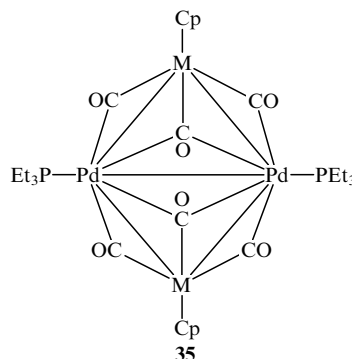
The complex $[\text{Pd}_2(\mu\text{-CO})_2](\text{SO}_3\text{F})_2$ has been characterised by elemental analysis IR spectroscopy ($\nu_{\text{CO}} = 1977 \text{ cm}^{-1}$), and X-ray diffraction data. Its molecular structure consists of cyclic, almost planar four-membered $\text{Pd}_2(\mu\text{-CO})_2$ species, in which the palladium atoms are linked together as a result of direct metal–metal interaction (the Pd–Pd distance is $2.698 \text{ \AA}$) and by two symmetrical carbonyl bridges. The individual metalocycles are joined by symmetrical bridging bidentate fluorosulfate groups, forming a planar polymer chain. Thus the coordination sphere of each palladium atom incorporates the two carbon atoms of two *cis*-disposed carbonyl groups, two oxygen atoms of two fluorosulfate groups, and a neighbouring palladium atom. If the metal–metal bonding is ignored, the geometrical environment of each palladium atom can be regarded as a slightly distorted square.

d. Other palladium(+1) complexes containing carbonyl and organic ligands

The interaction of the complex $\text{Pd}_2(\mu\text{-Cp})(\mu\text{-Br})(\text{PR}_3)_2$ and CO in toluene leads to the displacement of the bromide and cyclopentadienyl bridges to axial positions and to the formation of

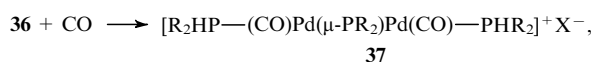
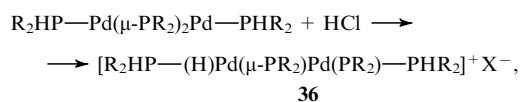
$\text{Pd}_2(\mu\text{-CO})(\eta^5\text{-Cp})(\text{Br})(\text{PR}_3)_2$ **32** [$\text{R} = \text{Et}$ (**32a**), $\text{R} = \text{Pr}^i$ (**32b**)].¹¹³ The analogous initial compound containing an acetate instead of a bromide bridge reacts with CO also with formation of complex **32**.¹¹⁴ Complexes **32a,b** have been characterised by IR spectroscopy ($\nu_{\text{CO}} = 1804$ and 1828 cm^{-1} respectively) and NMR spectroscopy on different nuclei. The structure of complex **32b** has been investigated by X-ray diffraction. The metal atoms in the molecule of the complex are linked both to one another (direct metal–metal interaction, the Pd–Pd distance is $2.67 \text{ \AA}$) and with the bridging carbonyl. The phosphine ligands are *trans*-located relative to the metal–metal axis. It has been shown that the carbonyl bridge in complex **32** is readily substituted by other small molecules, for example SO_2 or CH_3NC . The dinuclear complexes $(\text{PR}_3)_2\text{Pd}_2(\mu\text{-Cp})(\mu\text{-X})$ ($\text{X} = \text{Cl}$ or CH_3COO) readily react with $\text{NaCpM}(\text{CO})_3$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) or $\text{NaCo}(\text{CO})_4$. Such interaction affords the heteronuclear clusters $(\text{PR}_3)_2\text{Pd}_2(\mu\text{-Cp})[\mu\text{-M}(\text{CO})_3\text{Cp}]$ **33** and $(\text{PR}_3)_2\text{Pd}_2(\mu\text{-Cp})[\mu\text{-Co}(\text{CO})_4]$ **34** respectively.¹¹⁵ These complexes have been characterised by spectroscopic methods. It has been established that the cyclopentadienyl and carbonylmetallate ligands function as bridges between the two palladium atoms, while the phosphines occupy the axial position. The attempt to substitute the cyclopentadienyl ligand in complexes **33** and **34** by a second carbonylmetallate in order to obtain tetranuclear clusters was unsuccessful, but such clusters have been obtained by another method.

The interaction of *trans*- $\text{Pd}(\text{PEt}_3)_2\text{Cl}_2$ and $[\eta^5\text{-CpM}(\text{CO})_3]^-$ results in the formation^{116,117} of the tetranuclear clusters $\text{Pd}_2\text{M}_2(\eta^5\text{-Cp})_2(\mu_3\text{-CO})_2(\mu\text{-CO})_4(\text{PEt}_3)_2$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) **35**. All three complexes have been characterised by X-ray diffraction data. The metal atoms in complex **35** ($\text{M} = \text{Mo}$) are in the same plane and form a rhombus with a short Pd–Pd diagonal. One $\mu_3\text{-CO}$ group is linked to each Pd_2Mo triangle ($\nu_{\text{CO}} = 1772 \text{ cm}^{-1}$), while a $\mu\text{-CO}$ group is linked to each Pd–Mo edge ($\nu_{\text{CO}} = 1842$ and 1801 cm^{-1}).



A similar cluster with another phosphine ligand, $\text{Pd}_2\text{Mo}_2(\eta^5\text{-Cp})_2(\mu_3\text{-CO})_2(\mu\text{-CO})_4(\text{PBzPh}_2)_2$ (the Pd–Pd and Pd–Mo distances are 2.58 and 2.86, 2.82 $\text{ \AA}$ respectively), has been synthesised.¹¹⁸

Palladium(+1) complexes with terminal carbonyl groups have been obtained¹¹⁹ in a study of the reactions of a dimeric univalent palladium complex with phosphide bridges as a result of the following transformations in solution in dimethoxyethane:



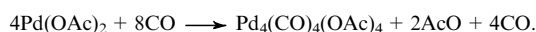
where $\text{X}^- = \text{CF}_3\text{SO}_3^-$ or BF_4^- . Complexes **36** and **37** have been characterised by NMR and IR spectroscopy ($\nu_{\text{CO}} = 2080$, 2055, and 2045 cm^{-1} for complex **37**) and also by X-ray diffraction data (the Pd–Pd distances are 2.611 and 2.682 $\text{ \AA}$ for complexes **36** and **37** respectively). The NMR spectra have shown that complex **37** exists in the form of a mixture of isomers differing in the relative

disposition of the carbonyl and phosphine ligands. Complex **37** is stable only under a carbon monoxide atmosphere; it is readily decarbonylated *in vacuo*, on passing nitrogen, on heating, or on UV-irradiation.

e. Palladium(+1) carbonyl carboxylates

All the carbonyl-containing univalent palladium complexes presented above are as a rule dimers or linear polymers. The tetranuclear carbonyl carboxylates having a planar cyclic metal core are an exception. The structure and chemical properties of compounds of this group have been thoroughly investigated.

The complexes containing simultaneously both carbonyl and carboxylate ligands are usually obtained by reduction of palladium(+2) carboxylates with carbon monoxide in a carboxylic acids or in an inert solvent containing the corresponding carboxylic acid. The second method of synthesis involved the substitution of ligands in the presynthesised palladium(+1) carbonyl carboxylates. The cluster $\text{Pd}_4(\mu\text{-CO})_4(\mu\text{-OAc})_4$ **38** was obtained^{11,12} by the first methods, *i.e.* by carbonylating ($P_{\text{CO}} = 1$ atm) palladium acetate in glacial acetic acid at 323 K.



The cluster crystallises with two molecules of acetic acid to give $\text{Pd}_4(\mu\text{-CO})_4(\mu\text{-OAc})_4 \cdot 2\text{AcOH}$ **38a**, while on drying *in vacuo* over KOH it loses an acetic acid molecule and is converted into $\text{Pd}_4(\text{CO})_4(\text{OAc})_4$ **38b**. The IR spectra of the complexes each contain intense bands corresponding to the stretching vibrations of the CO groups (1934 and 1975 cm^{-1} for **38a** and 1940 and 1975 cm^{-1} for **38b**) and bands due to the stretching vibrations of acetate groups coordinated as bidentate species. According to X-ray diffraction data, the cluster as an almost rectangular metal core with angles of 83.4° and 96.6° . The sides of the rectangle, linked by acetate bridges are longer ($2.909\text{ \AA}$), while the sides linked by carbonyl bridges are shorter ($2.663\text{ \AA}$) than the metal—metal distance in metallic palladium ($2.751\text{ \AA}$) (Fig. 6).¹²⁰

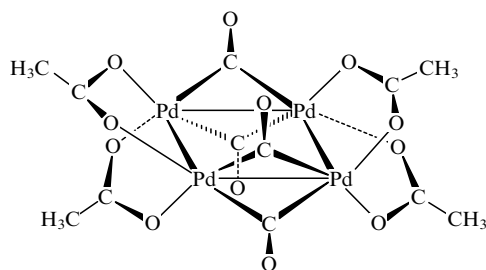
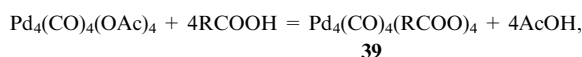


Figure 6. The structure of the cluster $\text{Pd}_4(\mu\text{-CO})_4(\mu\text{-OAc})_4$ according to X-ray diffraction data.¹²²

The mechanism of the formation of cluster **38** has been investigated by spectroscopic and kinetic methods. The data obtained led to the conclusion that the formation of complex **38** involves the transfer of an oxygen atom from the carboxylate group to the coordinated carbonyl group. This results in the formation of the coordinated acyl $[\text{CH}_3\text{CO}]$ and in the elimination of carbon dioxide.^{121–123}

It has been established that the coordinated acetate groups in complex **38** are substituted by other carboxylates in the reactions with the corresponding acids, for example:



$\text{R} = \text{CD}_3, \text{C}_2\text{H}_5, \text{C}_6\text{H}_5, \text{CF}_3, \text{CCl}_3, \text{CH}_2\text{Cl}.$

According to IR spectroscopic data, all the complexes contain bridging carbonyl and carboxylate groups. Comparative analysis of X-ray diffraction data for palladium carbonyl acetate and of

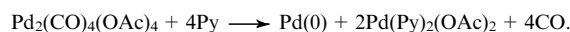
EXAFS data for all carbonyl carboxylate complexes permitted the conclusion that they all have a similar structure — a planar metal core (rectangle, square, or rhombus) to the sides of which bridging carboxylate and carbonyl ligands are coordinated.¹²⁴

Together with the existence of isomers having different metal cores, there is also a possibility of the existence of isomers with different relative dispositions of ligands: disposition of ligands in pairs (for example as in complex **38** characterised by X-ray diffraction analysis) and uniform distribution of similar ligands. The influence of substituents in carboxylated groups on the isomerism of the metal core of the carbonyl carboxylates has been examined in detail.^{125,126}

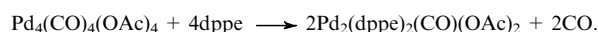
f. Derivatives of palladium(+1) carbonyl carboxylates with N- and P-donor ligands

The interaction of complex **38** with ligands such as Py, dppe, PPh_3 , Bipy, and Phen leads to a series of complexes, the composition of which depends on the initial Pd/ligand(L) ratio. The palladium complexes formed with the Pd/L = 2 ratio are unstable. With decrease in the ratio, more stable compounds appear.

The interaction of complex **38** with Py and its alkyl derivatives (with the ratio Pd/Py = 1) entails the disproportionation of Pd(+1) to Pd(0) and Pd(+2):



The interaction of complex **38** and dppe (Pd/dppe = 1) in benzene affords the complex $\text{Pd}_2(\text{dppe})_2(\text{CO})(\text{OAc})_2$.^{127,128}



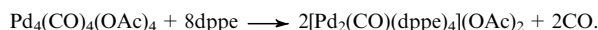
40

According to IR spectroscopic data, the group CO in complex **40** is of the bridging type ($\nu_{\text{CO}} = 1790\text{ cm}^{-1}$). The fairly low stretching vibrational frequency in the compound where the metal atoms are linked also by a further two diphosphine bridges indicates an increase in the Pd–Pd distances compared with the analogous distances in complex **38**. Analysis of the stretching vibrational frequencies of the acetate group in the IR spectrum of complex **40** [$\nu_{\text{as}}(\text{COO}) = 1580\text{ cm}^{-1}$, $\nu_{\text{s}}(\text{COO}) = 1380\text{ cm}^{-1}$, $\Delta\nu = 200\text{ cm}^{-1}$] permits the conclusion that monodentate coordination of the acetate groups takes place. Apparently the structure of complex **40** is analogous to that of palladium(+1) carbonyl halide complexes with diphosphine and diarsine groups.^{9,10} The coordination sphere of each metal atom consists of two phosphorus atoms of the two diphosphine ligands, the carbon atom of the carbonyl group, and the oxygen atom of the terminal acetate group.

The analogous complex $[\text{Pd}(\text{dppm})(\text{O}_2\text{CCF}_3)]_2(\mu\text{-CO})$ has been isolated in the course of the study of the kinetics of the interaction of the dimer $[\text{Pd}(\text{dppm})(\text{O}_2\text{CCF}_3)]_2$ and carbon monoxide in dichloromethane.¹²⁹ The complex has been characterised by IR spectroscopy ($\nu_{\text{CO}} = 1720\text{ cm}^{-1}$) and NMR spectroscopy involving different nuclei and also by X-ray diffraction analysis.

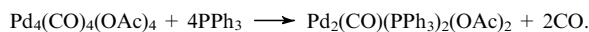
The two palladium atoms in the molecule of the complex, linked by a bridging CO group, are at a distance of $2.896\text{ \AA}$. This is less than the sum of the covalent radii of palladium ($2.98\text{ \AA}$) and is appreciably shorter than the Pd–Pd distance ($\sim 2.7\text{ \AA}$) characteristic of the Pd(+1) dimers. Each palladium atom in the molecule is surrounded by the same set of atoms: the carbon atom of the carbonyl group, two phosphorus atoms of the two diphosphine ligands, and one oxygen atom of the terminal carboxylate ligand. If the Pd–Pd bond is excluded from consideration, then environment of each palladium atom consists of an almost planar square (the deviation from the plane of the square is not more than $0.02\text{ \AA}$), whereas the environment of the second metal atom is close to being tetrahedral. The authors believed that in this case the distortion of the symmetrical structure may be caused by a redistribution of electron density in the complex and that the latter can be regarded as an intermediate in the dissociation of the trifluoroacetate complex leading to $[\text{Pd}_2(\mu\text{-dppm})_2(\mu\text{-CO})(\text{O}_2\text{CCF}_3)]^+(\text{CF}_3\text{CO}_2)^-$.

The interaction of complex **38** and dppe, taken in ninefold excess in tetrahydrofuran, leads to the formation of a cationic complex in accordance with the equation



According to ^{31}P NMR data the diphosphine ligands in the complex are involved in both bridging and terminal coordination, whereas the carbonyl group serves as a bridge between the two metal atoms.

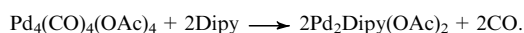
Treatment of complex **38** with PPh_3 leads to the complex $\text{Pd}_2(\text{CO})(\text{PPh}_3)(\text{OAc})_2$:



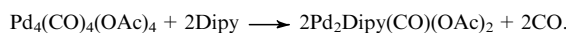
41

Complex **41** contains a bridging CO group ($\nu_{\text{CO}} = 1800 \text{ cm}^{-1}$). Depending on the conditions in the synthesis, compounds differing in the coordination of the acetate groups are formed. Thus, when the process is carried out in tetrahydrofuran a complex with acetate bridges is produced [$\nu_{\text{as}}(\text{COO}) = 1530 \text{ cm}^{-1}$, $\nu_{\text{s}}(\text{COO}) = 1400 \text{ cm}^{-1}$, $\Delta\nu = 130 \text{ cm}^{-1}$], whereas the reaction of complex **38** with PPh_3 in benzene leads to a compound with terminal OAc groups [$\nu_{\text{as}}(\text{COO}) = 1610 \text{ cm}^{-1}$, $\nu_{\text{s}}(\text{COO}) = 1350 \text{ cm}^{-1}$, $\Delta\nu = 260 \text{ cm}^{-1}$].

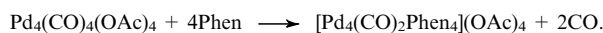
In the interaction of complex **38** and Bipy at an initial Bipy concentration $> 0.5 \text{ M}$ and a concentration of complex **38** of $5 \times 10^{-3} \text{ M}$ all the CO molecules are displaced:^{49, 50}



At low Bipy concentrations ($< 5 \times 10^{-3} \text{ M}$), only half of the CO's are displaced from complex **38**:

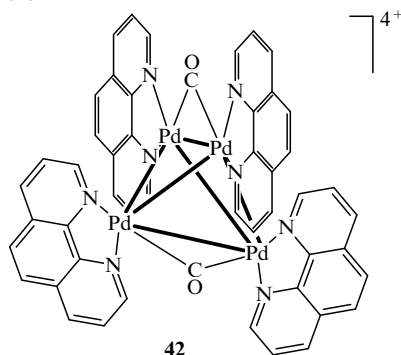


In contrast to Bipy, *o*-phenanthroline (Phen) displaces from complex **38** only half of the CO groups present even at the highest ligand concentrations. In the reaction of complex **38** with Phen, in the proportions Phen: Pd = 1:1, in acetic acid, a tetranuclear cationic complex is formed:¹³⁰



42

The complexes have been characterised by IR spectroscopy ($\nu_{\text{CO}} = 1800 \text{ cm}^{-1}$) and X-ray diffraction data.¹³⁰ In the cation **42**, the four metal atoms form a tetrahedron, to the two mutually perpendicular edges of which bridging CO groups are coordinated. The remaining metal-metal bonds are unbridged. One Phen molecule is coordinated as a chelate species to each palladium atom, while all the acetate groups are displaced to the outer sphere



On passing from complex **38** to **42**, all the metal-metal distances change significantly. The Pd-Pd distance in the $\text{Pd}(\mu\text{-CO})\text{Pd}$ fragments increases from 2.667 Å in complex **38** to 2.890 Å in complex **42**, while the unbridged Pd-Pd bond is shortened from 2.909 to 2.718 Å to compare with the $\text{Pd}(\mu\text{-OAc})\text{Pd}$ fragment in the initial carbonyl acetate.

It has been suggested that the conversion of the neutral molecule of complex **38** into the cationic cluster **42** involves the

interaction of complex **38** and Phen, which results in the displacement of the acetate groups and the formation of the dication $[\text{PhenPd}(\text{CO})_2\text{PdPhen}]^{2+}$. This is followed by the elimination of half of the coordinated CO groups and the dimerisation of coordinatively unsaturated species produced, which leads to the appearance of cluster **42**.

g. The structure of palladium(+1) complexes containing a bridging CO group

The palladium(+1) complexes containing a bridging CO group have been reliably characterised by the results of spectroscopic and structural studies (Table 3).

In the complexes where the palladium atoms are not linked to *n*-donor atoms (Nos 1–3), the metal-metal distances are close to

Table 3. Certain spectroscopic and structural data for palladium(+1) complexes containing a bridging carbonyl group.

No. Complex	<i>n</i> -Do- nor atom	Pd-Pd /Å (XRD)	ν_{CO} /cm ⁻¹	Ref.
1 [cyclo-Pd ₂ (μ-CO) ₂](SO ₃ F) ₂		2.698	1977	35
2 [Pd ₂ (μ-CO) ₂ Cl ₄] ²⁻		2.697	1903	22
3 Pd ₄ (μ-CO) ₄ (μ-OAc) ₄		2.663	1934, 1975	7, 8
4 Pd ₄ (μ-CO) ₄ (μ-O ₂ CCF ₃) ₄		2.700 ^a	2002, 1940	45
5 Pd ₂ (μ-CO)(Cl)(PEt ₂ Ph) ₃	P	2.652	—	27
6 Pd ₂ (μ-CO)(η ⁵ -Cp)(Br)(PPr ₃) ₂	P	2.670	1828	38
7 [Pd ₄ Phen ₄ (μ-CO) ₂](OAc) ₄	N	2.890	1800	52
8 Pd ₂ (μ-CO)(μ-dppm) ₂ (OAc) ₄	P	2.980	1720	51
9 Pd ₂ (μ-CO)(μ-dmpm) ₂ Cl ₂	P	3.169 ^b	1720	32, 33
10 Pd ₂ (μ-CO)(μ-dam) ₂ Cl ₂	As	3.274 ^b	1710	5, 6, 29

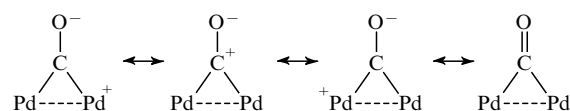
^a According to EXAFS data. ^b For comparison, the Pd-Pd distance in $\text{Pd}_2(\mu\text{-dppm})_2\text{Br}_2$ is 2.699 Å.

that in metallic palladium, which is 2.7 Å. The stretching vibrational frequencies of the CO group in these complexes vary from 1900 to 2000 cm⁻¹. The presence of powerful electron-withdrawing groups, for example CF₃COO (complex No. 4), increases the stretching vibrational frequency of the CO group to 2000 cm⁻¹.

After the insertion of *n*-donor phosphorus atoms (axial phosphine ligands in complex Nos 5 and 6) into the coordination sphere of palladium, the Pd-Pd distance does not change, but ν_{CO} falls sharply. Only the presence of chelating phenanthroline molecules, linked to one palladium atom (No. 7), or of bridging diphosphino and diarsine ligands (complexes Nos 8–10) leads to a simultaneous increase in the Pd-Pd distance and decrease in the stretching vibration frequency of the bridging carbonyl ligand.

It is of interest that powerful electron-accepting ligands, for example trifluoroacetate groups, in the axial positions in complex No. 4 (Table 3) somewhat 'extinguish' the effect involving the donation of *n* electrons by phosphorus atoms, which is probably the reason for the shortening (compared with other complexes containing diphosphines and diarsines) of the Pd-Pd distance.

As mentioned above, all the complexes discussed are diamagnetic. On the other hand, the metal-metal distance in complexes with diphosphines and diarsines (complexes Nos 9 and 10 in Table 3) greatly exceeds the sum of the covalent radii palladium and for this reason the pairing of electrons as a result of the formation of the Pd-Pd bond is impossible. The diamagnetism of such complexes has been explained by the exchange of charges in the $\text{Pd}_2(\mu\text{-CO})$ fragment with participation of the structure



Evidently the hypothesis of the resonance of structures with different numbers of unpaired electrons ($\text{Pd}^+ \dots \text{Pd}^+$ and $\text{Pd}^{2+} \dots \text{Pd}^0$) conflicts with the main principles of the resonance theory.¹³¹ At the same time, the bond in the group made up of two palladium atoms and one carbon atom of the carbonyl group can be described approximately in terms of a localised three-centre system of molecular orbitals, similar to that which occurs in the allyl radical. The diamagnetism of the dinuclear palladium(+1) compounds under consideration implies, in terms of this approximation, that four electrons (one from each palladium atom and two from the carbonyl ligands) fill the bonding and nonbonding molecular orbitals of the system (Fig. 7).

Within the framework of this approximation, all the changes in the Pd–Pd distance and ν_{CO} frequencies should be considered from the standpoint of the variation of the electron density on the metal atoms and the variation of the levels of the atomic orbitals in view of the change in the nature of the ligand atoms coordi-

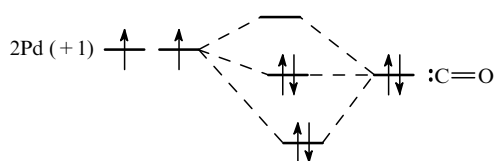
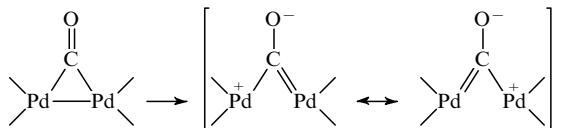
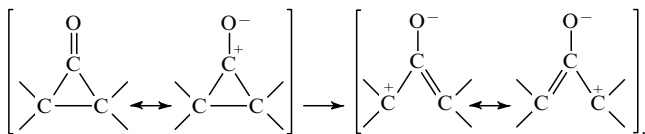


Figure 7. The three-centre system of molecular orbitals in the group comprising two palladium atoms and one carbon atom.

nated to palladium. It is easily seen that in the isomeric ylide the frequencies of the carbonyl group should be significantly reduced compared with the frequencies of the dimetallocyclopropanone. The complexes presented in Table 3 may be regarded as models of the intermediate states on the path to the isomerisation of the dimetallocyclopropanone to the corresponding dimetalloylide:



The strong electron-donating influence of the ligands linked to the palladium atom may weaken the Pd–Pd bond and increase the distance between the atoms involved. This is equivalent to the isomerisation of the cyclopropanone to an ylide with an opened ring:



2. The reactivity of palladium(+1) carbonyl complexes

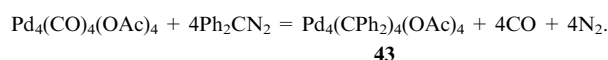
The available information about the chemical properties of palladium(+1) carbonyl halides is limited to data concerning their behaviour in relation to water and under thermal decomposition conditions. The reactivity of the carbonyl carboxylate complexes and their derivatives has been investigated much more fully.

a. Ligand substitution reactions in palladium(+1) carbonyl carboxylates

Synthesis of a carbene cluster by the substitution of CO groups

When certain acido-ligands (for example, the acetate groups in complex **38**) are substituted by other carboxylates, new carbonyl carboxylate complexes are formed.

The substitution of neutral carbonyls has been observed in the interaction of complex **38** with diphenyldiazomethane.¹³² The interaction of complex **38** and Ph_2CN_2 , which is capable to generate diphenylcarbene groups *in situ*, results in the displacement of the CO groups and the formation of a new complex (Fig. 8);



Complex **43** contains bridging acetate groups. It has been established by IR spectroscopic studies that $\nu_{\text{as}}(\text{COO}) = 1560 \text{ cm}^{-1}$, $\nu_{\text{s}}(\text{COO}) = 1400 \text{ cm}^{-1}$, and $\Delta\nu = 160 \text{ cm}^{-1}$. The signals due to the protons of the phenyl and acetate groups in the ratio $\text{H}_{\text{Ph}}/\text{H}_{\text{OAc}} = 10/3$, *i.e.* there is one CPh_2 ligand per acetate group, have been observed in the ^1H NMR spectrum. According to EXAFS data, the coordination sphere of each palladium atom in cluster **43** includes two metal atoms at a distance of 2.67 Å, one metal atom at a distance of 3.65 Å, and also two light atoms in each case (in all six) at distances of 1.86, 2.03, and 3.25 Å. These values agree with the structure proposed by Stromnova *et al.*^{132, 133} (Fig. 8).

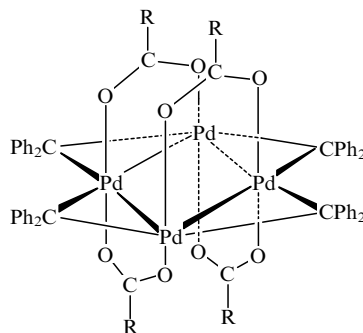
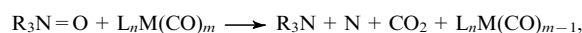


Figure 8. The structure of the cluster $\text{Pd}_4(\mu\text{-CPh}_2)_4(\mu\text{-OAc})_4$ according to EXAFS data.^{132, 133}

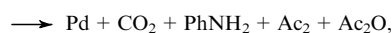
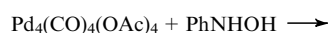
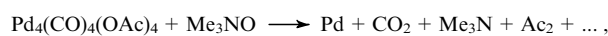
Oxidative substitution of carbonyl ligands

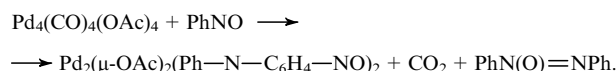
The coordinated carbon monoxide in transition metal carbonyl complexes may be oxidised by an outer-sphere oxidant, for example trimethylamine *N*-oxide:



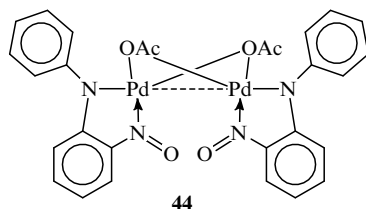
or by other compounds containing the N–O group.^{73, 134}

In a study of the interaction of complex **38** with organic compounds containing the N–O group, such as nitrobenzene, nitrosobenzene, azoxybenzene, phenylhydroxylamine, and trimethylamine *N*-oxide, it has been established¹³⁵ that only nitrosobenzene and phenylhydroxylamine are capable of oxidising the coordinated carbon monoxide under mild conditions, like trimethylamine *N*-oxide:





The complex $\text{Pd}_2(\mu\text{-Ac})_2(\text{Ph-N-C}_6\text{H}_4\text{-NO})_2$ **44**, containing a new ligand — phenyl-*o*-nitrosophenylamide, is formed in the reaction between complex **38** and nitrosobenzene together with organic products (azoxybenzene, azobenzene, and aniline) of the transformation of the NO-containing compound.¹³⁶



This ligand is obtained by the reaction of a nitrene species (the product of the deoxygenation of nitrosobenzene when the latter is acted upon by the CO group) and a second nitrosobenzene molecule.

Reactions of complex **38** with anionic carbonylmetallates

Presumably, like the substitution of the OAc groups in complex **38** by carboxylate groups, the same groups might be substituted by more complex ones, for example the carbonylmetallates $\text{Co}(\text{CO})_4^-$, $\text{V}(\text{CO})_6^-$, and $\text{CpMo}(\text{CO})_3^-$. Such reactions would make it possible to obtain heteronuclear palladium-containing clusters. Indeed, the reaction of complex **38** with $\text{NaCpMo}(\text{CO})_3$ in tetrahydrofuran entails the formation of the octanuclear cluster $\text{Na}_2\{\text{Pd}_4[\text{CpMo}(\text{CO})_3]_4\} \cdot 2\text{THF}$.^{137, 138}

X-Ray diffraction analysis has shown that the structural unit in the crystals investigated consists of the centrosymmetric anion $\{\text{Pd}_4[\text{CpMo}(\text{CO})_3]_4\}^{2-}$, two sodium cations, and two tetrahydrofuran molecules. The palladium atoms are located at the vertices of a square (the Pd–Pd distances are 2.675–2.691 Å). Each molybdenum atom forms an almost regular triangle with the two palladium atoms (the Pd–Mo distances are 2.723–2.741 Å), and all the metal atoms lie in the same plane. The observed metal–metal distances correspond to single bonds. Three carbonyl ligands are linked to each molybdenum atom and one of the carbonyls is a μ_3 -bridge on the Pd_2Mo face, while the other two are bridges on the Pd–Mo bonds (Fig. 9).

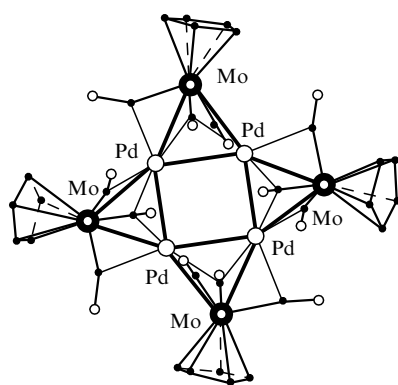
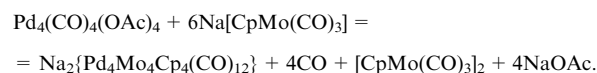


Figure 9. The structure of the anion $\{\text{Pd}_4[\text{CpMo}(\text{CO})_3]_4\}^{2-}$ according to X-ray diffraction data.^{137, 138}

The IR spectrum of the complex contains bands at 2000, 1945, 1900, 1870, and 1830 cm^{-1} referring to the coordinated CO groups.

In the course of the formation of the octanuclear cluster, not only are the acetate ligands substituted by the $\text{CpMo}(\text{CO})_3^-$ anions, but the neutral CO molecules are also displaced. The

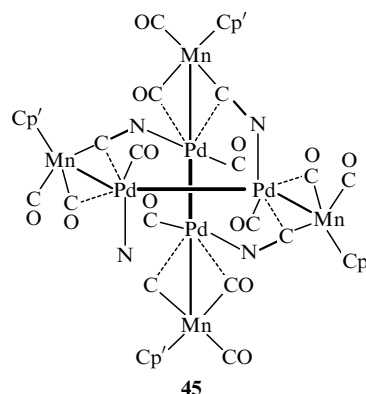
vacancies liberated in the coordination sphere of palladium in this process are occupied by the CO molecules coordinated to the molybdenum atom, which are converted into bridging ligands. However, it is significant that the process is not restricted to the substitution of ligands: during the reaction, the Pd(+1) atoms are reduced, apparently as a result of the one-electron oxidation of the $\text{CpMo}(\text{CO})_3^-$ anions. The overall process is described by the equation



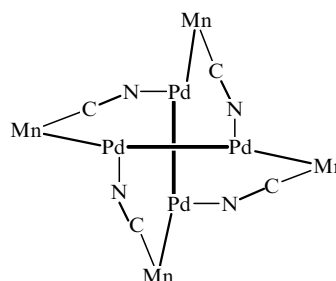
The dimer $[\text{CpMo}(\text{CO})_3]_2$ has been found in the reaction products

If it is assumed that the molybdenum atoms incorporated in the complex retain a zero oxidation state, then the observed reaction can be regarded as the reduction of the Pd(+1) atoms to Pd(+0.5). The resulting cluster is the first example of a compound in which eight metal atoms linked by the metal–metal interaction lie in the same plane.

The interaction of the another carbonylmetallate — $[(\eta^5\text{-C}_5\text{H}_4\text{Me})\text{Mn}(\text{CN})(\text{CO})_2]^-$ (in the form of the sodium salt) — and complex **38** leads,¹³⁹ as in the preceding case, to the displacement of all the ligands and the formation of the octanuclear cluster $[(\text{OC})\text{Pd}(\mu\text{-NC})\text{Mn}(\eta^5\text{-C}_5\text{H}_4\text{Me})(\text{CO})_2]_4$ **45**. In contrast to the preceding reaction, in this case the formation of the cluster is not accompanied by any kind of oxidation-reduction reactions and, if it is assumed that the carbonylmanganate ligand retains a formal –1 charge, then the formal oxidation state of palladium in cluster **45** remains +1.



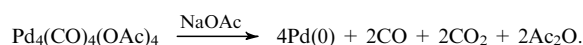
The structure of cluster **45** is unusual. It can be regarded as two mutually orthogonal bent metal chains Mn–Pd₂–Mn with short metal–metal distances. The metal chains are linked to one another by four cyanide bridges.



Furthermore, one terminal carbonyl group is linked to each palladium atom, while the coordination environment of each manganese atom is supplemented by the methylcyclopentadienyl ligand and two carbonyl groups (one terminal and the second behaving as a semibridge in relation to the nearest palladium atom).

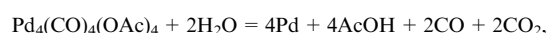
b. Reactions of palladium carbonyl acetate with oxygen-containing nucleophiles

In the presence of alkali metal acetates in solution in glacial acetic acid, complex **38** decomposes to metallic palladium in accordance with the equation



Analysis of the kinetic data permits the conclusion that the reaction mechanism involves a repeated alternation of the following cycles: insertion of CO in the Pd–OAc bond, elimination of CO₂ with formation of an acyl fragment, liberation of Ac₂O, and the formation of the Pd–Pd bond. Overall, the process proceeds *via* the reductive condensation of the palladium clusters.^{124, 140}

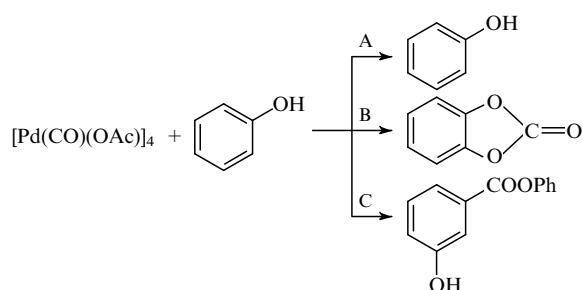
Presumably the interaction of complex **38** and water described by the equation



also takes place *via* a reductive condensation mechanism.

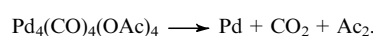
The reaction of complex **38** with aliphatic C₁–C₃ alcohols proceeds simultaneously *via* several paths with formation of CO₂ and dialkyl carbonate — the products of the oxidation of the coordinated CO molecules, as well as carbonyl compounds arising owing to the oxidation of the corresponding alcohols. It has been observed that the reaction with ethanol results in the appearance of both dialkyl carbonates and carbonyl compounds — acetaldehyde and its acetals. In the case of isopropyl alcohol, dialkyl carbonate and carbonyl compounds are produced. The reaction of cluster **38** with methanol leads to the formation of only methyl acetate. It has been shown^{141, 142} that the reactions of complex **38** with alcohols proceed *via* several paths with formation of carbonyl [L_nM(CO)], alkoxy- (L_nMOR), alkoxycarbonyl (L_nMCOOR), and acyl [L_nMC(O)R] derivatives of palladium.

In the interaction of complex **38** with phenol,¹⁴³ reactions *via* three paths, leading to the formation of phenyl acetate, diphenyl carbonate, and phenyl salicylate (paths A, B, and C), are also observed.

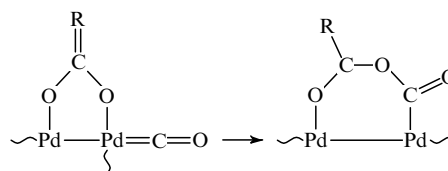


c. Oxidation of the coordinated CO groups in the carbonyl carboxylate complexes

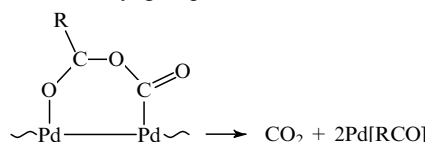
The thermal decomposition of carbonyl complexes leads as a rule to the elimination of carbon monoxide. The thermolysis of the carbonyl carboxylate clusters proceeds *via* a fundamentally different path. It has been observed that the thermolysis of the clusters in the absence of oxygen entails the inner-sphere oxidation of the neutral ligand with formation of CO₂. In the reaction, an oxygen atom is transferred from the carboxylate group to the carbonyl group, *i.e.* the acetate group functions as an oxygen donor (oxidant).^{124, 144, 145}



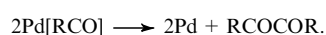
The oxidation-reduction process which has been put forward, in which carbon monoxide is oxidised by the oxygen of the coordinated carboxylate groups, apparently involves the insertion of CO in the metal–oxygen bond with formation of an unstable intermediate:



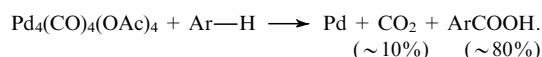
The decomposition of the intermediate leads to the elimination of CO₂ and the formation of reduced forms of palladium and coordinated acyl groups:



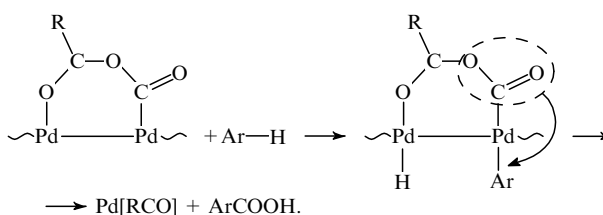
The recombination of the two acyl ligands bound to the core of the cluster affords the biacyl:



If the thermolysis of the carbonyl carboxylate clusters is carried out in benzene or toluene solution, the main product of the oxidation of the coordinated CO groups is not CO₂ but an arenecarboxylic acid:



Presumably oxidative addition of an arene molecule to the palladium core with dissociation of the H–Ar bond, followed by the insertion of CO₂ in the Pd–C_{aryl} bond, takes place simultaneously with the transfer of an oxygen atom from the carboxylate to CO:



The inner-sphere transfer of an oxygen atom from the carboxylate group to the neutral carbonyl group is a fairly general reaction. Complexes containing as ligands carboxylate groups having both powerful electron-donating substituents at the carboxylate group [the acetate CH₃COO and the pivalate (CH₃)₃COO] and powerful electron-accepting substituents (the trifluoroacetate CF₃COO and the monochloroacetate CH₂ClCOO) are capable of entering into this reaction. The CO₂ produced by the reaction is coordinated to the palladium atoms of the decomposing cluster, exhibits unusual properties, and is capable of being inserted into the C–H bonds of aromatic compounds.

Summarising the data on the synthesis, structures, and reactivities of the carbonylpalladium(+1) complexes, one should note that their number is appreciably smaller than that of the carbonylpalladium(0) complexes.

All the palladium(+1) complexes contain an even number of metal atoms (2 or 4). Since the main structural element of polymeric carbonyl halides is the species [X–Pd(μ-CO)₂Pd–X] and there is no metal–metal bond between such species, it appears legitimate to regard them as dinuclear. Complexes with a higher nuclearity have not been described for Pd(+1). All the palladium(+1) carbonyl complexes are diamagnetic and the pairing of electrons at the two metal atoms, having the *d*⁹ electronic configuration, takes place either as a result of the formation of a metal–metal bond (with a Pd–Pd distance of ~2.7 Å) or *via* the formation of a three-centre four-electron bond incorporating two palladium atoms and one carbon atom of the bridging carbonyl ligand.

In complexes containing only carbonyl and halide, carboxylate, or fluorosulfate ligands, the Pd–Pd distance is close to 2.7 Å and the stretching vibrational frequency of the μ -CO group is in the range from 1900 to 2000 cm^{-1} . Being relatively resistant to thermal decomposition, these complexes are fairly sensitive to the action of oxygen-containing nucleophiles and, when treated with, for example, water or lower aliphatic alcohols, decompose with formation of palladium metal.

The introduction of n -donor ligands into the complexes leads as a rule to an increase in the metal–metal distance in the Pd(μ -CO)Pd fragment and to a decrease in the stretching vibrational frequency of the μ -CO group. The resistance of these complexes to reductive decomposition on treatment with nucleophiles increases simultaneously and some of them, for example, $[\text{Pd}_4(\text{CO})_2\text{Phen}_4](\text{OAc})_4$ or $[\text{Pd}(\mu\text{-dmpm})\text{Cl}]_2(\mu\text{-CO})$, are readily soluble and are stable even in aqueous solutions.

In contrast to palladium(0) carbonyls, the reactivity of palladium(+1) carbonyls is not limited to ligand substitution reactions and has been investigated much more fully. In our view, the oxidation–reduction reactions of carbonyl carboxylate clusters is of greatest interest. In the first place, this is the reaction involving the intramolecular transfer of an oxygen atom from the carboxylate ligands to the coordinated carbonyl group. This reaction can serve as a model for the whole series of oxidation–reduction processes occurring with participation of CO and catalysed by palladium compounds.

V. Palladium(+2) carbonyl complexes

A considerably smaller number of palladium(+2) complexes with carbonyl ligands than palladium carbonyls containing the metal in other oxidation states have been synthesised and reliably characterised at the present time. This can probably be accounted for primarily by the striking tendency of Pd(+2) to be reduced by carbon monoxide and hence by the high lability of Pd(+2) carbonyls in proton-donating basic solvents.

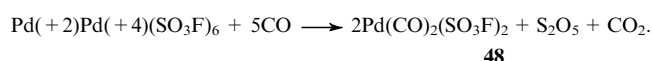
1. Binary carbonyls

The first studies on the chemistry of palladium(+2) carbonyls date back as early as the past century,⁶ but sufficiently definite conclusions concerning the structure of the palladium(+2) carbonyl complexes have been reached on the basis of studies carried out in the last three–five years. In these investigations, the key compounds were characterised by X-ray diffraction. This applies primarily to the binary cationic carbonyls.

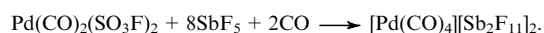
A series of cationic carbonyls have been obtained quite recently in strong protic acids (HSO_3F) or superacids ($\text{HSO}_3\text{F}\cdot\text{SbF}_5$).^{146, 147} In the solid state, the carbonyl cations were stabilised by very weakly basic anions SO_3F^- or $\text{Sb}_2\text{F}_{11}^-$. These are singly-charged linear cations $[\text{M}(\text{CO})_n]^+$ [$\text{M} = \text{Au}$ or Ag , $n = 1$ or 2 ;^{148–150} $\text{M} = \text{Hg}$, $n = 1$ (Ref. 151)] or square-planar cations $[\text{M}(\text{CO})_4]^{2+}$ [$\text{M} = \text{Pd}(\mathbf{46})$ or $\text{Pt}(\mathbf{47})$]^{152, 153}.

Complexes **46** and **47** have been obtained as a result of the reductive carbonylation of $[\text{Pd}(\text{SO}_3\text{F})_3]_2$ or $\text{Pt}(\text{SO}_3\text{F})_4$ respectively and the subsequent solvolysis of the resulting neutral complex in liquid antimony(+5) fluoride.

Treatment of the solid salt containing Pd(+2) and Pd(+4) with CO ($P_{\text{CO}} = 0.5$ atm, 25 °C) affords $\text{Pd}(\text{CO})_2(\text{SO}_3\text{F})_2$ in accordance with equation



According to IR spectroscopic data, when the reaction is carried out in the absence of solvent, complex **48** is formed exclusively as the *cis*-isomer. On the other hand, when fluorosulfonic acid HSO_3F is used as the solvent, a mixture of isomers is produced. In liquid antimony fluoride in the presence of free carbon monoxide ($P_{\text{CO}} = 0.5$ atm, 60–80 °C), complex **48** is converted into $[\text{Pd}(\text{CO})_4][\text{Sb}_2\text{F}_{11}]_2$ in accordance with the equation



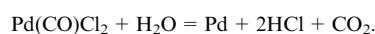
Complex **47**, the platinum analogue of complex **46**, was obtained in the same manner. Complexes **46** and **47**, isolated in the form of white powders, are thermally fairly stable (they begin to decompose at 155 and 200 °C respectively), but are extremely sensitive to moisture. The stretching vibration frequencies of the CO groups in both complexes are very high (2259 cm^{-1} for complex **46** and 2261 cm^{-1} for complex **47**) and are higher by approximately 120 cm^{-1} than for free carbon monoxide. These data suggest that, as in the neutral and anionic divalent palladium carbonyl halides, in these compounds the σ -donor properties of the CO group greatly predominate over its π -acceptor properties.

Dicarbonylpalladium fluorosulfate **48** (a precursor of complex **46**) has been obtained¹⁵⁴ in the form of a thermally fairly stable yellow substance (decomposition temperature 117 °C). Complex **48** is the first example of a thermally stable compound in which two monodentate carbonyls are coordinated to one Pd(+2) atom. Two other complexes of the type $\text{Pd}(\text{CO})_2\text{R}_2$ ($\text{R} = \text{C}_6\text{F}_5$ or C_6Cl_5),¹⁵⁵ where two terminal carbonyls are coordinated to one palladium atom, are much less stable and already begin to decompose at a temperature below –30 °C. The fluorosulfate group in complex **48**, which has a pronounced electron-withdrawing capacity, probably enhances the electron-accepting properties of the metal atom. The stretching vibrational frequency of the CO group is 2218 cm^{-1} , which is the highest observed for all the known neutral carbonyl complexes of platinum metals.

Complex **48** is the first example of a structurally characterised neutral palladium carbonyl.¹⁵⁶ Crystals of the *cis*-isomer of compound **48**, suitable for X-ray diffraction, have been obtained on slow recrystallisation of the complex from its saturated solution in fluorosulfonic acid. The palladium atom in the molecule of compounds **48** is surrounded by two *cis*-disposed terminal carbonyl groups and monodentate fluorosulfate groups located at the corners of a planar square. The C–O bond is fairly short (1.106 Å), which agrees well with its high frequency ν_{CO} in the IR spectra and with the conclusion that the π -back-donation from the metal to the carbonyl group is absent or at least greatly reduced. A weak interaction of the noncoordinated oxygen atom with the carbon atom of the carbonyl groups has been noted (the C–O distance is 2.819–3.172 Å). In the absence of π -back-donation, secondary contacts, with participation of the electrophilic carbon atom of the CO group as an electron acceptor probably promote somewhat charge compensation and exert a stabilising influence on the entire molecule.

2. Neutral and anionic palladium(+2) carbonyl halides

The synthesis of the three carbonyl derivatives of palladium $\text{PdCl}_2 \cdot (\text{CO})$, $\text{PdCl}_2 \cdot (\text{CO})_2$, and $\text{PdCl}_2 \cdot (\text{CO})_3$ on interaction of solid PdCl_2 with carbon monoxide at 260 °C, described by Fink,⁶ could not be reproduced subsequently. Manchot¹⁵⁷ showed that complexes having this composition are actually formed by the platinum present as an impurity in the initial palladium salt. However, one of these complexes has been obtained from pure palladium chloride. The divalent palladium carbonyl $\text{Pd}(\text{CO})\text{Cl}_2$, which is extremely unstable when acted upon by atmospheric moisture, has been obtained¹⁵⁸ at 20 °C from solid PdCl_2 and carbon monoxide, from which water vapour had been carefully removed and which had been saturated with anhydrous methanol vapour, and also from a suspension of PdCl_2 in anhydrous methanol on treatment with dry carbon monoxide:



A similar complex $\text{Pd}(\text{CO})\text{Br}_2$ has been obtained by the interaction of PdBr_2 and carbon monoxide saturated with methanol vapour and also on treatment of a suspension of K_2PdBr_4 in dioxane containing 0.5%–2.0% of H_2O with carbon monoxide. Palladium(+2) bromide complexes are not carbonylated in anhydrous dioxane.^{96, 158} It has been suggested¹⁵⁸ that the above palladium(+2) carbonyl halides are dimeric and that the anions

$[\text{Pd}(\text{CO})\text{X}_3]^-$ are also present in a solution containing an excess of halide ions. In these anionic complexes, isolated in the form of a salt with the tetrabutylammonium cation,¹⁵⁹ the CO molecule may be bound as a monodentate ligand, like the alkene in a π -complex of the Zeise's salt type.

The complexes listed above (both neutral and anionic) were initially insufficiently fully characterised and the information available about their structure was tentative. However, later the structure of analogues of these compounds was established quite definitely.

Thus the carbonylation of PdCl_2 in thionyl chloride under fairly strong conditions ($P_{\text{CO}} = 50$ atm, 120°C) yielded¹⁶⁰ $\text{Pd}_2(\text{CO})_2\text{Cl}_4$ **49**:



The interaction of $\text{NH}_2\text{Et}_2\text{Cl}$ and compound **49** in solution in CH_2Cl_2 leads to the formation of the anionic complex $\text{NH}_2\text{Et}_2[\text{Pd}(\text{CO})\text{Cl}_3]$ **50**. Complexes **49** and **50** have been characterised by elemental analysis and IR spectroscopy ($\nu = 2167\text{ cm}^{-1}$ for complex **49** and 2141 cm^{-1} for complex **50**).

Complex **49** is stable only in a CO atmosphere, decomposing in the absence of CO. The terminal CO groups are readily substituted by tertiary phosphines, forming initially $\text{Pd}_2(\mu\text{-Cl})_2\text{Cl}_2(\text{PPh}_3)_2$ and then *trans*- $\text{PdCl}_2(\text{PPh}_3)_2$.

It has been suggested that complex **49** is a dimer with two chloride bridges; the two terminal carbonyl ligands are *trans*-disposed relative to the metal-metal axis. This is in fact the structure of the platinum analogue $\text{Pt}_2(\text{CO})_2\text{I}_4$ isolated in a crystalline form and characterised by IR spectroscopy ($\nu_{\text{CO}} = 2122\text{ cm}^{-1}$) and X-ray diffraction data.¹⁶¹ This is a dimer with a nonbonding metal-metal spacing, two bridging iodide ligands, and two *trans*-disposed terminal carbonyl groups.

The complex to which the authors attribute the composition $\text{PdCOCl}_2(\text{PPh}_2\text{-polymer})$ may have a similar structure (but with carbonyl and not halide bridges). The complex has been obtained¹⁶² by carbonylating the corresponding benzonitrile derivative 'attached' to the polymeric support *via* a phosphide bridge. The stretching vibrational bands of the CO group in the range $1944\text{--}1964\text{ cm}^{-1}$ have been found in the IR spectrum of the complex, indicating that these groups are of the bridging type.

On the basis of spectroscopic data for the anion of complex **50**, a structure has been proposed in which the metal atom has a planar environment (three chlorine atoms and one carbon atom of the terminal carbonyl ligand). It has been found that the anion of the salt $(\text{NBu}_4^+)[\text{Pd}(\text{CO})\text{Br}_3]^-$ **51** has precisely this structure. Complex **51** has been obtained by treating a solution of $(\text{NBu}_4^+)(\text{PdBr}_3)$ in tetrachloroethane with CO ($P_{\text{CO}} = 1$ atm).¹⁶³

The carbonylation of PdBr_2 ($P_{\text{CO}} > 70$ atm) leads to the formation of $\text{Pd}_2(\text{CO})_2\text{Br}_4$, which, judging from the IR spectra ($\nu_{\text{CO}} = 2145\text{ cm}^{-1}$), is constructed similarly to complex **49**. The iodide analogue of complex **49** could not be obtained. However, treatment of a solution of PdI_2 in toluene with CO in the presence of stoichiometric amounts of I^- leads to $[\text{Pd}(\text{CO})\text{I}_3]^-$. The latter has been isolated as a salt with (NBu_4^+) and has been characterised by IR spectroscopy ($\nu_{\text{CO}} = 2015\text{ cm}^{-1}$).

According to X-ray diffraction data for complexes **50** and **51**, the palladium atoms in the anions $[\text{Pd}(\text{CO})\text{Cl}_3]^-$ and $[\text{Pd}(\text{CO})\text{Br}_3]^-$ have a square-planar environment with the usual Pd-C_{CO} (1.87 Å for both anions) and C-O (1.10 and 1.11 Å respectively) distance. The stability of the palladium carbonyl halide complexes (both neutral and anionic) decrease in the sequence $\text{Cl} > \text{Br} > \text{I}$.¹⁶³

The study of the kinetics of the exchange of the carbonyls in the carbonyl halides between $[\text{M}^{(13}\text{CO})\text{X}_3]^-$ and ^{12}CO (IR and ^{13}C NMR spectroscopy) showed that the carbonyl ligands in these complexes are bound fairly strongly and that the rate of exchange of the carbonyls is lower almost by six orders of magnitude than the rate of exchange of ethene in the analogous ethene π -complexes.¹⁶⁴

The formation of complex **49** in thionyl chloride has been investigated and the thermodynamic constants of the process have been determined, which made it possible to estimate the energy of the Pd-CO bond ($\sim 24\text{ kcal mol}^{-1}$).¹⁶³ Analysis of the thermodynamic and spectroscopic data led to the conclusion^{155,165} that the contribution of metal-to-ligand the π -back-donation in the palladium carbonyls is slight and that the strength of the Pd-CO bond is determined almost exclusively by the σ -donor capacity of the carbonyl ligand.

This conclusion appears fairly justified for the neutral and anionic palladium(+2) carbonyl halides, but the question of the contribution of the σ -donor and π -acceptor interactions in organopalladium compounds with carbonyl ligands (see below) requires additional discussion.

The contribution of a particular type of bonding of the carbonyl ligands may be inferred from spectroscopic data.²⁹ As a result of the predominance of the σ -donor properties over the π -acceptor properties in the coordinated carbon monoxide molecule, the stretching vibration frequency of the CO group becomes higher than in free CO, while the chemical shift of the carbon atom in the ^{13}C NMR spectra is observed at $\delta = 120\text{--}130$ ppm, in contrast to $190\text{--}220$ ppm for the classical carbonyls.

3. Palladium(+2) carbonyl halides containing additional stabilising ligands

Palladium(+2) carbonyl halide complexes with additional stabilising ligands have been obtained in both neutral and anion forms. For example, the reaction of CO with a suspension of the $[\text{Pd}_2\text{Cl}_2(\text{PET}_3)_4]^{2+}$ fluoroborate in chloroform afforded the cationic complex $[\text{PdCl}(\text{CO})\text{PET}_3][\text{BF}_4]$, which has been characterised by elemental analysis and IR spectroscopy ($\nu_{\text{CO}} = 2140\text{ cm}^{-1}$) and which is comparatively stable under a CO atmosphere. In the absence of CO from the gas phase over the complex a carbon monoxide molecule is evolved and the initial complex is reformed.^{166,167} In this case it is reasonable to postulate that the CO groups are terminal if the palladium atom contains four ligands in the coordination sphere, as in the majority of other palladium(+2) complexes. For the complex anion $[\text{Pd}(\text{CO})(\text{SnCl}_3)\text{Cl}]^-$ isolated¹⁶⁸ as a salt with NEt_4^+ the frequency ν_{CO} is equal 2054 cm^{-1} .

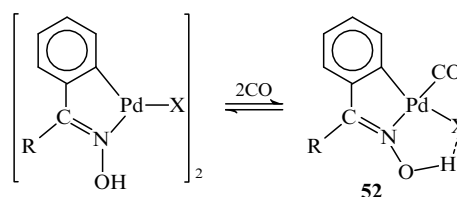
The neutral complexes $\text{Pd}(\text{CO})(\text{L})\text{Cl}_2$, where L = dimethyl sulfoxide, diethyl sulfoxide, or diethyl sulfide, have been obtained^{169,170} by carbonylating $[\text{PdLCl}_2]_2$. The authors attribute a mononuclear structure to these compounds, but on the basis of IR spectroscopic data ($\nu_{\text{CO}} = 1927\text{--}1977\text{ cm}^{-1}$) one may postulate that the complexes are at least dinuclear and contain bridging CO groups.

The complex $\text{Pd}(\text{PhN}=\text{NPh})\text{Cl}_2(\text{CO})$, obtained by the reaction of CO and $\text{Pd}(\text{PhN}=\text{NPh})\text{Cl}_2(\text{PhCN})$,¹⁷¹ should also probably be at least dimeric. The stretching vibrational frequency of the CO group in the complex is 1900 cm^{-1} , which definitely indicates a bridging coordination of the ligand.

Unfortunately, none of the complexes of this type have been characterised by X-ray diffraction analysis.

4. Organopalladium compounds containing carbonyl ligands

The complexes obtained by the reaction of carbon monoxide and dimeric palladium complexes containing oxime ligands may be regarded as an example of palladium(+2) compounds containing both the carbonyl ligand and an organopalladium group with a Pd-C σ -bond.¹⁷²



R = Ph, Me, H.

Table 4. Palladium(+2) carbonyl complexes characterised by X-ray diffraction.

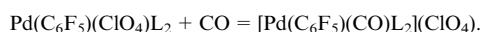
No. Complex	No. of CO groups bound to Pd	Mode of coordination of CO groups	ν_{CO} / cm^{-1}	Pd–C carbonyl bond length	C–O bond length	Geometrical environment of Pd atom	Ref.
1 $\text{Pd}(\text{CO})_2(\text{SO}_3\text{F})_2$	2	η	2218 ^a	1.94	1.106	<i>cis</i> -configuration, planar square	152, 153
2 $(\text{NH}_2\text{Et})_2[\text{PdCl}_3(\text{CO})]$	1	η	2141	1.87	1.100	planar square	160
3 $(\text{Bu}_4\text{N})[\text{PdCl}_3(\text{CO})]$	1	η	2132	1.87	1.100	the same	163
4 $(\text{Bu}_4\text{N})[\text{PdBr}_3(\text{CO})]$	1	η		1.87	1.110	"	163
5 $[\text{PPh}_3(\text{CH}_2\text{Ph})]\{\text{Pd}(\text{R})\text{Cl}_2(\text{CO})\}$	1	η	2100	1.853	1.145	"	175
6 $\text{dmdbaPd}(\mu\text{-Cl})(\mu\text{-M}')\text{Pd}(\text{dmdba})$ ($[\text{M}'] = [\text{Co}(\text{CO})_4]^-$)	2	η (on Co	2018	2.17	1.150	distorted square (disregarding the Pd–CO bond)	173
		atom, w.r.t.	1963	2.13	1.140		
		Pd–Co bonds)	1880				
			1860				
7 $\text{dmdbaPd}(\mu\text{-Cl})(\mu\text{-M}')\text{Pd}(\text{dmdba})$ ($[\text{M}'] = [\text{CpMo}(\text{CO})_3]^-$)	2	μ (w.r.t.	1844	2.28	1.150	distorted octahedron (disregarding the Pd–Pd bond)	173
		Pd–Mo bonds)	1770	2.20	1.140		
		μ_3 (on the		2.39	1.130		
		Pd_2Mo triangle)					

^a For free carbon monoxide, $\nu = 2140 \text{ cm}^{-1}$.

Complexes of type **52** have been isolated in the solid state and characterised by elemental analysis and IR spectroscopy ($\nu_{\text{CO}} = 2108\text{--}2136 \text{ cm}^{-1}$).

The dimeric complexes containing an organopalladium group with a Pd–C σ -bond proved to be convenient precursors for the synthesis of heteronuclear compounds.¹⁷³ Thus the cyclopalladated dimers with the general formula $[\text{Pd}(\text{C}-\text{N})\text{Cl}]_2[\text{C}-\text{N} = \text{dimethylbenzylamine (dmdba), 2-(dimethylamino)-toluene (dmat), or 8-methylquinoline (8-mq)}]$ react with anionic carbonylmetalates M^- ($\text{M}^- = [\text{Co}(\text{CO})_4]^-$, $[\text{Fe}(\text{CO})_3(\text{NO})]^-$, or $[\text{M}(\text{CO})_3\text{Cp}]^-$, where $\text{M} = \text{Cr, Mo, or W}$), the carbonylmetalates substituting one of the bridging chloride ligands and forming thereby the heterometallic complexes $(\text{C}-\text{N})\text{Pd}(\mu\text{-Cl})(\mu\text{-M})\text{Pd}(\text{C}-\text{N})$ **53**. The structures of complexes **53a** ($\text{C}-\text{N} = \text{dmdba}$, $\text{M}^- = [\text{Co}(\text{CO})_4]^-$) and **53b** ($\text{C}-\text{N} = \text{dmdba}$, $\text{M}^- = [\text{Mo}(\text{CO})\text{Cp}]^-$) have been investigated by X-ray diffraction analysis. In both molecules the palladium atoms are at a distance exceeding the sum of the covalent radii (3.442 Å for **53a** and 3.241 Å for **53b**). In complex **53a**, the Co atom is linked to two Pd atoms, two carbonyl groups are bridging in relation to the Pd–Co bonds, and two others are coordinated terminally to the cobalt atom. In complex **53b**, having a similar metal core, among the three carbonyl ligands two are bridges on the Pd–Mo bonds, whilst the third is μ_3 -coordinated to the Pd_2Mo metallotriangle.

Organopalladium carbonyl complexes of another type have been synthesised¹⁷⁴ by ligand substitution on treatment the complexes of the type $\text{Pd}(\text{C}_6\text{F}_5)(\text{ClO}_4)\text{L}_2$, where $\text{L} = \text{Bipy, Phen, tetraethylenediamine, or } 2\text{PR}_3$ with CO ($P = 1 \text{ atm, } 0^\circ\text{C}$, toluene, chloroform, or acetone).



The available information about structures of this type is also limited to the results of elemental analysis, the conductivity of solutions, and IR spectroscopy ($\nu_{\text{CO}} = 2132\text{--}2160 \text{ cm}^{-1}$). There are no structural data for the complexes, but the frequencies, ν_{CO} , in the IR spectra indicate unambiguously the terminal coordination of the carbonyl.

The interaction of $[\text{PPh}_3(\text{CH}_2\text{Ph})]_2\text{Pd}(\text{R})\text{Cl}(\mu\text{-Cl})_2$ and carbon monoxide ($P_{\text{CO}} = 1 \text{ atm, } 20^\circ\text{C}$, CH_2Cl_2) yielded¹⁷⁵ the complexes $[\text{PPh}_3(\text{CH}_2\text{Ph})][\text{Pd}(\text{R})\text{Cl}_2(\text{CO})]$ [$\text{R} = \text{C}_6\text{H}_3(2\text{-Me})(6\text{-NO}_2)$ (**54**) or $\text{C}_6\text{H}_2(\text{NO}_2)_3\text{-2,4,6}$ (**55**)]. These complexes are stable in the solid state, but in solution they eliminate CO, reconvert to the initial state. The IR spectra of both complexes contain characteristic bands of terminal CO groups 2100 cm^{-1} for **54** and 2115 cm^{-1} for **55**). The frequencies ν_{CO} are lower than for the cationic complex $[\text{Pd}(\text{C}_6\text{H}_5)(\text{CO})\text{L}_2]^+$ ($2132\text{--}2163 \text{ cm}^{-1}$)¹⁷⁴ or the neutral complex $[\text{Pd}(\text{C}_6\text{F}_5)_2(\text{CO})_2]$ ($2152\text{--}2186 \text{ cm}^{-1}$),¹⁵⁵ but

higher than the frequencies ν_{CO} for the palladium carbonyl complexes containing the metal in lower oxidation states (for example, for $\text{Pd}(\text{CO})_n$, where $n = 4, 3$ or 2 , $\nu_{\text{CO}} = 2060, 2044$, and 2050 cm^{-1} respectively³³). IR spectroscopic data indicate the occurrence of the 'classical' π -donation in the complexes **54** and **55**.

The structure of complex **54** has been investigated by X-ray diffraction. In the anion, the palladium atom has a planar environment consisting of two *cis*-disposed chlorine atoms, the carbon of the terminal carbonyl group (the Pd–C bond length is $1.853 \text{ \AA}$ and the Pd–C–O angle is 175.4°) and the 2-methyl-6-nitrophenyl ligand. The C–O distance, amounting to $1.145 \text{ \AA}$, has the usual value for terminal carbonyl groups.

Summarising the data presented on the structure of palladium(+2) carbonyl complexes, one should note that all the reliably characterised homonuclear complexes (Table 4) are monomers with terminal CO groups. In complexes containing halide and alkyl ligands (No. 2–No. 5, Table 4) apart from the terminal carbonyl, the strength of the Pd–C_{CO} bond is low, which is the reason for the low thermal stability of the carbonyls. The presence of the fluorosulfate group, which possesses strong electron-withdrawing properties, in the complex $\text{Pd}(\text{CO})_2(\text{SO}_3\text{F})_2$ (No. 1, Table 4) leads to an increase in the electron-accepting capacity of the palladium atom. The consequence of such increase is, on the one hand, the strengthening of the Pd–C_{CO} bond, expressed by an unusually high thermal stability of palladium complexes with a terminal carbonyl group, and, on the other hand, extremely high stretching vibrational frequencies of the CO group.

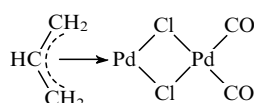
In the Pd(+2) complexes where the metal atom has the d^8 electronic configuration and a much smaller ability to donate the metal π electrons to the corresponding orbitals of the CO molecule than in the palladium(0) and palladium(+1) complexes, an enhancement of the σ -donor properties of the carbonyl has been observed. The enhancement of the σ -donor and the weakening of the π -acceptor properties of the carbonyl ligand are accompanied by an increase in the stretching vibration frequencies of the CO group (Table 4).

VI. Palladium carbonyl complexes containing the metal in fractional oxidation state

The appearance of unusual or 'intermediate', including fractional, oxidation states of transition metals is associated with the development of the chemistry of polynuclear compounds, especially the chemistry of clusters.

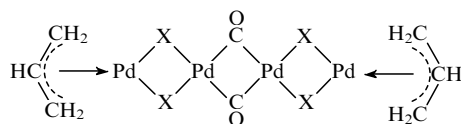
1. The synthesis and structure of clusters containing a metal in a fractional formal oxidation state

π -Allylbis(carbonylchloropalladium) having the composition $\pi\text{-C}_3\text{H}_5[\text{PdCl}(\text{CO})]_2$ **56**, described as early as 1964, should probably be regarded as the first palladium carbonyl in which the formal oxidation state of the metal atom proved to be nonintegral.¹⁷⁶ The authors proposed a composition for the complex where there are three singly-charged acido-ligands for two palladium atoms; the FOS of the metal in the complex is +1.5. The complex was obtained by passing carbon monoxide through a solution of a mixture of PdCl_2 and HCl in methanol in which π -allylpalladium chloride had been suspended. The IR spectrum of the resulting bright-yellow precipitate, which did not dissolve in the usual organic solvents, contained an intense band at 1940 cm^{-1} , which the authors attributed to the stretching vibrations of the terminal CO group. The absence of bands in the range $286\text{--}360\text{ cm}^{-1}$, characteristic of the vibrations of the Pd–Cl bond, led to the conclusion that the chloride ligands were involved in bridging coordination. The following structure of **56** was proposed:



However, the structure of complex **56** is somewhat more complicated. On the basis of current data concerning the structure of palladium carbonyls, one may postulate that the carbonyl groups in this compound are bridges, like the chloride ligands. The bridging coordination of the allyl ligands cannot be ruled out either.

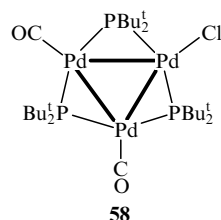
Similar complexes with the composition $\pi\text{-C}_3\text{H}_5[\text{PdX}]_2(\text{CO})$ **57**, where $\text{X} = \text{Cl}$ or Br , have been obtained by passing carbon monoxide through a methanol solution of π -allylpalladium chloride.⁸⁹ The authors suggest that the compounds formed are tetramers, in which bridging halide and semibridging carbonyl groups alternate:



$\nu_{\text{CO}} = 1937\text{ cm}^{-1}$ (for $\text{X} = \text{Cl}$), $\nu_{\text{CO}} = 1929\text{ cm}^{-1}$ (for $\text{X} = \text{Br}$).

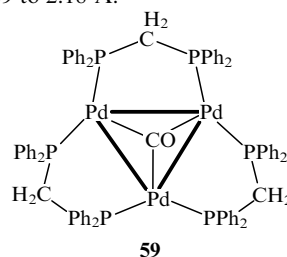
The presence of three singly-charged acido-ligands in the molecule containing two metal atoms makes it possible to assign a formal oxidation state of +1.5 to palladium. Unfortunately, in both cases the substances were characterised only by elemental analysis and IR spectroscopy, so that the interpretation of their structure does not appear sufficiently reliable. However, the presence in these compounds of bridging carbonyl groups is undoubtedly reliable. Furthermore, the data on the magnetic properties of complexes **56** and **57** might prove useful in the interpretation of their structure. Thus if the proposed formulae are correct, it follows that complex **56** should be paramagnetic and complex **57** diamagnetic.

The trinuclear carbonyl clusters synthesised later were more fully and reliably characterised. Thus the interaction of LiPBu_2^t and the polymeric carbonyl chloride $[\text{Pd}(\text{CO})\text{Cl}]_n$ in THF at -78°C afforded (together with other products) the cluster $\text{Pd}_3(\mu\text{-PBu}_2^t)_3(\text{CO})_2\text{Cl}$ **58**, in which the metal has a formal oxidation state of +1.33.¹⁷⁷



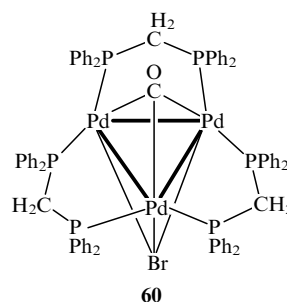
According to X-ray diffraction data, the palladium atoms in complex **58** form a triangle with Pd–Pd distances ranging from 2.949 to 3.000 Å which indicates a weak metal–metal interaction. All the phosphide groups are bridges along the Pd–Pd bonds, while one chloride and two carbonyl ligands are terminal. The relatively low stretching vibrational frequencies of the terminal CO groups (two bands in the IR spectrum at 2035 and 2030 cm^{-1}) compared with the ν_{CO} in the mononuclear complexes (usually above 2100 cm^{-1}) are due to the presence of phosphide species with their high electron content.

Another type of carbonyl trinuclear clusters represented by the dication $[\text{Pd}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$ **59**, was described for the first at time by Manojlovic-Muir *et al.*¹⁷⁸ and Puddephatt¹⁷⁹ and was characterised in detail by Lloyd and Puddephatt¹⁸⁰. Cluster **59** has been obtained by the reaction of $\text{Pd}(\text{OAc})_2$ and dppm with carbon monoxide ($P_{\text{CO}} = 1\text{ atm}$) in solution in aqueous acetone containing an excess of trifluoroacetic acid and was isolated as a salt with CF_3COO^- **59a**. The interaction of complex **59a** with an excess of $\text{NH}_4(\text{PF}_6)$ leads to the formation of $[\text{Pd}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3](\text{PF}_6)_2$ **59b**. Complex **59** has been characterised by IR spectroscopy ($\nu_{\text{CO}} = 1820\text{ cm}^{-1}$) and X-ray diffraction. The palladium atoms in the cation form a triangle (the Pd–Pd sides are 2.576, 2.607, and 2.610 Å, to the sides of which diphosphine bridges are coordinated symmetrically, while the carbonyl group is linked to all three metal atoms (the Pd–C distance ranges from 2.09 to 2.18 Å).



In the clusters of type **59** containing only neutral ligands, there are two positive charges on three metal atoms and hence the FOS of each palladium atom is +0.67.

The interaction of halides or of the trifluoroacetate anion with the dication **59** is reversible, without change in the FOS of the metal atoms, and leads to the formation of $[\text{Pd}_3(\text{X})(\mu_3\text{-CO})(\mu\text{-dppm})_3]^+$ ($\text{X} = \text{CF}_3\text{COO}, \text{Cl}, \text{Br}, \text{I}$) **60**. It has been established that the capacity for coordination diminishes in the sequence $\text{I} > \text{Br} > \text{Cl} > \text{CF}_3\text{COO}$ and that each successive ligand can be quantitatively substituted by the preceding one.^{181, 182}



Clusters **60** have been isolated in the form of a salt with CF_3COO^- and have been characterised by X-ray diffraction analysis for $\text{X} = \text{I}$ ¹⁸⁰ and Cl .¹⁸¹ In both cases, the anionic ligand X is μ_3 -coordinated to the side of the Pd_3 triangle opposite the side to which the $\mu_3\text{-CO}$ group is coordinated.

It is noteworthy that the Pd–X distances in the $\text{Pd}_3(\mu_3\text{-X})$ groups are fairly large (the Pd–X distance is 2.741–3.161 Å for $\text{X} = \text{Cl}$ and 2.951–3.083 Å for $\text{X} = \text{I}$) and an unambiguous conclusion concerning the incorporation of X in the coordination sphere of the cluster cannot be reached on the basis of X-ray diffraction data. However, the results of studies of the molar conductance of solutions of the clusters and of their spectra in the

Table 5. Palladium complexes containing the metal in fractional oxidation states.

Compound	FOS	Physicochemical methods	$\nu_{\text{CO}}/\text{cm}^{-1}$	Metal core, Pd–Pd distances /Å	Ref.
$\pi\text{-C}_3\text{H}_5[\text{PdCl}(\text{CO})]_2$	+0.67	elemental analysis, IR spectroscopy	1940		176
$\{\pi\text{-C}_3\text{H}_5[\text{PdX}]_2(\text{CO})\}_2$ ($\text{X}^- = \text{Cl}^-$ or Br^-)	+1.5	the same	1937 ($\text{X} = \text{Cl}$) 1929 ($\text{X} = \text{Br}$)		89
$\text{Pd}_3(\mu\text{-Bu}_2\text{P})_3(\text{CO})_2\text{Cl}$	+1.33	elemental analysis, IR spectroscopy, XRD	2035, 2030	triangle, 2.949–3.000	177
$[\text{Pd}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]\text{X}_2$ ($\text{X}^- = \text{CF}_3\text{COO}^-$ or PF_6^-)	+0.67	elemental analysis, IR spectroscopy, XRD, ^{31}P NMR	1820	triangle, 2.576, 2.607, 2.610	178, 179, 180
$[\text{Pd}_3(\mu_3\text{-X})(\mu_3\text{-CO})(\mu\text{-dppm})_3]\text{X}$ ($\text{X}^- = \text{CF}_3\text{COO}^-$, Cl^- , Br^- , I^-)	+0.67	the same	1712 ($\text{X} = \text{CF}_3\text{COO}$)	triangle, 2.584–2.603	181, 182
$[\text{Pd}_3(\eta^5\text{-C}_5\text{Me}_5)_3(\mu_3\text{-CO})_2]\text{CF}_3\text{COO}$	+0.33	elemental analysis, IR spectroscopy, XRD	1769	triangle, 2.63	183

visible region on titration of the cluster solution with a solution of KX ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) showed that the anionic ligand is incorporated into the coordination sphere of the palladium cluster and that the contribution of the covalent component to the formation of the $\text{Pd}-\text{X}$ bond greatly exceeds that of the ionic component.

The mechanism of the formation of clusters **59** and **60** has been investigated¹⁸² by ^{31}P NMR. The NMR monitoring of the reaction solution containing initially $\text{Pd}(\text{OAc})_2$, dppm , and CO in an acetone– $\text{CF}_3\text{COOH}-\text{H}_2\text{O}$ mixture made it possible to identify the formation of the complexes $\text{Pd}(\text{CF}_3\text{COO})_2(\text{dppm})$ **61**, $\text{Pd}_2(\text{CF}_3\text{COO})_2(\mu\text{-dppm})_2$ **62**, $\text{Pd}_2(\text{CF}_3\text{COO})_2(\mu\text{-CO})(\mu\text{-dppm})_2$ **63**, and $[\text{Pd}_3(\mu\text{-CF}_3\text{COO})(\mu_3\text{-CO})(\mu\text{-dppm})_3](\text{CF}_3\text{COO})$ **64**. There are grounds for the postulate that a short-lived palladium(0) complex with diphosphine is formed initially and then reacts with complex **61** to form compound **62** or **63**. The subsequent reaction of the palladium(0) complex containing bis(diphenylphosphino)methane with compound **62** or **63** leads to the appearance of $[\text{Pd}_3(\mu_3\text{-X})(\mu_3\text{-CO})(\mu\text{-dppm})_3]^+$ ($\text{X} = \text{CF}_3\text{COO}$) **60**. It can be assumed arbitrarily that the two palladium atoms in the base of the triangle, linked by a shortened $\text{Pd}-\text{Pd}$ bond (2.567 Å), have a FOS of +1. The third metal atom at the apex of the triangle than has a zero FOS. Incidentally, such treatment should be regarded as a marked simplification, which is used only for a clear representation of a more complex situation. The bridging halide ligand in the inner coordination sphere of complex **60** is readily substituted by another halide when the complex interacts with KX in acetone.

Palladium carbonyl complexes with a nonintegral FOS of the metal are few in number, are not distinguished by a structural diversity, and are represented (among reliably characterised complexes) only by clusters with a triangular metal core (Table 5). Whereas, the $\text{Pd}-\text{Pd}$ distances are fairly short (2.58–2.61 Å) in clusters **59** and **60**, where each metal atom has a FOS of +0.67, and indicate the occurrence of a direct metal–metal interaction, in cluster **58** (the FOS of the metal is +1.33) such interaction is weaker, which is reflected in the length of the metal–metal bonds (2.95–3.00 Å).

Certain heteronuclear complexes should apparently be assigned to compounds in which the metal atom has a nonintegral FOS. Thus in the octanuclear complex $\text{Na}_2[\text{Pd}_4\{\text{Cp-Mo}(\text{CO})_3\}_4]$,¹³⁸ there are two positive charges on the four palladium atoms (the palladium atoms form a square with 2.675–2.691 Å sides), *i.e.* the FOS is +0.5.

Another example is provided by the anionic cluster $[\text{Pd}_6\text{Ru}_6(\text{CO})_{24}]^{2-}$ **64** obtained¹⁸³ by the interaction of $[\text{Ru}_3\text{H}(\text{CO})_{11}]^-$ and $\text{Pd}(\text{PhCN})_2\text{Cl}_2$. The palladium atoms in the cluster form an octahedron, the ruthenium atoms serve as ‘caps’ on the faces of the octahedron, while the carbonyl ligands are involved in terminal (12 molecules) and bridging (six molecules are μ -coordinated and six are μ_3 -coordinated) coordination. If it is

assumed by analogy with the preceding cluster that the ‘capping’ ruthenium atoms represent together with the carbonyl ligands anionic carbonylmetallates, then a formal charge somewhat exceeding +1 should be attributed to the palladium atoms forming the inner octahedron, but in principle such a procedure does not appear sufficiently legitimate.

The picture becomes even more complex with increase in the number of atoms in the cluster. Thus the interaction of $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ and $[\text{Ni}_6(\text{CO})_{12}]^-$ afforded¹⁸⁴ the anionic cluster $(\text{Pd}_{33}\text{Ni}_9(\text{CO})_4(\text{PPh}_3)_6)^{4-}$ isolated in the form of a salt with $[\text{PPh}_4]^+$ and characterised by X-ray diffraction (Fig. 10).

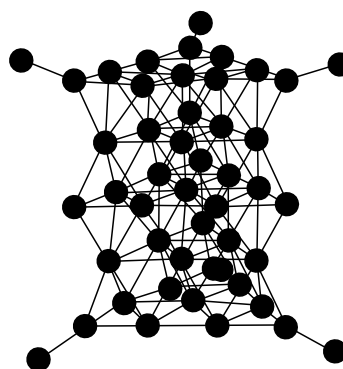


Figure 10. The structure of the metallopolyhedron of the heterometallic cluster anion $(\text{Pd}_{33}\text{Ni}_9(\text{CO})_4(\text{PPh}_3)_6)^{4-}$ according to X-ray diffraction data.¹⁸⁴

The metal atoms in the cluster form five triangular layers and the vertices of the upper, lowest, and middle triangles are occupied by nickel atoms. The carbonyl ligands (not shown in Fig. 10) consist of five terminal and 36 bridging groups the terminal carbonyl being linked to the three nickel atoms of the middle layer and the central palladium atoms of the upper and lowest layers.

2. The reactivity of clusters containing the metal in a fractional formal oxidation state

The reactivity of the clusters under discussion is characterised by two distinctive features: the coordinative unsaturation of the clusters (and hence their ability to coordinate additional ligands) and the ability of clusters containing metal atoms in the lowest oxidation states to enter into oxidative addition reactions.

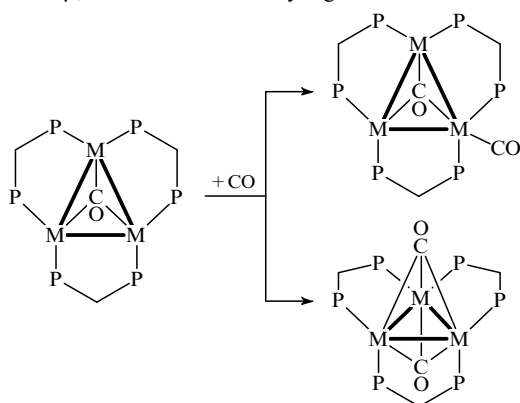
Such features are most characteristic of the type **59** clusters $[\text{M}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$, the reactivity of which has been characterised in fair detail.

a. Coordination of additional ligands

It has been shown that cluster **59** ($M = \text{Pd}$ or Pt) is capable of coordinating two- and four-electron donor ligands and the newly introduced ligands can be both terminal and bridging on the M_3 triangle, or on the sides of this triangle, and their coordination has an appreciable influence on the coordination of the carbonyl ligand.

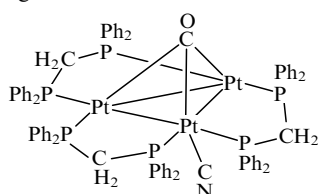
Since cluster **59** and the products of its interaction with various reagents are much more stable in the case where $M = \text{Pt}$ than for $M = \text{Pd}$, the authors were as a rule able to characterise fairly reliably the platinum-containing products, the analogous properties and structures being merely attributed to the palladium complexes.

Thus it has been shown in relation to the platinum complex by NMR involving different nuclei¹⁸⁵ that complex **59** can combine with a second CO molecule with formation of two isomers; the first with terminal and μ_3 -coordinated carbonyls and the second with two μ_3 -coordinated carbonyl ligands:



Phosphines and phosphites (L) are coordinated as monodentate species in reactions with complex **59**, forming $[\text{Pt}_3(\mu_3\text{-CO})(L)(\mu\text{-dppm})_3]^{2+}$. The coordination of the carbonyl group and of the diphosphines does not then change.^{186, 187}

Treatment of cluster **59** ($M = \text{Pd}$ or Pt) with the cyanide ion in acetone solution at -78°C and subsequent heating of the solution to room temperature lead to the formation¹⁸⁸ of the adduct $[\text{M}_3(\text{CN})(\mu_3\text{-CO})(\mu\text{-dppm})_3]^+$. According to X-ray diffraction data for $M = \text{Pt}$, the cyanide ligand in such an adduct is linked to one of the platinum atoms in such a way that the $\text{Pt}-\text{C}-\text{N}$ line is virtually perpendicular to the plane of the Pt_3 triangle.



The study of the behaviour of this adduct by ^{31}P NMR in solution at -90°C showed that the central ligand migrates rapidly around the Pt_3 triangle. This migration is not accompanied by the dissociation of the carbonyl or cyanide ligand and involves in all probability an intermediate with a μ_3 -coordinated cyanide ion.

On interaction of cluster **59** ($M = \text{Pt}$) with isocyanides RNC ,¹⁸⁹ initially one isocyanide molecule is coordinated and then a second one is attached to the same metal atom. On coordination of a second isocyanide molecule, a CO molecule is displaced and the cluster $[\text{Pt}_3(\text{RNC})_2(\mu\text{-dppm})_3]^{2+}$ is formed.

If the isocyanide molecule contains a bulky group, its reaction with complex **59** proceeds in a somewhat different manner.¹⁹⁰ Thus, the interaction of complex **59** ($M = \text{Pd}$) with $\text{XyN}=\text{C}$ ($\text{Xy} = 2,6\text{-C}_6\text{H}_3\text{Me}_2$) results in the formation of $[\text{Pd}_3(\text{XyNC})(\mu\text{-dppm})_3]^{2+}$ **64**, in which the μ_3 - η^2 -isocyanide ligand is coordinated

(according to X-ray diffraction data) over the Pd_3 plane. Cluster **64**, containing 42 valence electrons, combines reversibly with a second isocyanide molecule, forming the 44-electron cluster $[\text{Pd}_3(\mu_3\text{-CNXy})_2(\mu\text{-dppm})_3]^{2+}$. The reaction of complex **59** ($M = \text{Pd}$) with 0.5 mole of $1,4\text{-C}=\text{NC}_6\text{Me}_4\text{N}=\text{C}$ also leads to the substitution of CO. The cationic cluster $\{\text{Pd}_3(\mu\text{-dppm})_3\}_2(\text{CNC}_6\text{Me}_4\text{NC})\}^{4+}$ **65** is then formed. It was isolated in the; form of a salt with PF_6^- or CF_3COO^- . X-Ray diffraction analysis showed that the diisocyanide ligands in complex **65** serve as bridges between the $\text{Pd}_3(\mu\text{-dppm})_3$ species.

By analogy with the isocyanides, the anion SnX_3^- ($X = \text{F}$ or Cl) initially forms the 1:1 adduct $[\text{Pt}_3(\mu_3\text{-CO})(\mu_3\text{-SnX}_3)(\mu\text{-dppm})_3]^+$ in the reaction with complex **59** ($M = \text{Pt}$) and then combines with a second equivalent of SnX_3^- . This leads to the displacement of CO and the formation of $[\text{Pt}_3(\mu_3\text{-SnX}_3)(\mu\text{-dppm})_3]$.^{53, 191}

It has been shown by the NMR method¹⁹² that the interaction of complex **59** and NaBH_4 entails the initial formation of the fragment $[\text{Pt}_3(\mu_3\text{-CO})(\mu_3\text{-H})(\mu\text{-dppm})_3]^+$, which affords $[\text{Pt}_3(\mu_3\text{-H})(\mu\text{-dppm})_3]^+$ after eliminating CO.

The reaction of complex **59** with halide ligands proceeds similarly to the reaction with hydrides but terminates at the first stage. Complex **59** combines with a halide ligand to form $[\text{M}_3(\mu_3\text{-CO})\text{X}(\mu\text{-dppm})_3]^+$. In the case where $M = \text{Pd}$, it has been established by X-ray diffraction study that the halide μ_3 -coordinated to the second side of the Pd_3 triangle is built into the $\text{Pd}_3(\mu_3\text{-CO})(\mu_3\text{-X})$ bipyramid.^{180, 181}

The pseudohalide SCN^- also forms 1:1 adducts, but it has been established by X-ray diffraction that in $[\text{Pt}_3(\mu_3\text{-CO})(\text{SCN})(\mu\text{-dppm})_3]^+$ the thiocyanate ion assumes the role of a terminal ligand coordinated to one metal atom.¹⁹³ Complex **59** does not react directly with diphosphine ligands (even in the presence of their large excess). Other bidentate ligands, such as R_2NCS_2^- and R_3PCS_2^- , form¹⁹⁴ the complexes $[\text{Pt}_3(\mu\text{-CO})(\mu\text{-dppm})_3(\mu\text{-S}_2\text{CNR}_2)]$ or $[\text{Pt}_3(\mu\text{-CO})(\mu\text{-dppm})_3(\mu\text{-S}_2\text{CBr}_3)]^{2+}$.

Thus complex **59** can combine with one- or two-electron ligands or a bidentate four-electron ligand with formation of 44- and 46-electron clusters. On addition of weakly coordinated halide or trifluoroacetate, the number of valence electrons of the cluster may reach 48. In the cluster, the M_3P species is planar and the $M-M$ bond lengths vary within a very narrow range. Additional ligands may bind to complex **59** via the unoccupied P_z orbitals of the metal and not the unoccupied σ^* orbitals of the metal-metal bond of the cluster. This conclusion has been confirmed by a theoretical analysis.^{195, 196} The additional ligands can interact with one, two, or three metal centres, the first case being most frequently encountered. The degree of displacement of the carbonyl group from the symmetrical μ -coordination (expressed by a change in the $M-C$ bond lengths) reflects the donor properties of the additional ligand. It increases in the sequence $\mu_3\text{-I} < \mu_3\text{-}\eta^2\text{-CF}_3\text{COO}^- < \text{SCN}^- < \text{P}(\text{OPh})_3$.

b. Oxidative addition reaction

In the cluster $[\text{M}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$ or $[\text{M}_3(\mu_3\text{-H})(\mu\text{-dppm})_3]^+$, the formal +2 charge is distributed among three metal atoms, which corresponds to a FOS of +2/3. After the removal of a further two electrons from these complexes the formal 4+ charge is distributed among three palladium atoms, which corresponds to a FOS of +4/3. In the oxidised complexes, one of the sides of the metal triangle increases to a size exceeding the sum of the covalent radii of palladium and precluding direct metal-metal interaction. In this case, one may assume that the complexes contain the $(\text{M}_2)^{2+}\text{M}^{2+}$ species, where M^{2+} is linked to the $(\text{M}_2)^{2+}$ cations only via two $\mu\text{-dppm}$ groups and the outer μ_3 -ligand introduced during the oxidation process.

The oxidative addition reactions have been examined in relation to platinum compounds.¹⁹⁷⁻¹⁹⁹ The complex $[\text{Pt}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$ reacts with H_2E or REH ($\text{E} = \text{S}$ or Se , $\text{R} = \text{Et}$ or Ph) with the elimination of the CO molecule and the formation of $[\text{Pt}_3\text{H}(\mu_3\text{-ER})(\mu\text{-dppm})_3]^{2+}$ or $[\text{Pt}_3\text{H}(\mu_3\text{-E})(\mu\text{-dppm})_3]^+$. The

palladium cluster reacts similarly, but the Pd–H bond is more labile and the complexes formed could not be isolated in a crystalline form. The reactions described above are of interest as model processes involving the poisoning of platinum or palladium catalysts by hydrogen sulfide.

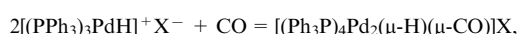
The complex $[\text{M}_3(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$ reacts with SCN^- to form $[\text{M}_3(\mu_3\text{-CO})(\text{SCN})(\mu\text{-dppm})_3]^+$ which undergoes a thermal or photochemical rearrangement¹⁹³ with dissociation of the S–C bond and the formation of $[\text{M}_3(\text{CN})(\mu_3\text{-S})(\mu\text{-dppm})_3]^+$. The mechanism of this reaction has been investigated²⁰⁰ and it has been established that the principal characteristic features of the process extend also to the interaction of complex **59** and the heterocumulenes $\text{S}=\text{C}=\text{E}$ ($\text{E} = \text{N}^-, \text{O}, \text{S}, \text{or NR}$). In all cases, the reaction proceeds with formation of the adduct $[\text{M}_3(\text{S}=\text{C}=\text{E})(\mu_3\text{-CO})(\mu\text{-dppm})_3]^{2+}$, which is followed by the oxidative addition of the heterocumulene to the C=S bond, the elimination of CO, and the appearance of $[\text{M}_3(\mu_3\text{-S})(\text{C}=\text{E})(\text{dppm})_3]^{2+}$.

VII. Palladium carbonyl hydride complexes

The palladium complexes containing simultaneously both carbonyl and hydride ligands are of great interest primarily as possible intermediates (or models of intermediates) in catalytic reactions occurring with participation of carbon monoxide and hydrogen. This is a wide range of processes including the industrially important alkene hydroformylation, alkoxy carbonylation, *etc.* reactions. The carbonyl hydride complexes are believed to be intermediates in the key stages of the processes, but the evidence for the formation of such complexes is extremely scanty or completely absent.^{201–203} There are few reliably characterised palladium carbonyl hydride complexes.²⁰⁴

The first communication about the synthesis of a carbonyl hydride complex appeared as early as 1969.²⁰⁵ A solution of palladium chloride in 2-methoxyethanol was treated with carbon monoxide until the formation of a yellow solution. A brown diamagnetic complex was precipitated on treatment with AsPh_4Cl . The sparing solubility of this complex precluded the study of its ^1H NMR spectra. On the basis of the results of elemental analysis, conductimetric measurements (the compound behaved as a 1 : 1 electrolyte in solution in dimethylformamide), and IR spectroscopic data (the weak band at 1960 cm^{-1} was assigned to the stretching vibrations of the M–H bond, while the intense band at 1900 cm^{-1} was assigned to the stretching vibrations of the terminal CO group), the authors postulated that the compound is the carbonyl hydride $[\text{AsPh}_4][\text{Pd}(\text{CO})(\text{H})\text{Cl}_2]$. In the light of later data on palladium carbonyl and hydride complexes, taking into account the new interpretation of the IR spectra of these compounds (both bands in the IR spectra should be more correctly assigned to the stretching vibrations of bridging groups), this hypothesis appears insufficiently well founded. The complex probably has a more complicated dinuclear structure, particularly since mononuclear compounds are absent among the palladium carbonyl halides described later.

On protonation of $\text{Pd}(\text{PPh}_3)_4$ with aqueous trifluoroacetic acid at 25°C or on reduction of $(\text{PPh}_3)_2\text{Pd}(\text{CF}_3\text{COO})_2$ with hydrogen in solution in aqueous CF_3COOH at 70°C , the complex $[(\text{PPh}_3)_3\text{PdH}]^+$ is formed *in situ*, carbonylation of the complex afforded^{206–208} the carbonyl hydride $[(\text{PPh}_3)_4\text{Pd}_2(\mu\text{-H})(\mu\text{-CO})](\text{CF}_3\text{COO})$ in accordance with the equation



66

$\text{X} = \text{CF}_3\text{COO}.$

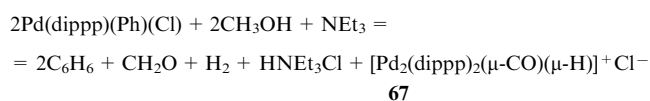
Complex **66** has not been isolated in the solid state but it has been fairly completely characterised by NMR data, which agree well with those for platinum analogues.^{209, 210}

The protonation of $\text{Pd}(\text{PPh}_3)_4$ in toluene under a CO atmosphere or of $(\text{PPh}_3)_3\text{Pd}(\text{CO})$ in toluene on treatment with the sulfonic acid $\text{H}_2\text{C}(\text{SO}_2\text{CF}_3)_2$ also leads to the formation of

complex **66** [$\text{X} = \text{HC}(\text{SO}_2\text{CF}_3)_2$], which has been isolated in the solid state and characterised by elemental analysis and IR spectroscopy ($\nu_{\text{CO}} = 1851\text{ cm}^{-1}$), while the complex in solution in CD_2Cl_2 has been characterised by NMR spectroscopy involving different nuclei.²¹¹

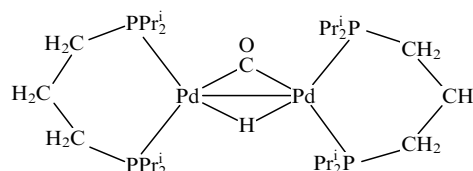
Complex **66** ($\text{X} = \text{BPh}_4$) has been obtained^{212, 213} in a study of the nature of the compounds responsible for the catalysis of the reduction of nitro-compounds by carbon monoxide in the $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{CO}/\text{PhNO}_2/\text{Bu}^n\text{OH}/\text{H}_2\text{SO}_4$ system.

The only palladium carbonyl hydride the structure of which has been investigated by X-ray diffraction has been synthesised^{214, 215} by a fairly unusual method — the interaction of the organopalladium compound $\text{Pd}(\text{dipp})\text{Ph}(\text{Cl})$, where $\text{dipp} = 1,3\text{-bis}(\text{diisopropylphosphino})\text{propane}$, and methanol in the presence of an excess of triethylamine at 60°C in accordance with the equation



Experiments using CH_3OD showed that methanol is in fact the source of hydride ions in the synthesis of complex **67**. The carbonyl groups also arise as a result of the decarbonylation of methanol. The ^1H NMR spectrum of complex **67** contains a signal at $\delta = -5.17\text{ ppm}$ (quintet, $^2J_{\text{P-H}} = 41.1\text{ Hz}$); the IR spectrum contains an intense band at 1789 cm^{-1} , which does not change when the hydride is replaced by deuterium and which has been assigned to the stretching vibrations of the CO group. The relatively low stretching vibrational frequency of the carbonyl group reflects the presence of an increased electron density on the metal atom, arising as a consequence of the high donor capacity of the chelating phosphines.

According to X-ray diffraction data, the two palladium atoms in complex **67** are at a distance of $2.767\text{ \AA}$, indicating a metal–metal single bond.



The hydride ligand is localised and the Pd–H distance is $1.53\text{ \AA}$, which is within the range of distances determined for the structurally characterised palladium hydrides.^{216–218}

A complex analogous to complex **67** has also been obtained by decarbonylating methanol.²¹⁹ On heating to 80°C a solution of the acetyl complex $\text{Pd}(\text{COMe})(\text{Cl})\{(\text{S,S})\text{-bdpp}\}$, where $(\text{S,S})\text{-bdpp} = (2\text{S},4\text{S})\text{-2,4-bis}(\text{diphenylphosphino})\text{pentane}$, in a methanol–toluene- d_8 mixture in an inert gas atmosphere, an equimolar mixture of $(\text{bdpp})\text{PdCl}_2$ and $[\text{Pd}_2(\mu\text{-H})(\mu\text{-CO})(\text{bdpp})_2]^+\text{Cl}^-$ is formed.

The interconversions of the polynuclear palladium hydride and carbonyl hydride complexes have been described.^{2, 220–226} The reduction of $\text{Pd}(\text{OAc})_2$ by molecular hydrogen in glacial acetic acid in the presence of L ($\text{L} = \text{Phen}$ or Bipy) leads to the formation of X-ray-amorphous substances with the approximate composition $[\text{Pd}_4\text{L}(\text{OAc})_2\text{H}_4]_n$, where $n \sim 100$. The reaction of polynuclear hydrides with carbon monoxide leads to the carbonyl hydride clusters $[\text{Pd}_4\text{L}_3(\text{CO})_3(\text{H})_2(\text{OAc})_3]_n$ ($n = 2, 3$). The interaction of CO with a 1 : 1 solution of $\text{Pd}(\text{OAc})_2$ and Phen in acetic acid at 20°C leads to the formation of the complex $[\text{PhenPd}(\text{-CO})(\text{OAc})]_n$, which does not contain hydrides.

If the temperature of the reaction mixture is raised to 50°C , a polymeric carbonyl hydride having the general formula $[(\text{Phen})_2\text{Pd}_2(\text{CO})(\text{H})(\text{OAc})\cdot\text{AcOH}]_n$ is formed; the signal of its hydride hydrogen atoms in the ^1H NMR spectrum is $\delta = -15.5\text{ ppm}$. Finally, the interaction of $\text{Pd}(\text{OAc})_2$ and Phen

in acetic acid under a mixed H_2/CO atmosphere affords the carbonyl hydride $[(\text{Phen})_3\text{Pd}_4(\text{CO})_3\text{H}_3(\text{OAc})_2 \cdot \text{AcOH}]$.

All the carbonyl hydrides have been characterised by elemental analysis and IR, ^1H NMR, and EXAFS spectroscopy. On the basis of the data obtained from these compounds, a structure has been proposed. It is based on tetrahedral palladium fragments with chelating phenanthroline ligands and bridging CO groups, which are linked to one another by bridging hydrides.

Thus the palladium carbonyl hydride complexes described are represented either by dinuclear singly charged cations with bridging carbonyl and hydride ligands or by polynuclear compounds also containing bridging carbonyls and hydrides. In all cases, the FOS of the palladium atoms has an intermediate value between 0 and +2.

VIII. Palladium carbonyl complexes in zeolites

In the early studies devoted to the adsorption of carbon monoxide on palladium(0) deposited on oxide carriers,^{227, 228} it was established that two types of adsorption exist: weak reversible and strong irreversible adsorption. In the former case, the carbon monoxide molecules are involved in terminal coordination according to IR spectroscopic data ($\nu_{\text{CO}} = 2085 \text{ cm}^{-1}$), while in the latter bridging CO groups predominate ($\nu_{\text{CO}} = 1960 \text{ cm}^{-1}$).

The authors of later studies^{229–236} obtained additional data on the structures of palladium carbonyls in the cavities of the NaY and 5A zeolites by employing modern physical research methods (Fourier transform IR spectroscopy, atomic radial distribution methods, and EXAFS), as well as data obtained for the structurally characterised palladium(0) carbonyls. Thus comparative analysis of the IR spectra of compounds of palladium and carbon monoxide, located in the cavities of the NaY zeolites, and data on the molecular clusters of ruthenium and iridium carbonyls in zeolites led to the conclusion that the principal form of the palladium carbonyl consists of the clusters $\text{Pd}_{13}(\text{CO})_x$ containing both bridging and terminal CO groups.²³⁷ The size of the cluster is determined by the size of the zeolite cavity and is almost independent of either the initial form of palladium or of the cluster formation conditions.²³⁰

Subsequent studies by the EXAFS method confirmed the hypothesis that the Pd_{13} clusters predominate. These can have a metal core in the form of both a cubooctahedron and an icosahedron.²³¹ In the initial stage of the formation of the compound on treatment of palladium immobilised on the surface of the zeolite with carbon monoxide at room temperature, the formation of the Pd_6 cluster was observed. The subsequent migration of such clusters and species with a smaller nuclearity into the zeolite cavity leads to Pd_{13} . On raising the temperature to $\sim 200^\circ\text{C}$, there is a possibility of the growth of the metal core right up to Pd_{40} . However, all the conclusions concerning the nuclearity of clusters in the zeolite and their composition and nature are tentative.

It is believed that, under the conditions where the $\text{Pd}_{13}(\text{CO})_x$ clusters are formed on the NaY zeolites, clusters having the composition $\text{Pd}_6(\text{CO})_x$ predominate on the surface of the 5A zeolite. The presence of mainly terminal and μ_3 -bound CO groups is characteristic of $\text{Pd}_6(\text{CO})_x$.²³²

The ability of various zeolites to form palladium carbonyls with different nuclearities has been used in the preparation of catalysts altering the selectivity in various processes. Thus the hydrogenation of CO on Pd/5A leads to methanol and dimethyl ether, whereas the employment of Pt/NaY leads mainly to the formation of C_2 hydrocarbons.²³⁴

IX. Conclusion

The organic chemistry of palladium was initiated by the study of the π -complexes and alkyl derivatives of this metal.²⁰¹ The carbonyl complexes played only a modest role at this stage.

The last quarter of the century has been marked by the development of a series of processes which have found industrial applications or for which prospects for an industrial application exist. Carbon monoxide plays the role of one of the substrates in this series, whilst the active component of the catalytic system consists of palladium compounds.²³⁷

Simultaneously with this field of chemistry, the chemistry of palladium carbonyl complexes developed, its importance growing far beyond the framework determined by utilitarian needs.

The synthesis and study of palladium carbonyl complexes, regarded as a chemical rarity as late as 25 years ago, posed a series of problems before the theory of the chemical bond and of the reactivity of compounds. Modern ideas about the nature of the metal–metal and metal–organic ligand chemical bonds²³⁸ are based in many respects on the existing factual data and the chemistry and structure of platinum group metal carbonyl complexes.

The analysis of these data carried out in the present review has confirmed the existing hypothesis that the stability of polynuclear compounds diminishes with increase in the formal oxidation state of the central atom in palladium carbonyls and hence the number of reliably characterised compounds diminishes sharply on passing from Pd(0) to Pd(+2). Thus, whereas binary carbonyls and mononuclear and polynuclear compounds with various forms of the metal core and all the forms of the coordination of carbonyl ligands have been described for palladium(0), all the known palladium(+2) carbonyls are limited by mononuclear compounds with terminal carbonyl groups.

Among the fairly wide range of methods of synthesis of transition metal carbonyl complexes^{239–241} (direct carbonylation of the metal, reductive carbonylation, oxidative carbonylation, reduction of carbonyl complexes, substitution of ligands *etc.*), only some have been applied in the chemistry of palladium carbonyls, different numbers of compounds being obtained by the application of a particular method. Thus only four complexes have been synthesised by the coprecipitation of palladium metal and CO at low temperatures; the reaction involving the substitution of ligands by carbon monoxide has also been successful in only isolated instances. The method involving the insertion of CO in the metal–metal bond in dinuclear and polynuclear palladium complexes and reductive carbonylation of palladium compounds have proved much more productive. It is noteworthy that the vast majority of compounds have been obtained by the latter method and not only palladium(0) or palladium(+1) complexes but also palladium(+2) complexes.

Palladium(0) carbonyls constitute the most numerous class among palladium carbonyl complexes, polynuclear carbonyls, including also large clusters with several tens of palladium atoms in the metal core, predominating. Probably one of the most important causes of such diversity of the complexes is the stability of the Pd–CO bond determined by the combination of the σ -donor and π -acceptor properties of the CO molecule and the ability of the palladium atom (d^{10} electronic configuration) to donate the electron density from the $3d$ metal orbital to the π^* -orbital of the CO molecule.

The stability of the Pd–CO bond in palladium(+1) complexes, where the metal atom has the d^9 electronic configuration, is lower and hence the number of such complexes is much smaller than that of palladium(0) carbonyls. All the palladium(+1) complexes contain an even number of metal atoms — 2 or 4. They are diamagnetic and the pairing of electrons at the two metal atoms, having the d^9 configuration, occurs either as a result of the formation of a metal–metal bond (with a Pd–Pd distance of $\sim 2.7 \text{ \AA}$) or by the formation of a three-centre four-electron bond incorporating two palladium atoms and one carbon atom of the bridging carbonyl ligand.

The palladium(+1) complexes are fairly sensitive to the action of oxygen-containing nucleophiles and, when treated with, for example, water or lower aliphatic alcohols, they decompose with the formation of palladium metal. The insertion of π -donor

ligands into these complexes promotes an increase in their resistance to reductive decompositions.

In the palladium(+2) complexes where the metal atom has the d^8 electronic configuration and the possibility of the donation of electrons from the metal to the corresponding orbitals of the CO molecule is much smaller than for Pd(0) and Pd(+1), an enhancement of the σ -donor properties of the carbonyl is observed. All the palladium(+2) carbonyl complexes are monomeric with terminal CO groups. The strength of the Pd–CO bond is as a rule small, which leads to a low thermal stability of the complexes. The presence in the palladium(+2) carbonyl complex of groups with strong electron-withdrawing properties, for example SO_3F^- , enhances the electron-accepting properties of the palladium atom and hence leads to an increase in the thermal stability of the complexes.

There are few palladium carbonyl complexes containing the metal in fractional oxidation states. In fact, only compounds having the $\text{Pd}_3(\mu_3\text{-CO})$ core can be regarded as reliably characterised. The reactions involving the coordination of additional ligands are characteristic of these compounds and the newly introduced ligands can be both terminal or can function as μ_3 -bridges on the Pd_3 triangle. Reactions of the second type are oxidative addition reactions. As a consequence of the change in the charge on the Pd_3 triangle, the metal core is altered and the charges are redistributed, which actually leads to a species with nonequivalent metal atoms.

Palladium carbonyl hydrides are of enormous interest primarily as possible intermediates (or models of intermediates) in catalytic processes occurring with participation of carbon monoxide and hydrogen and catalysed by palladium and its compounds. The number of such complexes, which have been postulated in a large number of studies, is small. All the palladium carbonyl hydrides are represented either by dinuclear singly-charged cations with bridging carbonyl and hydride ligands or by polynuclear compounds also containing bridging carbonyl and hydride ligands. In all cases, the FOS of the palladium atoms is intermediate between 0 and +2.

Summarising the data described above concerning the characteristic features of the Pd–CO bond in the carbonyl-containing complexes, one should note that such a bond may be described by several models distinguished by different contributions of the σ - and π -interactions. The symbolism introduced by Willner and Aubke (Fig. 11) appears very clear in the simplest case where the overlap of orbitals in an individual M–CO fragment with CO groups bound as terminal species is considered.²³⁸

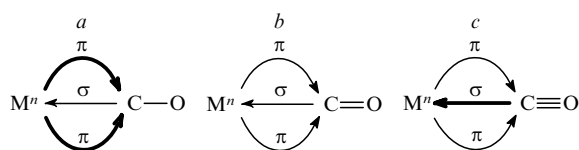


Figure 11. A schematic model of the formation of the bond in the M–CO fragment.

In this scheme, the σ -donor bond arising from the 5σ molecular orbital of CO is shown as an arrow directed from the carbon atom to the metal atom, while the π -acceptor bond, responsible for the donation from the nd_{xz} or nd_{xy} orbital of the metal to the π^* molecular orbitals of CO is shown by arrows directed towards CO. The thin lines indicate a weak bond, whereas thick lines demonstrate the dominant type of bond and the boundary situations. Figure 11a illustrates the dominant π -back-donation (this involves predominantly highly reduced carbonylmetallates), whilst Fig 11c illustrates the predominance of σ -bonding (cationic carbonyls). Figure 11b characterises the bonding in typical metal carbonyls, where the bonds of the types indicated in Fig. 11a and Fig. 11c may overlap depending on the

oxidation state of the metal. Apparently there are at present no physicochemical data which would make it possible to assign the type of bonding in the carbonyl fragments solely to the ' π -interaction' or the ' σ -interaction' and both types of bonding occur in any of the existing compounds.

The palladium carbonyls where the bond might be assigned to the type presented in Fig. 11b and which should have a large positive charge, for example $[\text{M}(\text{CO})_4]^{4+}$ ($\text{M} = \text{Cr}, \text{Mo}, \text{W}$) and $[\text{M}(\text{CO})_4]^{3+}$ ($\text{M} = \text{Co}, \text{Rh}, \text{Ir}$)²⁴² have not so far been described and the possibility of the synthesis of such reduced carbonyl carbonylpalladates appears doubtful. In the vast majority of the palladium carbonyl complexes, the bond is of the type presented in Fig. 11b (the σ - and π -interactions are combined). Only one complex — the palladium(+2) carbonyl complex $[\text{Pd}(\text{CO})_4]^{2+}$ — may be assigned to complexes in which a bond of the Pd–CO type presented in Fig. 11c is achieved. Only in this complex is an anomalously high stretching vibrational frequency of the CO (2248 cm^{-1}) observed, exceeding the value of ν_{CO} for free carbon monoxide.

In the case of all other palladium carbonyl complexes, the energy of the Pd–CO bond and the vibrational frequencies ν_{CO} , indirectly characterising this bond, depend on a whole series of ancillary factors. Thus the vibrations of the terminal CO groups are manifested in the shortest-wavelength region ($2000\text{--}2050\text{ cm}^{-1}$), those of the μ -CO groups are in the middle region ($1850\text{--}\sim 1950\text{ cm}^{-1}$), while the vibrations of the μ_3 -groups are in the longest-wavelength region. The regions corresponding to absorption by the last two types of CO ligands overlap appreciably. Complexes of different nuclearity, containing CO ligands of the same type, do not exhibit stable distinctive features in their IR spectra.

On the other hand, the presence at one atom of only one terminal carbonyl and of three n -donor atoms [for example in $\text{Pd}(\text{CO})(\text{PPh}_3)_3$, $\text{Pd}(\text{CO})(\text{NP}_3)$, and $\text{Pd}(\text{CO})[\text{MeC}(\text{CH}_2\text{PPh}_2)_3]$ leads to a decrease in ν_{CO} to values characteristic of the stretching vibrations of the bridging CO group, *i.e.* the regions of the stretching vibrations of the bridging and terminal carbonyls overlap.

The appearance of strong electron-withdrawing groups increases ν_{CO} to values characteristic of the stretching vibrations of the terminal CO groups. For example, ν_{CO} for the complex $\text{Pd}_4(\mu\text{-CO})_4(\mu\text{-OCOCF}_3)_4$ is 2003 cm^{-1} , which is characteristic of the terminal CO groups. At any rate, bearing in mind the foregoing one should treat with caution the description of the structure of carbonyls and the estimation of the strength of the metal–ligand bond on the basis of spectroscopic data.

The reactivity of palladium carbonyl complexes is restricted to a narrow range of reactions. Thus ligand substitution, which does not lead to a serious structural rearrangement, has been described for all types of palladium carbonyl complexes. Reactions leading to a change in the metal core have been described for polynuclear complexes containing Pd(0), Pd(+1), and palladium in fractional oxidation states, and such changes can occur with decrease or increase in the nuclearity of the complex [for example, the formation of various carbonyl phosphine complexes of palladium(0)] and with retention of the nuclearity [for example, the formation of the tetrahedral complex $[\text{Pd}_4(\text{CO})_2\text{Phen}_4](\text{OAc})_4$ from the carbonyl acetate $\text{Pd}_4(\text{CO})_4(\text{OAc})_4$, which has a rectangular metal core].

The reactivity of the palladium(+1) carbonyl carboxylate complexes has been studied much more widely than for the other complexes. Among the reactions investigated the greatest interest attaches to the oxidative-reduction reactions of the tetranuclear clusters. In the first place, this is the reaction involving the intramolecular transfer of an oxygen atom from the carboxylate ligands to the coordinated carbonyl, which may serve as a model of a whole series of oxidation–reduction processes proceeding with participation of CO and catalysed by palladium compounds.

The extensive field of the chemistry of palladium comprising the synthesis, the structure, and the reactivity of heteronuclear

palladium-containing complexes with carbonyl ligands has remained outside the scope of the present review.

The authors hope that the compilation of data on the synthesis, structures, and properties of palladium carbonyl complexes presented in the review will prove useful not only to chemists occupied with different aspects of the synthesis of carbonyl complexes but also to specialists in the application of these complexes in catalysis and in the study of the details of their electronic structure.

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Open-chain poly(organophosphazenes). Synthesis and properties

S V Vinogradova, D R Tur, V A Vasnev

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Abstract. Various methods for the synthesis of open-chain poly(organophosphazenes) are considered. The mechanism of polymerisation of hexachlorocyclotriphosphazene and the basic principles of formation of poly(organophosphazene) macromolecules by polymeranalogous reactions of poly(dichloro-phosphazene) with various nucleophilic reagents are analysed from a new viewpoint. The potential of this synthetic method for targeted design of poly(organophosphazenes) of various structures is shown. The possibility of synthesising poly(organo-phosphazenes) by polymerisation of cyclophosphazenes is also discussed. The problem of unit non-uniformity of poly(organophosphazenes) and its influence on the properties of these polymers are considered. The properties of poly(organo-phosphazenes) are considered in detail and it is shown that these polymers possess unusual valuable properties, which provide opportunities for their successful practical application. The bibliography includes 276 references.

I. Introduction

Open-chain poly(organophosphazenes) $[-PR_2=N-]_n$ constitute a relatively new class of organoelement polymers. They occupy a peculiar place among organoelement polymers. The inorganic nature of their backbone built of alternating phosphorus and nitrogen atoms and organic framing of the phosphorus atoms determine a number of specific properties in some of these polymers, namely, flexibility combined with elasticity at low temperatures; enhanced flame resistance and low smoke formation, resistance to hydrocarbon fuels and oils, low thrombogenicity, good biocompatibility, and others.

The first representatives of phosphazenes (halophosphazenes) were obtained back in the early XIX century; however, definite progress in the synthesis of poly(organophosphazenes) was achieved only in 1965–1966.

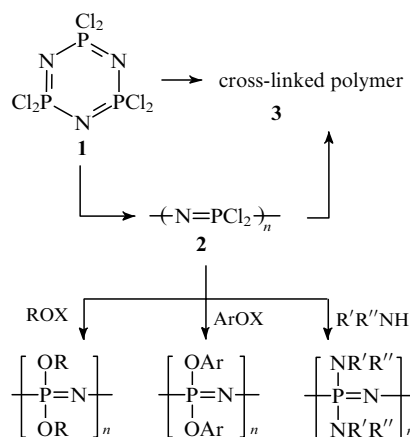
During the last two decades, studies dealing with poly(organophosphazenes) have been vigorously pursued. High-molecular-mass poly(organophosphazenes) with side groups of various structures have been synthesised. Considerable attention is being paid to the basic principles of polymer formation and to comprehensive studies of the properties of poly(organophosphazenes).

The accumulated data certainly need to be generalised. Some aspects concerning the synthesis and properties of polyphosphazenes have been outlined in several reviews.^{1–39}

In this review, we consider the synthesis of various poly(organophosphazenes) and the structure of their macromolecules. The properties of these polymers are discussed as functions of the molecular structure. The prospects for practical application of poly(organophosphazenes) are also presented.

II. Synthesis of polyphosphazenes

The search for new valuable synthetic materials has stimulated the intense development of the chemistry of polyphosphazenes during the last three decades. Considerable attention has been paid to halo-substituted polyphosphazenes, in particular poly(dichloro-phosphazene) (PDCP), which is characterised by a broad high-elasticity region (from -30 to 300°C), low glass transition temperature (-60 to -58°C), non-flammability, etc.^{1, 32, 38, 40, 41} However, since PDCP contains chlorine, it suffers from a serious drawback, namely, instability to hydrolysis: during storage in air, it rapidly and irreversibly ages and loses its properties. However, it was found that the high reactivity of the chlorine atoms in PDCP offers wide opportunities for synthesising new polymeric materials based on it by polymeranalogous transformations. Analysis of the published data demonstrates that the two-stage synthetic scheme shown below (Scheme 1) is



R = Alk, Alk_F; X = H, Na, K, Li; R' = H, R'' = Alk, Ar;
R' = R'' = Alk.

S V Vinogradova, D R Tur, V A Vasnev A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation.
Fax (7-095) 135 50 85. Tel. (7-095) 135 61 78

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currently the most realistic way for preparing high-molecular-mass open-chain poly(organophosphazenes).

In the first stage, high-molecular-mass soluble PDCP **2** is obtained by polymerisation of hexachlorocyclotriphosphazene (HCCTP) **1**. The second stage is a macromolecular reaction of the soluble PDCP with various nucleophilic reagents.

1. General features of the formation of PDCP

Polymerisation of cyclic halophosphazenes with ring opening is a very complicated process. Thermal polymerisation of HCCTP in the melt gives cross-linked PDCP **3** in a high yield (Scheme 1). However, this polymer is not suitable for the synthesis of poly(organophosphazenes), because of the low degrees of conversion of the P–Cl groups in reactions with nucleophilic reagents; hence, these reactions give poly(organophosphazenes) with low hydrolytic stability.

Allcock and Kugel⁴² have shown that the cross-linked polymer **3** is not an immediate product of the polymerisation of HCCTP **1** but it is rather produced from non-cross-linked PDCP **2**. A completely soluble PDCP^{42,43} was obtained by restricting the degree of conversion of HCCTP (heating was terminated at the instant when a decrease in the fluidity of the polymerisation mixture was observed) under strictly controlled temperature conditions. The data listed in Table 1 indicate that raising the temperature accelerates the formation of an insoluble cross-linked polymer.⁴⁴

Table 1. Influence of the temperature and duration of the polymerisation of HCCTP on the yield of soluble PDCP.

Duration/ h	Yield of soluble PDCP (%)	Duration/ h	Yield of soluble PDCP (%)
250 °C		300 °C	
3	12.0	0.08	0
4	13.8	0.25	13.7
5	17.0	0.41	19.3
6	23.4	0.50	27.3
21	30.8	0.66	37.9
48	70.1	1.00	50.3
96	gel	1.17	gel

According to the data of Table 1, polymerisation at 250 °C affords the cross-linked polymer over a period of 96 h, while at 300 °C this product is formed in 1.17 h.

Numerous attempts have been made to select catalysts for the polymerisation of HCCTP that would enable conducting it under milder conditions.^{1,8,9,32,37} However, these attempts have not met with success so far. Therefore, thermal polymerisation of chlorocyclophosphazenes still remains the main method for the preparation of PDCP.

Meanwhile, this method for the synthesis of PDCP suffers from one more serious drawback: the results of polymerisation are not reproducible. The yields of soluble PDCP obtained by various researchers under seemingly identical conditions vary over wide limits (from 5% to 70%).^{2,44–47}

Various opinions about the structure of soluble PDCP have been expressed.^{1–4,32} Apparently, the polymerisation product (before gelation) is a polymer with a fairly heterogeneous structure, characterised by variable and hardly controllable unit non-uniformity.² Most likely, this accounts for the irreproducibility of the yield and the properties of both PDCP itself and poly(organophosphazenes) based on it.^{12,45,48–51} Therefore, it is important to study the mechanism of polymerisation of HCCTP and side reactions resulting in the formation of branched and cross-linked polymers, in order to find the ways of controlling these processes.

The possible mechanisms of polymerisation of HCCTP have been discussed in earlier reviews;^{2,12} however, there is still no agreement on this point.^{1,2,8,12,32,46,52–54} Here we discuss the

mechanism that appears most probable from our viewpoint. A special study aimed at elucidating the influence of the residual water on the polymerisation of HCCTP in a closed system has revealed interesting and fundamental features of this process.^{2,45} It was found that the intrinsic viscosity of the PDCP formed depends on the experimental conditions and on the amounts of water and the evolved hydrogen chloride in the system; this implies that polymerisation might be catalysed by hydrogen chloride.^{2,45,50}

It has been found⁵⁵ that hydrolysis of the P–Cl bonds in HCCTP at 250 °C occurs only when the reaction mixture contains admixed higher chlorocyclophosphazenes, for example, octachlorocyclotetraphosphazene (OCCTP). Controversial opinions have been expressed in the literature about the role of this compound in the polymerisation of HCCTP. In fact, both accelerating⁵⁶ and inhibiting⁵⁷ effects as well as the absence of any activity during the polymerisation⁵⁸ have been reported for this tetramer.

Detailed study of this point has shown that the so-called ‘non-catalytic’ polymerisation of HCCTP **1** is catalysed, in reality, by the hydrogen chloride resulting from hydrolysis of the P–Cl bonds in OCCTP by the residual water.⁵⁵ There exist the optimum quantities of the tetramer and the residual water needed for successful polymerisation of the trimer. None of the reaction mechanisms proposed previously for the polymerisation of HCCTP did imply active participation of hydrogen chloride.²

It was found that highly pure HCCTP (containing ~10^{–3} mol.% of OCCTP) neither undergoes hydrolysis nor polymerises at a noticeable rate under the conditions of formation of virtually linear poly(dichlorophosphazene) (250 °C, 50 h).^{45,49} The optimum quantity of OCCTP is ~0.1 mol.%–0.2 mol.% (Table 2), which corresponds to the amount of residual water in the polymerisation vessels. Larger amounts of the tetramer markedly retard the polymerisation of HCCTP.

The known fact that the tetramer is more readily hydrolysed

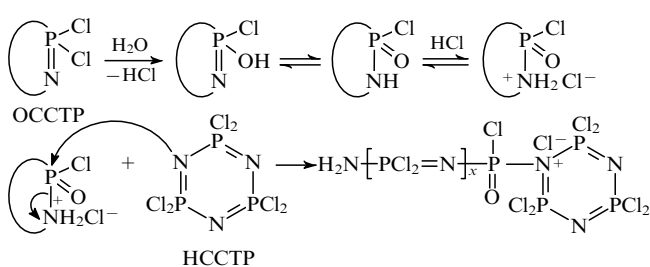
Table 2. Results of polymerisation of HCCTP in the presence of various amounts of OCCTP (250 °C, 50 h).

Amount of OCCTP mixed with HCCTP (mol.%)		Yield of PDCP (%)	Intrinsic viscosity of PDCP in toluene (25 °C)/ dl g ^{–1}
total	especially admixed		
0.003	0	< 1	—
0.004	0	< 1	—
0.048	0	42	4.10
0.078	0.075	45	5.04
0.083	0.080	74	4.25
0.103	0.100	63	4.40
0.120	0	63	5.10
0.290	0	12	0.71
0.383	0.380	< 1	—
0.563	0.560	< 1	—

than the trimer **1** was rationalised based on electronic effects.⁵⁵ Study of the electronic structure by the extended Hückel method demonstrated that the P–Cl bond in OCCTP is weaker than that in HCCTP (the Mulliken populations are 0.687 and 0.724, respectively).

The above results provided grounds for the conclusion that OCCTP plays a dual role in the polymerisation of HCCTP: it acts as the source of the catalyst (hydrogen chloride) needed for the chain growth to start and as an inhibitor of the polymer growth. Thus, the process of HCCTP polymerisation could be controlled by varying the ratio of the residual water and OCCTP in the system.⁵⁵ The mechanism of polymerisation of HCCTP in the

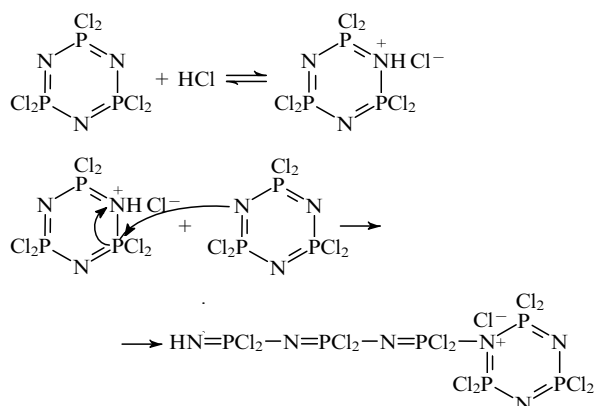
Scheme 2



presence of OCCTP, water, and hydrogen chloride^{2, 12, 50} is presented in Scheme 2.

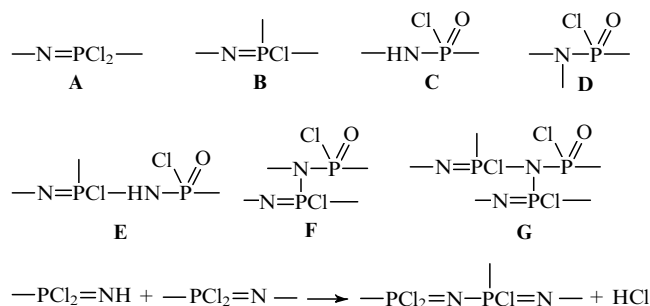
The first step of the reaction is hydrolysis of the P–Cl bonds in OCCTP by the residual water, which gives gaseous hydrogen chloride and hydroxyphosphazene, the latter being converted into the tautomeric oxophosphazane form. The subsequent protonation of the oxophosphazane ring with hydrogen chloride and the nucleophilic attack by the nitrogen atom of the phosphazene ring of HCCTP results in opening of the oxophosphazane ring and onset of the growth of a polymeric chain containing a terminal amino group. The chain growth occurs through subsequent addition of HCCTP molecules to the active site. When hydrolysis of the P–Cl bonds does not occur but HCl is present,⁵⁰ the phosphazene ring is also protonated; this yields molecules with terminal imino groups (Scheme 3).

Scheme 3



This mechanism of chain initiation and growth⁴⁵ is formally consistent with the view about the ionic character of the polymerisation of HCCTP but implies a completely different chemistry of this process. The possibility of polymerisation according to two pathways is fundamentally important, because it opens up way of controlling this process.^{2, 12, 50} In fact, if the reaction starts with hydrolysis of the P–Cl bonds of the ring, this affords polymeric chains with terminal amino groups. These terminal groups can react with the P–Cl bonds of adjacent macromolecules; this accounts for side reactions. Due to these processes and also to the participation of oxophosphazane rings in the polymer chain growth, anomalous units of types **B–G** arise in the polymer, together with the predominant units of type **A**. Eventually, this leads to the formation of polydichlorophosphazene with a fairly high unit non-uniformity, to poor reproducibility of the experimental results, and to relatively low yields of the soluble polymer.

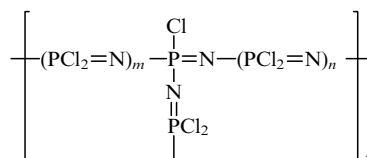
It is promising to carry out the polymerisation process under conditions permitting no hydrolysis; in this case, the reaction starts with protonation of the phosphazene ring with hydrogen chloride. This permits the preparation of PDCP with more inert terminal imino groups and, hence, with a more perfect defectless final chemical structure.



Elucidation of the mechanism of polymerisation of HCCTP made it possible to find a practical method for controlling the synthesis of PDCP; this method ensures good reproducibility of the results and the formation of a practically linear PDCP with molecular masses of about $(5-10) \times 10^6$ and with a much narrower molecular-mass distribution ($M_w/M_n < 1.4$) compared to that of the polyphosphazenes described previously ($M_w/M_n \approx 7-79$ ^{3, 33, 59-63}), its yield being more than 80%.^{2, 12, 50}

The problem was solved by preliminary removal of water from the reaction system; for this purpose, the residual water was made to react with the P–Cl groups of chlorocyclophosphazene and then the resulting phosphazene derivatives containing hydrolysed fragments, which are the main source of side reactions, were separated from the reaction mixture. Polymerisation was carried out at 250 °C in a jointless Pyrex apparatus.⁴⁹ In this case, hydrogen chloride needed to initiate the polymer chain growth is retained in the reaction system.

The study of the polymerisation process has shown that the intrinsic viscosity of PDCP decreases, whereas the Huggins constant simultaneously increases following an increase in the polymerisation time. This apparently indicates that at larger degrees of conversion, branched PDCP molecules are formed.⁵⁰



The content of branched molecules and the unit non-uniformity of the polymer depend on the experimental conditions [the extent to which the reaction tubes are filled with the monomer, quantity of the catalyst (hydrogen chloride), temperature, and reaction time].

The influence of the duration of the process in a preheated polymerisation system on the yield and intrinsic viscosity of PDCP and its fluoroalkoxy-derivatives has been studied.⁶³ A nearly quantitative degree of conversion of the trimer (97%) is attained when the polymerisation is carried out for 130 h (250 °C), the resulting PDCP being completely soluble in benzene and toluene. The high degrees of polymerisation $[(4-5) \times 10^5]$ and also the fact that the molecular-mass distribution curves of various PDCP samples at low degrees of conversion of the trimer virtually coincide, together with the narrow molecular-mass distribution of the polymer, imply that the chain growth reaction occurs much faster than competing side processes. The results obtained led the researchers⁶³ to the conclusion about a cationic mechanism of HCCTP polymerisation in the melt. The same mechanism was proposed for the polymerisation of the trimer carried out in solution in 1,2,3-trichlorobenzene in the presence of sulfamic acid, ammonium sulfamate, toluenesulfonic acid, and other catalysts.⁶⁴

The polymerisation of HCCTP in the melt at 250 °C has been studied by electron microscopy.⁶⁵ In the early stages of the reaction, large spherical particles were detected, indicating a high

rate of chain growth. It was noted that poly(dichlorophosphazene) specimens prepared by the conventional procedure (method A) differ markedly from those obtained with preliminary removal of the residual water and the phosphazene products of hydrolysis from the reaction medium (method B).^{49, 50} The formation of an organised supermolecular structure in the polymer synthesised by method A is apparently hampered by the presence of cross-links between its macromolecules. On the contrary, in the case of the material prepared by method B, supermolecular associates of the lamellar type can be clearly seen in some parts of the electron photomicrography. Thus, the structure of PDCP in the aggregated state obtained at high degrees of polymerisation depends on the synthetic procedure used.

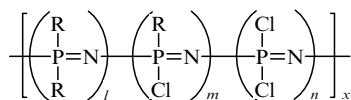
In general, it should be noted that despite the certain progress achieved in the synthesis of PDCP suitable for subsequent polymeranalogous substitution reactions, numerous important problems still need to be solved. The search for efficient catalysts for the thermal polymerisation of HCCTP, which would permit decreasing the reaction temperature and duration and increasing the yield of soluble PDCP, appears a promising and important aspect of investigations.

2. Synthesis of poly(organophosphazenes) based on poly(dichlorophosphazene)

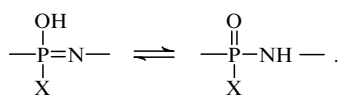
The commonest and most available method for the synthesis of poly(organophosphazenes) is the polymeranalogous substitution of chlorine in PDCP. It should be noted that the regularities of these reactions have not yet been adequately studied, and the majority of published data on the synthesis of poly(organophosphazenes) reduces mostly to the description of the procedures used to prepare one or another particular polymer.

An important characteristics of poly(organophosphazenes) is the possible unit non-uniformity.^{2, 3, 12, 14} The properties of these polymers are known to depend on the presence of a small number of anomalous units in their chains.

The anomalous units can arise for several reasons during the synthesis of poly(organophosphazenes) from PDCP and have different chemical structures. First of all, these are branching points, which were present in the initial polymer. The data on the influence of branching points on the properties of poly(organophosphazenes) available to date are scarce, probably, since there are no sufficiently strict characteristics for them. However, this type of unit non-uniformity can be virtually eliminated by using linear PDCP in the polymeranalogous transformations. Yet another type of anomalous units arises due to incomplete substitution of the chlorine atoms in PDCP. This affords non-uniform polymers, which contain partially substituted and non-substituted chain units, in addition to the completely substituted ones.



The presence of even small proportions of the anomalous units (< 1 mol. %) with non-substituted P–Cl groups substantially decreases thermal, hydrolytic, and thermohydrolytic stabilities of poly(fluoroalkoxy- and poly(aryloxy-phosphazenes) and also facilitates their decomposition during photolysis.^{3, 12} Hydrolysis proceeding as a side process can lead to the formation of anomalous partially hydrolysed units, which occur in the polymer chain as two tautomeric forms



These units are even less stable and promote destruction of the polymeric chains.

Due to the diversity of anomalous units arising during the synthesis of poly(organophosphazenes), it is difficult to obtain well-reproducible results. Therefore, to obtain poly(organophosphazenes) possessing valuable properties, one should conduct the polymeranalogous substitution up to very high degrees of conversion under conditions ensuring almost complete suppression of hydrolysis.

The polymeranalogous substitution of chlorine in PDCP by fluoroalkoxy groups has been studied in most detail (see early reviews^{2, 3}). Sodium,^{3, 42, 44, 46, 47, 66–76} potassium,^{75, 77, 78} and lithium^{36, 74, 75, 77, 79–81} alkoxides and also fluorinated alcohols (in the presence of triethylamine) have been used as nucleophilic agents.^{3, 48, 82}

Since some regularities of the formation of poly(fluoroalkoxyphosphazenes) have been considered in our previous review,³ we do not discuss them here. We only would like to mention that the degree of chlorine substitution and the occurrence of the extremely undesirable side reactions of hydrolysis during the polymeranalogous substitution of chlorine in PDCP by sodium trifluoroethoxide, depend appreciably on the experimental conditions.^{69, 76, 83–85} The efficiency of these reactions is largely determined by the reaction medium, temperature, and duration of substitution. The amount of water in the reaction system (even at the level 10^{–2} vol. %–10^{–3} vol. %) is also significant. Hydrolysis is suppressed most efficiently when the reaction is carried out at room temperature and lasts for no more than 3 h when poly(fluoroalkoxyphosphazene) precipitates, for example, from a toluene–tetrahydrofuran solvent mixture during the process, and when all the reactants and reaction vessels have been thoroughly dried before the process.^{5, 83} The latter problem has been successfully solved, for instance, by using molecular sieves as desiccants.^{83, 86} The molecular-mass characteristics of the resulting polymer remained unchanged during the subsequent high-temperature hydrolysis in boiling aqueous acetone, indicating that the use of molecular sieves as desiccants had ensured virtually complete suppression of hydrolysis during the synthesis of poly(fluoroalkoxyphosphazenes). In particular, poly[bis(tri-fluoroethoxy)phosphazene] (PBTFEP) with a residual chlorine content of 0.04 mass % and a molecular mass of 10⁷ was obtained in this way. The molecular-mass characteristics of the polymer did not change after boiling in 10% aqueous acetone for 10 h.⁸⁶

Hydrolytic processes play a crucial role in the synthesis of poly(fluoroalkoxyphosphazenes) regarding the possibility of producing high-molecular-mass polymers. It has been noted (Table 3) that when the degree of hydrolysis of the P–Cl groups is less than 1 × 10^{–4}%, the molecular mass of PBTFPP is practically insensitive to hydrolytic destruction. The increase in the degree of conversion to ~1 × 10^{–3}% may decrease the molecular mass by a factor of two, and when the degree of conversion is ~1 × 10^{–2}%, even by a factor of ten.¹⁴

Table 3. Influence of the degree of conversion of P–Cl groups in side hydrolysis reactions on the molecular mass of poly[bis(tetrafluoropropoxy)phosphazene] (PBTFPP) according to Ref. 14.

Number of macromolecules (%)	Number of P–C groups in a macromolecule	Degree of conversion of P–Cl groups	10 ⁶ $\bar{M}_n$	Intrinsic viscosity $[\eta]^a$ of PBTFPP in THF/dl g ^{–1}
0	0	0	13.2	6.94
1	1	1.16 × 10 ^{–5}	13.1	6.89
10	1	1.16 × 10 ^{–4}	12.0	6.40
100	1	1.16 × 10 ^{–3}	6.6	3.85
100	10	1.16 × 10 ^{–2}	1.2	0.90

^a $[\eta] = 6.15 \times 10^{-6} M^{0.85}$ (Ref. 59).

Table 4. Conditions of synthesis and characteristics of some poly(alkoxyphosphazenes) (PAP).

Nucleophilic agent	Reaction medium	$T/^\circ\text{C}$	$[\eta]$ of PDCP/ dl g ⁻¹ (toluene, 25 °C)	Characteristics of PAP		
				$[\eta]$ / dl g ⁻¹ (THF, 25 °C)	Cl content ^a (mass %)	content of P–Cl groups ^b (mol.%)
C ₃ H ₇ ONa	CH ₃ C ₆ H ₅ –C ₃ H ₇ OH	95	4.10	3.30	< 0.01	< 0.02
C ₄ H ₉ ONa	CH ₃ C ₆ H ₅ –THF	25	3.50	0.36	6.85	17.21
C ₄ H ₉ ONa	CH ₃ C ₆ H ₅	25	5.74	0.53	5.26	11.40
C ₄ H ₉ ONa	CH ₃ C ₆ H ₅ –C ₄ H ₉ OH	110	5.74	4.03	< 0.01	< 0.02
C ₇ H ₁₅ ONa	CH ₃ C ₆ H ₅ –C ₇ H ₁₅ OH	110	4.10	5.62	< 0.01	< 0.03
C ₂ H ₅ OC ₂ H ₄ ONa	CH ₃ C ₆ H ₅	25	5.74	0.98	0.70	1.80
C ₂ H ₅ OC ₂ H ₄ ONa	CH ₃ C ₆ H ₅ –C ₂ H ₅ OC ₂ H ₄ OH	60	4.40	7.90	1.23	3.80
C ₂ H ₅ OC ₂ H ₄ OLi	CH ₃ C ₆ H ₅ –C ₂ H ₅ OC ₂ H ₄ OH	100	4.40	Insoluble	< 0.01	< 0.03

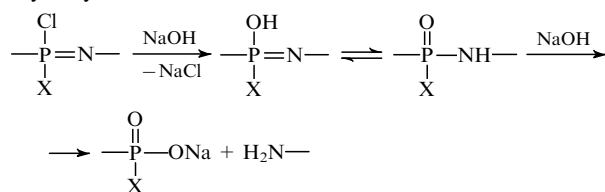
Note. Duration of the synthesis — 3 h; amount of sodium alkoxide — 3 moles per mole of P–Cl groups, concentration of PDCP in toluene — 0.17 mol litre⁻¹, concentration of the alkoxide in alcohol — 2.5 mol litre⁻¹. ^aDetermined by coulometric titration. ^bQuantity of P–OH groups in the samples < 0.1 mol.%.

Whereas synthesis and properties of poly(fluoroalkoxyphosphazenes) have been considered in a large number of papers (see reviews ^{1,3}), non-fluorinated poly(alkoxyphosphazenes) (PAP) have been much less studied. However, since ordinary alcohols are more accessible than fluorinated ones, it was highly desirable to study the synthesis of this type of poly(organophosphazenes). Data on the synthesis and properties of PAP can be found in a number of publications.^{44, 87–100}

To develop methods for the synthesis of high-molecular-mass PAP, a systematic study on the condensation of high-molecular-mass PDCP with several sodium alkoxides has been undertaken.⁹⁰ Data on the influence of the conditions of synthesis of PAP on the degree of conversion of the P–Cl groups in PDCP and on the intrinsic viscosity of the resulting polymers are listed in Table 4.^{90, 91}

It was found that the extent of substitution of the chlorine atoms in PDCP by alkoxy groups is much more dependent on the temperature and duration of the reaction, on the chemical nature of the nucleophilic reagent, and on the polarity of the reaction medium than similar substitution by fluoroalkoxy groups. Thus under the conditions optimum for the synthesis of poly(fluoroalkoxyphosphazenes),³ namely, when the reaction is carried out in a THF–toluene mixture at 25 °C for 3 h, the degree of conversion of the P–Cl groups into P–OC₄H₉ groups is only ~80%. This process was found to be best conducted in a mixture of toluene with the corresponding alcohol. In particular, in a mixture of toluene and butanol, the degree of conversion of the P–Cl groups at 110 °C is as high as > 99.98% over a period of 3 h and, what is especially important, these results are well reproducible.

It should be taken into account that in the synthesis of PAP, the problem of side reactions of hydrolysis proves to be much more complicated. Unlike the acidity of fluorinated alcohols, that of ordinary alcohols ($pK_a \approx 16–18$, in water) is nearly equal to or less than the acidity of water. Therefore, the reaction of the residual water with alkoxides affords NaOH, which causes the side hydrolysis.



X = Cl, OAlk.

The efficiency of hydrolysis is determined by the amount of residual water in the reaction system and by the ratio of the main and side reaction rates. The side reactions occur to the least degree when all the reactants and equipment have been thoroughly dried

prior to the reaction and when the experimental conditions employed ensure a high rate of the main reaction.⁹⁰

The set of identified regularities made it possible to synthesise successfully high-molecular-mass PAP with a low content of defective units (P–Cl, P–OH, P=O)^{90–93} as a result of the high degree of conversion of the P–Cl groups in the initial PDCP. The conditions used to synthesise PAP are presented in Tables 4 and 5.^{90–92}

Table 5. Conditions of synthesis and characteristics of poly(alkoxyphosphazenes) $[-P(OR)_2-N-]_n$.

OR	Conditions of synthesis		$[\eta]$ / dl g ⁻¹ (THF, 25 °C)	Content /mol. %	
	$T/^\circ\text{C}$	t/h		P–Cl ^a	P–OH ^b
OCH ₃	60	6	2.93	0.04	2.0
OC ₂ H ₅	70	5	6.50	0.06	2.7
OC ₃ H ₇	80	3	3.30	0.02	0.2
OC ₃ H ₇ ^c	80	3	1.36	0.02	2.1
OC ₄ H ₉	110	3	3.70	0.03	0.1
OC ₄ H ₉ ^c	110	3	2.70	0.03	2.7
OC ₅ H ₁₁	110	3	4.08	0.03	0.1
OC ₆ H ₁₃	110	3	5.62	0.03	0.1
OC ₇ H ₁₅	110	3	4.50	0.04	0.1
OC ₈ H ₁₇	110	3	6.07	0.04	0.1

Note. The reaction medium was CH₃C₆H₅–ROH (0.18 mol of RONa and 72 ml of ROH; 0.02 moles of PDCP in 116 ml of toluene); the intrinsic viscosity of PDCP in toluene at 25 °C was 4.1 dl g⁻¹. ^aCalculated from the content of chlorine found by coulometric titration. ^bFound by ¹H NMR. ^cContent of water in the system was > 3 × 10⁻³ vol.%; in other cases, it was < 3 × 10⁻³ vol.%.

A significant factor influencing the rate and the degree of substitution in the alcoholysis of PDCP is the reactivity of the P–Cl groups in the polyphosphazene, which can vary during the reaction under the influence of converted groups:^{14, 101, 102} the neighbouring group at the same phosphorus atom ('close neighbour' effect) and groups at the adjacent phosphorus atoms ('far neighbour' effect). The effects of neighbouring groups determine the structure of anomalous non-substituted units in the chain. Thus it has been found that fluoroalkoxy groups exert an accelerating 'close neighbour' effect in the alcoholysis of PDCP.¹⁰² Consequently, the resulting poly(fluoroalkoxy-phosphazenes), in addition to the completely substituted units, contain the original units with two chlorine atoms attached to phosphorus (–PCl₂–N–) even at high degrees of conversion of the P–Cl groups (> 99.9%). The results of quantum-chemical calculations led to

the suggestion that the accelerating influence of the neighbouring fluoroalkoxy groups during the polymeranalogous substitution in poly(dichlorophosphazene) is mostly due to polar effects.¹⁰² Unlike fluoroalkoxy groups, ordinary alkoxy groups exert a decelerating 'close neighbour' effect; as a result, the PAP formed contain partially substituted units of the type $-\text{PCl}(\text{OAlk})=\text{N}-$. Thus, for the same degree of conversion of the P–Cl groups in PDCP, the number of anomalous units in PAP is twice that in poly(fluoroalkoxyphosphazenes). In addition, extensive substitution of chlorines in PDCP by ordinary alkoxides requires more drastic conditions including elevated temperatures.⁹⁰ Due to the high activity and equal reactivity of chlorine atoms in the initial PDCP, the 'far neighbour' effect in the alcoholysis reactions is less pronounced than the 'close neighbour' effect. Like the behaviour in alcoholysis, the hydrolytic stability of the anomalous units with non-substituted P–Cl groups and, hence, the stability and reproducibility of the properties of poly(organophosphazenes), also depend on the effect of neighbouring groups.¹⁴

The microstructures of three specimens of PBTFFP with different degrees of conversion of the P–Cl groups, prepared at molar ratios of the P–Cl groups to sodium 2,2,3,3-tetrafluoropropoxide of 1:0.25, 1:0.50, and 1:0.75, have been studied by ³¹P NMR spectroscopy.¹⁰¹ It was found that the distribution of the $-\text{PCl}_2=\text{N}-$ (A) and $-\text{P}(\text{OR})_2=\text{N}-$ (B) units along the chain can be sketched as follows:

(a) for 25% degree of conversion

...AAAAA... → ...BAAABAAA...BBAAAAA...

(b) for 50% degree of conversion

...AAAAA... → ...BBAABBA...

(c) for 75% degree of conversion

...AAAAA... → ...BBBABBA...

When the degree of conversion is 25%, the polymer consists mostly of AAA triads and B units, small proportions of BB diads and AAAAA hexads being also present. In the case of 50% conversion, alternation of AA and BB diads predominates in the chain. At 75% conversion, triads BBB are separated by the initial A units.

The presence of the initial units A in poly(fluoroalkoxyphosphazenes) even at high degrees of conversion of the P–Cl groups is in good agreement with the data¹⁰³ on the photolysis of poly[bis(trifluoroethoxy)phosphazene]. According to these data, the destruction products contain chloro(trifluoroethoxy)cyclotriphosphazene with two geminal chlorine atoms.¹⁰³

The course of the polymeranalogous substitution of chlorine in PDCP depends appreciably on the chemical nature of the substituting reagent.^{80, 81, 101–109}

Fig. 1 presents the results of interaction of PDCP with lithium 2,2,3,3-tetrafluoropropoxide, phenoxide, and *o*-allylphenoxide.¹⁰⁵ It can be seen that a 96% degree of substitution of the chlorine in PDCP by tetrafluoropropoxy groups is attained as soon as after 15 min. The replacement of chlorine by phenoxy groups under similar conditions occurs efficiently during the first 2 h up to 50% degree of conversion. After 24 h, the degree of substitution increases only to 60%, and then the reaction sharply slows down. When lithium *o*-allylphenoxide is used in this reaction, the process is decelerated as soon as after a 25–30% degree of substitution.^{105, 106} A ³¹P NMR study of the nucleophilic substitution of the chlorine atoms in PDCP by the phenoxy groups has shown that one chlorine atom at each phosphorus atom is replaced first, and the polymer formed after 24 h is mostly built of $[-\text{N}=\text{PCl}(\text{OC}_6\text{H}_5)-]$ units. The substantial decrease in the reaction rate observed with phenoxides is apparently due to the fact that the chlorine atoms, the close environment of which consists of phenoxy groups, are less reactive towards subsequent nucleophilic attacks of both the phenoxide groups and other nucleophiles. In fact, unlike the initial PDCP, poly[chloro-(phe-

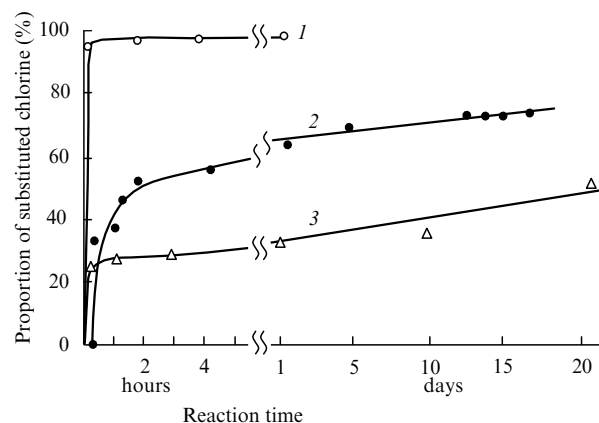


Figure 1. Dependence of the degree of substitution of chlorine atoms in PDCP (THF solution, concentration 0.5 mol litre⁻¹) on the duration of its reaction with a threefold molar amount of lithium tetrafluoropropoxide (1), phenoxide (2), and *o*-allylphenoxide (3) (THF solutions, concentration 2 mol litre⁻¹) at 20 °C.

noxy)phosphazene] is relatively stable to hydrolysis.¹⁰⁵ When it is made to react with lithium tetrafluoropropoxide under the conditions outlined above (reaction time 24 h), the polymers formed contain much more chlorine (6.64%) than poly(tetrafluoropropoxyphosphazene) (chlorine content < 1.00%). This indicates that chlorine in poly[chloro(phenoxy)-phosphazene] is less reactive than that in poly[chloro(tetrafluoro-propoxy)phosphazene].¹⁰⁵

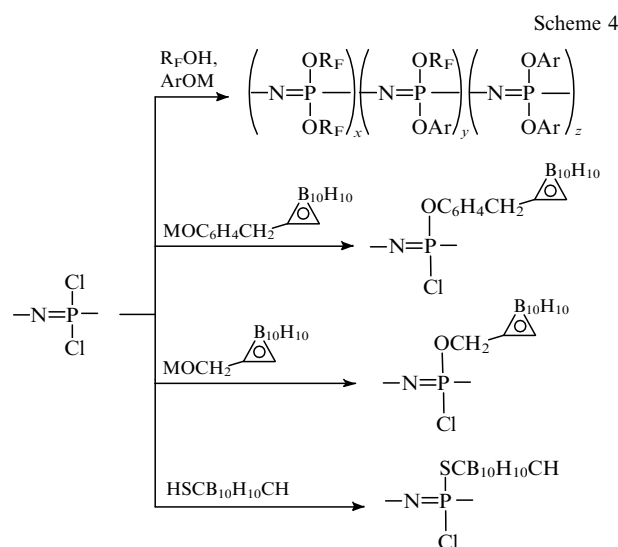
When poly(organophosphazenes) are synthesised by simultaneous addition to PDCP of a mixture of lithium tetrafluoropropoxide and lithium phenoxide, taken in a molar ratio of 1:1, a large portion of lithium phenoxide remains unreacted, and according to elemental analysis, the repeating unit of the resulting polymer can be represented as $\text{NP}(\text{OC}_6\text{H}_5)_{0.5}(\text{OCH}_2\text{CF}_2\text{CF}_2\text{H})_{1.5}\text{Cl}_{0.2}$. Thus, under the conditions of competitive nucleophilic substitution, the probability of formation of the $-\text{N}=\text{P}(\text{OCH}_2\text{CF}_2\text{CF}_2\text{H})$. $(\text{OC}_6\text{H}_5)-$ units or, especially, the $-\text{N}=\text{P}(\text{OC}_6\text{H}_5)_2-$ units dramatically decreases,^{80, 105} and thus the polymer becomes enriched in units containing the more reactive nucleophilic reagent; in this particular case, it is tetrafluoropropoxide. Based on the data of ³¹P NMR spectroscopy,⁸⁰ it can be assumed that competitive substitution yields a random heterounit polymer containing phosphorus atoms with different environments.



OR = $\text{OCH}_2\text{CF}_2\text{CF}_2\text{H}$, OAr = OC_6H_5 .

It was shown⁸⁰ that the final structure of poly(organophosphazenes) depends on the order in which nucleophilic reagents are introduced in the reaction medium. To prepare a poly(organophosphazene) with mixed phosphorus environments of a specified composition, the less reactive reagent should be introduced first in the reaction area, and the process should be carried out until the desired degree of substitution is attained. Then the more reactive component should be added (the first equation in Scheme 4).

Let us consider a particular aspect concerning the synthesis of poly(organophosphazenes) with mixed structures. Recently it has been reported¹⁰⁷ that the reaction carried out in the presence of tetra-*n*-butylammonium bromide or 15-crown-5 ether is complicated by the fact that the phenoxy groups in the $-\text{NP}(\text{OCH}_2\text{CF}_3)(\text{OC}_6\text{H}_5)-$ fragments formed can be replaced by trifluoroethoxy groups and that an excess of sodium trifluoroethoxide results in replacement of the phenoxy groups in the $-\text{NP}(\text{OCH}_2\text{CF}_3)(\text{OC}_6\text{H}_5)-$ units but not in $-\text{NP}(\text{OC}_6\text{H}_5)_2-$. This



$R_F = \text{CH}_2\text{CF}_2\text{CF}_2\text{H}, \text{CH}_2\text{CF}_3$;
 $\text{Ar} = \text{C}_6\text{H}_5, \text{C}_6\text{H}_4\text{Cl}, \text{C}_6\text{H}_4\text{CH}_2-\text{CH}=\text{CH}_2$;
 $M = \text{Na}, \text{Li}$.

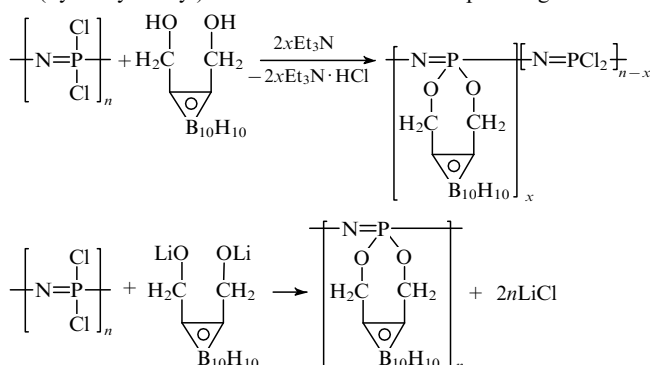
exchange is markedly retarded after a certain number of phenoxy groups have been substituted. The same investigators noted that tetra-*n*-butylammonium bromide can be successfully used as an agent accelerating the synthesis of poly(organophosphazenes) with bulky side groups or in those cases where chlorine is substituted by weak nucleophiles.

Carborane-containing poly(organophosphazenes) have been synthesised using lithium derivatives of phenyl-*o*-carborane and -*m*-carborane, *m*-carboranethiol, lithium *o*-carboranylmethoxide, and lithium *o*-carboranylmethylphenoxide, as well as bis(hydroxymethyl)-*o*-carborane and its lithium derivative as the nucleophilic reagents.^{108–112} The reactions involving lithium derivatives of phenyl-*o*-carborane and -*m*-carborane yielded products, the structure of which could not be determined, since they were highly unstable.¹⁰⁸ The use of lithium *m*-carboranylmethoxide, lithium *o*-carboranylmethoxide, and lithium *o*-carboranylmethylphenoxide (see Scheme 4) resulted in the synthesis of carborane-containing polyphosphazenes in 60%–70% yields.¹⁰⁸ The highest degree of chlorine substitution attained in these reactions was only 50%, evidently, due to the steric influence of the carborane substituents.

The chlorine atoms remaining in poly(chlorophosphazenes) containing *m*-carboranylmethoxy and *o*-carboranylmethoxy groups in

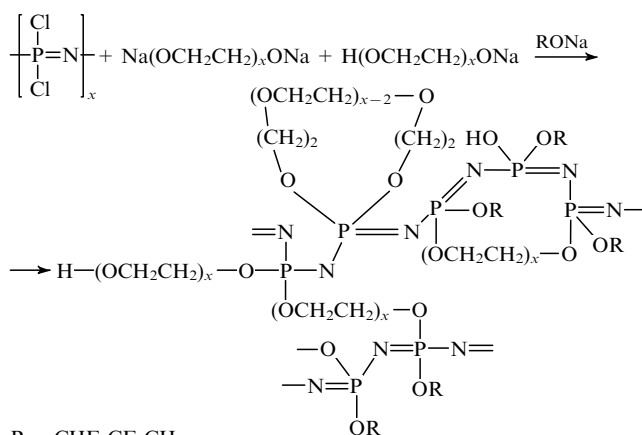
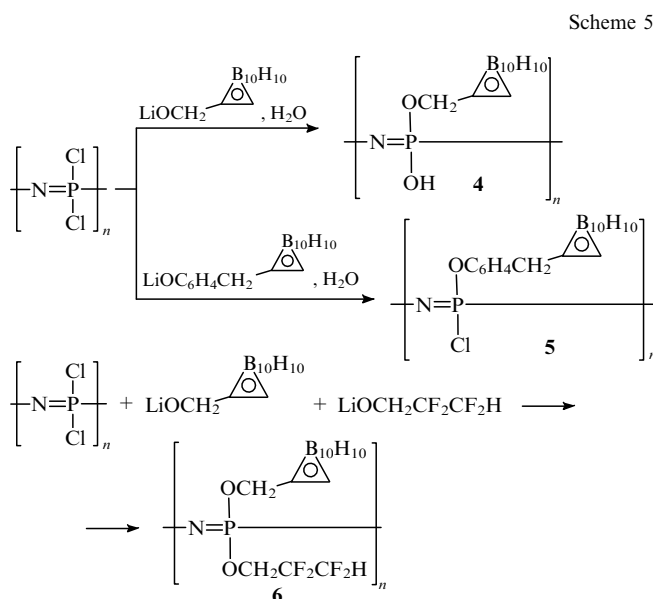
the side chains are hydrolytically unstable.¹⁰⁸ During the isolation of these polymers, the chlorine atoms contained in them are partially or completely hydrolysed (Scheme 5, polymer 4). The chlorine atoms in polymer 5 are not hydrolysed under similar conditions.

When lithium *o*-carboranylmethoxide and lithium tetrafluoropropoxide are added successively to PDCP, a polymer with carboranylmethoxy and tetrafluoropropoxy groups attached to the same phosphorus atom is produced (polymer 6). The reaction of bis(hydroxymethyl)-*o*-carborane with PDCP was carried out in THF in the presence of triethylamine at 20–50 °C or by the alkoxide method at 20–22 °C.^{109, 110, 112} The results obtained indicate that the two chlorine atoms at the same phosphorus atom in PDCP can, in principle, be replaced by a carborane-containing group yielding cardo-type polymers; this is accomplished using bis(hydroxymethyl)-*o*-carborane as the nucleophilic agent.



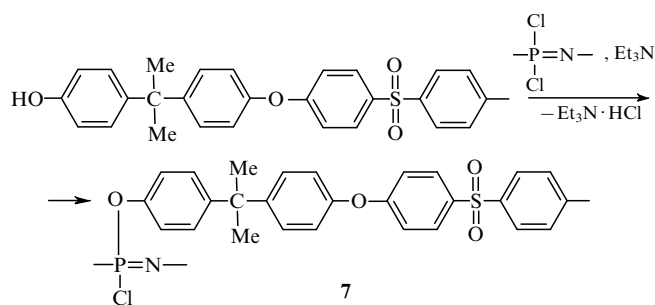
It should be mentioned that a higher degree of substitution of the chlorine atoms in PDCP is achieved in the presence of lithium alkoxide. However, in this case, the *o*-carborane rings are partially converted into dicarbaundecaborate groups, which are unstable with respect to hydrolysis and oxidation. Therefore, triethylamine appears to be the reagent of choice for trapping the hydrogen chloride evolved during the synthesis of carborane-containing polyphosphazenes. Replacement of the remaining chlorine atoms in these polymers by tetrafluoropropoxy groups (without isolation of the product formed in the first stage) has given poly(organophosphazenes) in which the surrounding groups are represented by fluoroalkoxy groups in addition to the cardo carborane groups.¹¹⁰

Poly(dichlorophosphazene) is a highly reactive initial compound for the synthesis of insoluble polymeric catalysts containing oligoethylenefragments.^{14, 113–115} The reaction is carried out with stirring in a mixture of anhydrous THF with toluene.



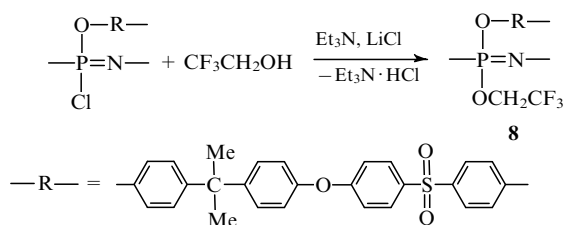
$R = \text{CHF}_2\text{CF}_2\text{CH}_2$.

PDCP has also served as the starting compound in the synthesis of graft copolymers. Thus copolymer 7 was synthesised by the reaction of PDCP with a polyarylene sulfone oxide, prepared from 2,2-bis(4-hydroxyphenyl)propane and 4,4'-dichlorodiphenyl sulfone, and containing a reactive terminal hydroxy group.^{116, 117}



The results obtained attest that this macromolecular reaction is fairly complicated. However, the fact that it yields graft copolymer, the composition of which is close to the specified one and the amount of which is no less than 45% of the total amount of the initial compounds indicates that this method can be used to prepare graft copolymers based on PDCP.

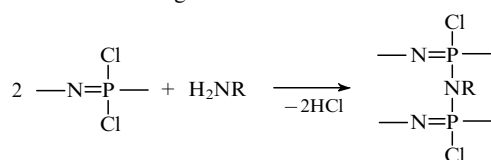
Since the copolymer **7** obtained in this way proved to be hydrolytically unstable, an attempt was made to replace the remaining chlorine atoms in the phosphazene moiety (one-pot procedure) by trifluoroethoxy groups in the presence of triethylamine and lithium chloride.



It was found that the polyarylene sulfoxide fragments present in the macromolecule of the graft copolymer **7** hamper the attainment of high degrees of the additional substitution of chlorine by the trifluoroethoxy groups. The substitution product **8** in which the residual chlorine content does not exceed 3 mass % is much more resistant to hydrolysis than the copolymer **7**.

Graft polyphosphazenes of yet another type have also been reported. Free radical reaction of poly[bis(4-ethylphenoxy)phosphazene] with maleic anhydride carried out in the presence of peroxides or with heating¹¹⁸ afforded a graft copolymer, poly[bis(4-ethylphenoxy)phosphazene-*g*-succinic anhydride], containing up to 14% of grafted succinic anhydride groups.

As shown in Scheme 1, amines can also be used as reagents replacing the chlorine atoms in PDCP. This yields poly(amino-phosphazenes),^{1, 9, 10, 17, 25, 32, 42, 91, 119–126} Non-branched primary amines substitute the chlorine atoms relatively easily; however, in this case, it is difficult to obtain a soluble polymer because of the possible cross-linking of macromolecules.



A detailed study of the aminolysis of linear PDCP by secondary amines made it possible to find conditions for the formation of poly(di-*n*-alkylaminophosphazenes) possessing highly chemically uniform structures with low contents of defective units and molecular masses of more than 10^6 .^{91, 119, 120} In particular, a homologous series of these polymers, $[-N=P(NHC_nH_{2n-1})_2-]_x$, where $n = 1-7$, was successfully synthesised in this way.¹¹⁹

3. Synthesis of poly(organophosphazenes) by polymerisation of cyclophosphazenes

Preparation of poly(organophosphazenes) by polymerisation of completely substituted organocyclophosphazenes would make it

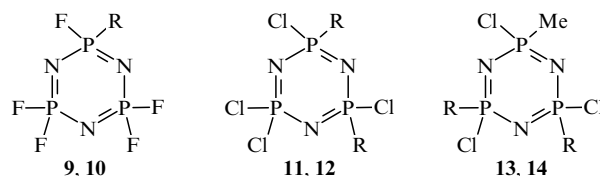
possible to avoid the undesirable side processes, which occur when these polymers are synthesised from PDCP because of the hydrolytic instability of chlorine. In addition, this method would permit preparation of poly(organophosphazenes) with a regular arrangement of substituting groups at the phosphorus atoms along the polymeric chain. However, as has been noted in a number of reviews,^{1, 3, 10, 11, 32} most of the numerous attempts to synthesise poly(organophosphazenes) by this approach were unsuccessful. The attempts to accomplish thermal polymerisation of alkyl-, aryl-, alkoxy-, and aryloxy-substituted cyclophosphazenes at 150–350 °C either failed or resulted in the formation of only low-molecular-mass polymers.^{127–131} The completely substituted fluoroalkoxycyclophosphazenes containing pentafluoropropoxy¹³² and trifluoroethoxy¹³³ groups could not be involved in thermal polymerisation at 200–300 °C, or at 200 °C under an elevated pressure.⁶⁴

Attempts have been made to carry out polymerisation of fluoroalkoxycyclophosphazenes^{64, 133, 134} in the presence of various catalysts. However, only in the presence of an equimolar amount of BCl₃, did this give a polyphosphazene with a molecular mass of 23 000–33 000; however, in this case, too, half of the fluoroalkoxy groups were replaced by chlorine.¹³⁴

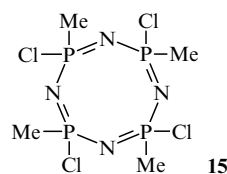
Nevertheless, chlorocyclophosphazenes with various degrees of substitution of chlorine by organic groups do enter into polymerisation and copolymerisation.^{132, 133, 135} Thus a polyphosphazene with a molecular mass of 110,000 was obtained by copolymerisation of hexakis(trifluoroethoxy)cyclophosphazene and hexachlorocyclophosphazene.¹³³ A rubber-like polymer has been prepared by copolymerisation of a mixture of trichlorotrimethylcyclophosphazene and tetrachlorotetramethylcyclophosphazene.¹³⁵ Thermal bulk polymerisation of geminally substituted cyclophosphazenes C₆H₅(X)P₃N₃Cl₄ (X = Cl, Br, CH₃, C₄H₉) has been studied.¹³⁶ At 250 °C, the compound with X = Cl polymerises over a period of 20–56 h, and that with X = Br reacts over a period of 4.5–24 h. The products of polymerisation of the monomers with X = CH₃ and C₄H₉ comprise a broad range of substances including both oligomers and polymers.

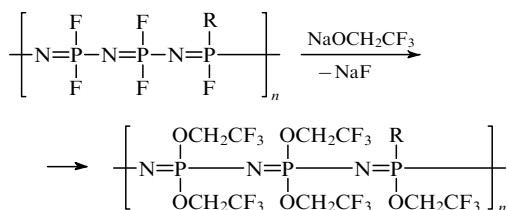
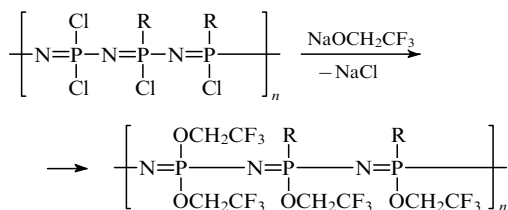
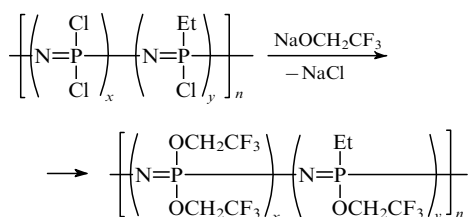
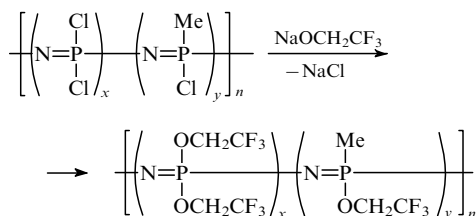
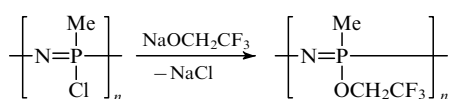
Allcock and Turner¹³⁷ have considered the thermal behaviour of substituted cyclophosphazenes of complex structures. It was found that thermolysis of these compounds at temperatures above 200 °C in the absence or in the presence of hexachlorocyclophosphazene, which could initiate polymerisation, affords only low-molecular-mass poly(organophosphazenes).

Below we present a number of substituted cyclic phosphazenes, products of their polymerisation and copolymerisation with hexachlorocyclophosphazene, and also poly(organophosphazenes) based on them; the latter were prepared by polymeranalogous substitution of the residual halogen atoms in the polymerisation products by the trifluoroethoxy groups.¹³⁸ Polymerisation of chlorocyclophosphazenes was carried out at 210–250 °C, while that of fluorine-substituted cyclophosphazenes was conducted at 250–300 °C. The molecular masses of the resulting polymers amounted to $(2.8-12.0) \times 10^5$.¹³⁸



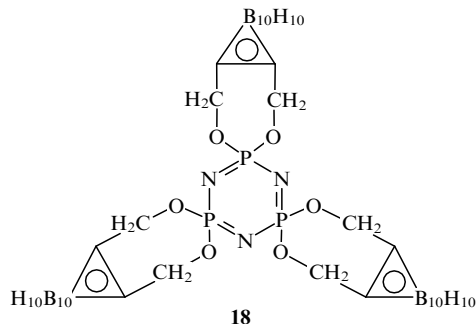
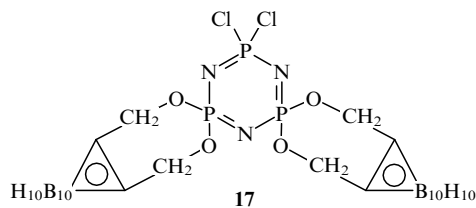
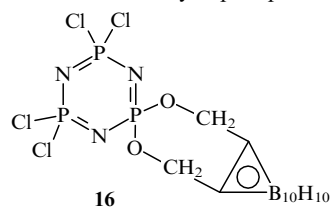
R = Bu^t (**9**), Ph (**10**), Me (**11**, **13**), Et (**12**, **14**).



R = Bu^t, Ph.R = Bu^t, Et.

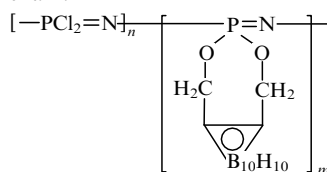
Allcock and Ngo¹³⁹ have synthesised a number of new phosphazene polymers by thermal polymerisation of 1,1-bis-(trichlorophosphazo)tetrachlorocyclotriphosphazene followed by replacement of the residual chlorine atoms in the polymerisation product by various organic pendent groups. Polymerisation was carried out at 150 °C at a reduced pressure for 2 h. Thermal polymerisation of phenylpentafluorocyclotriphosphazene at 300 °C for 48–72 h was used to synthesise poly(phenyl-fluorophosphazene) $[-\text{N}=\text{PPhF}-\text{N}=\text{PF}_2-\text{N}=\text{PF}_2-]_n$.¹⁴⁰ Polymeranalogous substitution of fluorine in this compound resulted in the synthesis of poly(organophosphazenes) with Me₃SiCH₂ side groups and poly(organophosphazenes) with mixed phosphorus environments containing trifluoroethoxy groups in addition to Me₃SiCH₂ groups.

Mono- (**16**), bis- (**17**), and tris- (**18**) *o*-carboranyl-substituted cyclotriphosphazenes have been prepared in order to synthesise carborane-containing polyphosphazenes.^{110, 141, 142} This polymer is formed under milder conditions than those resulting from polymerisation of hexachlorocyclotriphosphazene and previously known carboranecyclotriphosphazenes.¹⁴³ To increase the



hydrolytic stability of this carborane-containing polymer, the remaining chlorine atoms were substituted by tetrafluoropropoxy groups.¹⁴¹

Only polymerisation of mono-substituted derivative **16** gave a polymer (yield 60%) completely soluble in THF and having a reduced viscosity of 0.52 dl g⁻¹ in this solvent.¹⁴¹ Polymerisation of this monomer was carried out in the melt at 220 °C for 2 h. The data obtained by ³¹P NMR spectroscopy suggested an irregular arrangement of phosphorus atoms carrying the carboranyl groups. Apparently, the macromolecule of this polymer contains the following fragments, which are randomly distributed along the chain:

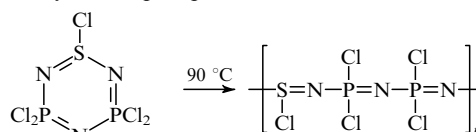


n = 1–4, m = 1–2.

This polymer is formed under milder conditions than those resulting from polymerisation of hexachlorocyclotriphosphazene and previously known carboranecyclotriphosphazenes.¹⁴³ To increase the hydrolytic stability of this carborane-containing polymer, the remaining chlorine atoms were substituted by tetrafluoropropoxy groups.¹⁴¹

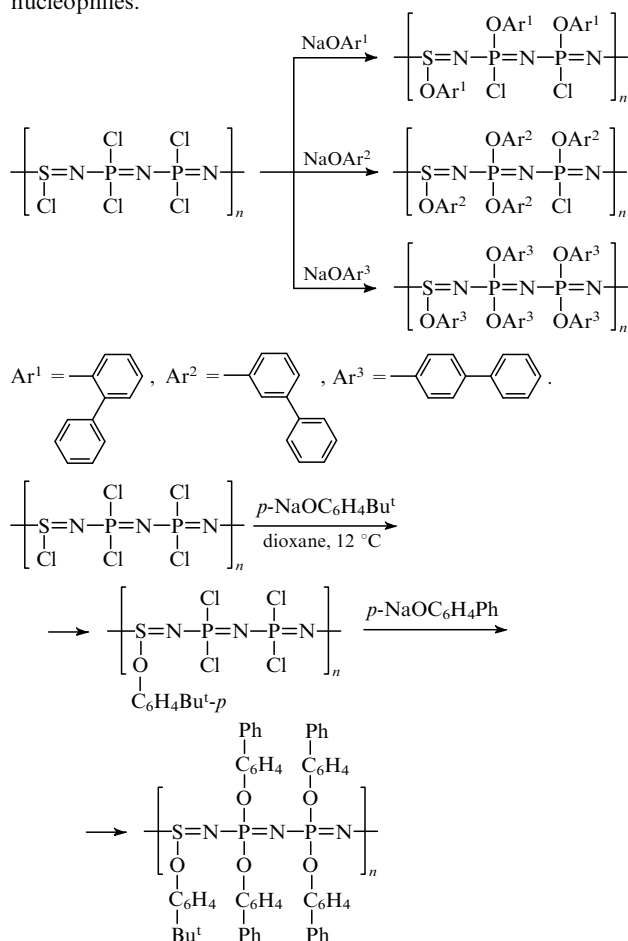
The synthesis of cyclic and polymeric phosphazenes with methyl- and phenyl-*o*-carboranyl groups has also been reported.^{144, 145} Thermal polymerisation of (methyl-*o*-carboranyl)- or (phenyl-*o*-carboranyl)-pentachlorocyclotriphosphazenes was conducted at 250 °C for 120 h. The chlorine atoms remaining in the polymer and susceptible to hydrolysis were replaced by trifluoroethoxy groups.

Let us discuss one more type of polyphosphazenes, namely, poly(thiaphosphazenes), the polymeric chains of which incorporate sulfur-containing fragments in addition to the –P=N– units. Poly(chlorothiaphosphazene) has been prepared by polymerisation of cyclic thiaphosphazene N₃P₂SCl₅.¹⁴⁶



The process was carried out in Pyrex tubes at 90 °C or at room temperature. It is of interest that polymerisation of a freshly distilled specimen requires several days at 90 °C, whereas a specimen that has been first kept overnight at room temperature polymerises over a period of 4–5 h. The yield of the polymer

after two reprecipitations was 32%. Poly(chlorothiaphosphazene) proved to be readily hydrolysable. It was involved in polymer-analogous transformations with various aryloxy-containing nucleophiles.



It should be noted that some of the chlorine atoms in polymers of this type still remain unsubstituted. Their molecular masses are $> 10^5$.

Thus, the data presented above demonstrate that despite the numerous attempts to prepare poly(organophosphazenes) directly from completely substituted organocyclophosphazenes, conditions for their successful polymerisation have not yet been found. More reassuring results have been obtained when halocyclophosphazenes, in which chlorine has been partially substituted by organic groups, were subjected to polymerisation. However, due to hydrolytic instability of the resulting polymers, subsequent replacement of the residual halogen atoms by organic groups of one or another type is required. Certainly, studies on the polymerisation of organo-substituted cyclophosphazenes require further development. Currently the two-stage procedure considered above is undoubtedly the most efficient method for the synthesis of poly(organophosphazenes).

III. Properties of poly(organophosphazenes)

1. Chemical properties

In a number of publications,^{1-3,9} it has been noted that poly(organophosphazenes) are chemically stable; however, their stability depends substantially on the structure and defectiveness of their chemical structure. Thus the presence of anomalous units in poly(organophosphazenes) markedly decreases their hydrolytic stability. Completely substituted poly(organophosphazenes) with inert alkoxy and aryloxy pendent groups are stable to atmospheric moisture and to weak acids and bases.^{1,4,9} Poly(diphenoxy)phosphazene remains unchanged after refluxing in 1 M HNO_3 or 1 M aqueous KOH for 48 h.¹⁴⁷

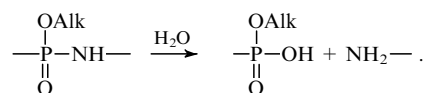
Data concerning the behaviour of poly(fluoroalkoxyphosphazenes) on treatment with various acids are contradictory. It has been reported that in the solid state, these polymers are resistant to concentrated sulfuric⁶⁷ and glacial acetic¹ acids at low temperatures. However, it has also been reported that strong inorganic acids or glacial acetic acid diminish their mechanical properties.¹⁴⁸ Cured poly(fluoroalkoxyphosphazenes) have been noted to be stable on treatment with boiling water^{67,148} and to remain unchanged when in contact with concentrated solutions of KOH or NaOH for many months in the cold.^{1,67,148} The hydrolytic stability of poly(fluoroalkoxyphosphazenes) at moderately elevated temperatures depends on the overall contents in the polymer of all the anomalous units with P-Cl, P-OH, and P(O)-NH groups (Table 6).^{3,66,76}

Table 6. Some characteristics of poly[bis(trifluoroethoxy)phosphazene] containing predominating units $-\text{P}(\text{OCH}_2\text{CF}_3)_2=\text{N}-$ and anomalous units $-\text{P}(\text{OCH}_2\text{CF}_3)\text{Cl}=\text{N}-$, $-\text{PCl}_2=\text{N}-$, $-\text{P}(\text{OCH}_2\text{CF}_3)(\text{OH})=\text{N}-$, $-\text{P}(\text{O})(\text{OCH}_2\text{CF}_3)-\text{NH}-$, $-\text{P}(\text{OH})\text{Cl}=\text{N}-$, and $-\text{P}(\text{O})\text{Cl}-\text{NH}-$.

Characteristics	Specimen	
	A	B
Total contents of anomalous units x , mol. %	< 0.18	$0.2 < x < 1.0$
Molecular mass	10×10^6	3×10^6
$[\eta]$ in acetone/ dl g ⁻¹		
after the synthesis	3.70	1.64
after 20 h	3.63	0.14
after 3 years	3.68	0.65
σ_r^a / kgf cm ⁻²		
after the synthesis	1920	810
after 3 years	2260	80
ε^b / %		
after the synthesis	680	510
after 3 years	760	13

^a σ_r is the tensile strength of a nonoriented film; ^b ε is relative elongation at break.

Table 6 presents some characteristics of poly[bis(trifluoroethoxy)phosphazene]. Two specimens of this polymer are considered: one of them (specimen A) contained < 0.18 mol. % of anomalous units, while the other one (specimen B), 0.2 mol. % $< x < 1.0$ mol. %. For polymer B, the intrinsic viscosity substantially decreases (from 1.64 to 0.14 dl g⁻¹) after a 20-h refluxing in aqueous acetone, while in the case of polymer A, it remains virtually the same.⁷⁹ This indicates that at a particular content of anomalous units, polyphosphazene undergoes hydrolytic destruction, which can occur, for example, as follows:



Poly[bis(trifluoroethoxy)phosphazene] containing ≥ 0.2 mol. % of residual chlorine is so hydrolytically unstable that even at room temperature, it becomes insoluble in organic solvents, apparently, due to cross-links between macromolecules arising from its chemical transformations.^{3,66,76}

Poly(organophosphazenes) can undergo various chemical transformations under appropriate conditions. Reactions of poly[bis(4-methoxyphenoxy)phosphazene] and poly[bis(benzyl-oxyphenoxy)phosphazene] with BBr_3 to give the polymer $[-\text{N}=\text{P}(\text{OC}_6\text{H}_4\text{OH})_2-]_n$ have been reported.¹⁴⁹ The pendent substituents in this polymer contain free OH groups, which enable its subsequent chemical modification.

The possibility of exchange reactions of poly[bis(trifluoroethoxy)phosphazene] with esters and hydroxyl-containing com-

pounds has been studied.¹⁵⁰ It was found that the substitution of trifluoroethoxy groups by alkoxy groups carried out in a saturated solution of polyphosphazene and dibutyl adipate containing tetrabutoxytitanium at 240 °C occurs by 10% over a period of 20 h. When polyphosphazene is made to react with *m*-cresol and undecyl alcohol at temperatures below 240 °C, the exchange hardly takes place. The replacement of trifluoroethoxy groups in polyphosphazenes by alkoxy groups occurs successfully only when the corresponding metal alkoxides are used. Thus treatment of the polyphosphazene $[=NP(OR)_2-]_n$ with $R'ONa$, where R and R' are monovalent radicals of the type $F(CF_2)_xCH_2$ or $H(CH_2)_yCH_2$ (x and y vary from 0 to 9) yielded polymers with mixed environments, $[NP(OR)(OR')-]_n$.^{107, 151–153} The reaction was carried out by mixing solutions of the initial compounds in dry THF at 25 °C followed by refluxing the mixture for 4 h.^{152, 153} The use of bifunctional alcoholates, for example, the disodium hexafluoropentane-diolate, permits curing of polyphosphazene.¹⁵¹

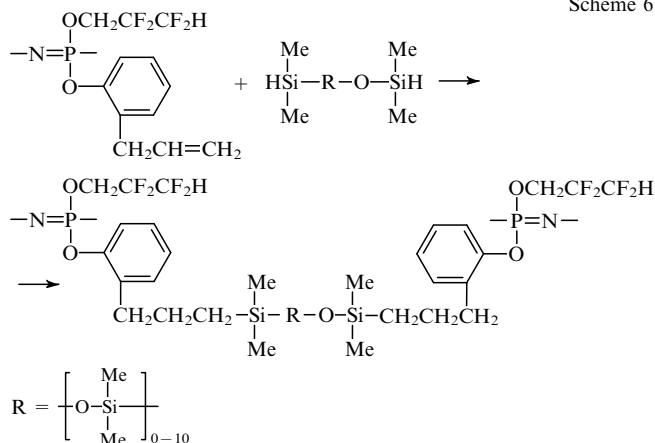
Poly(organophosphazenes) with mixed environment containing free hydroxyl groups in some of the pendent substituents, which can be cured by diisocyanates, dicarboxylic acid anhydrides, *etc.*, have been described.¹⁵⁴

Poly(organophosphazenes) containing 0.5 mol.% – 35 mol.% of organic radicals with NH bonds, in addition to side alkoxy, fluoroalkoxy, or aryloxy groups, can be cured at room temperature by cross-linking reagents containing epoxy, anhydride, or NCO groups.¹⁵⁵ Poly(fluoroalkoxyphosphazenes) containing a small amount (0.1% – 5%) of OC_6H_4Alk-o groups in the lateral chain can be cured in compositions with various filling agents by peroxides and sulfur on exposure to high-energy radiation giving tough compounds.¹⁵⁶ Poly(organophosphazenes) with the residues of allyl, *n*-butenyl, and isobutenyl alcohols^{157–159} and allyl hydroxybenzoate^{160–162} as the P-substituents have been synthesised. Under appropriate conditions, these polyphosphazenes can be cured or involved into copolymerisation with unsaturated monomers.¹⁶²

The attempts to cure poly(fluoroalkoxyphosphazenes) by procedures used in vulcanisation of fluorinated rubbers have not been a success.¹⁶³ However, the polymers obtained upon introduction of reactive *o*-allylphenoxy groups, $[N=P(CH_2CF_2CF_2H)_2-x(OC_6H_4CH_2CH=CH_2-x)]_n$ where $x = 0.02–1.00$, acquire the ability to undergo thermal curing in the presence of initiators as well as radiation-induced and chemically induced curing.¹⁶³ It was found that organosilicon hydrides of various structures can serve as the curing agents for these polyphosphazenes. Curing with these agents was accomplished in the presence of hydrogen hexachloroplatinate both in solution and in films at 20–65 °C for 0.25–10 h.^{163, 164} The curing process may occur according to Scheme 6.

However, the fact that polyphosphazenes are cured by organosilicon monohydrides suggests that interaction by a free radical mechanism is also possible.¹⁶³

Scheme 6



A method for the preparation of hybrid polyphosphazene copolymers has been developed. The method includes the reaction of poly(tetrafluoropropoxyphosphazenes) containing 2 mol.% and 5 mol.% of *o*-allylphenoxy groups, or poly(chlorophenoxyphosphazene) containing 2 mol.% of *o*-allylphenoxy groups with polysiloxanes.¹⁶⁵ The role of the latter component was played by a poly(dimethyl-)(or methylphenyl-)(or methylvinyl)siloxane rubber (the content of methylphenylsiloxane units was 8.0 mol.%, that of methylvinylsiloxane units was 0.3 mol.%) and also by a siloxane polymer of the composition $[OSiH\text{Et}]_m$, where $m = 10–15$. In the former case, the reaction was carried out by heating films containing 2 mol.% of benzoyl peroxide at 90 °C. After 5 h of heating, the content of the insoluble fraction amounted to ~30%–70% depending on the particular polyphosphazene used. The reaction of polyphosphazenes with siloxanes containing terminal Si–H groups was carried out in films in the presence of hydrogen hexachloroplatinate, by heating the films to 65 °C. In some cases, as soon as after 2 h, the content of insoluble fraction in the reaction products was ~90%. Judging from thermomechanical testing, polyphosphazene–siloxane hybrid systems of this type surpass poly(organophosphazenes) in elasticity and heat resistance.¹⁶⁵ Poly(aryloxyphosphazenes) are capable of self-extinguishing in air with only moderate smoke evolution.^{33, 166} The limiting oxygen index of their inflammability is 24–65. Poly(fluoroalkoxyphosphazenes) do not burn in air; the oxygen index of their inflammability is 47–65, and in some cases, it is as high as 80.^{3, 77, 167, 168}

It has been found that the probability of decomposition of polyalkoxy- and polyaryloxyphosphazenes during photolysis^{103, 169} depends on the content of unsubstituted P–Cl groups. In the absence of these groups, poly(organophosphazenes) possess high light resistance.

Data on the influence of high temperatures on poly(organophosphazenes) have been reported in numerous publications.^{1, 3, 8, 9, 11, 32, 34, 36, 44, 47, 104, 121–123, 131, 170–180} Allcock¹ has noted that heat treatment of poly(organophosphazenes) is accompanied by depolymerisation and decomposition and that the size of the pendent groups attached to phosphorus has an appreciable influence on the polymer stability with respect to depolymerisation. Thus poly(aryloxyphosphazenes) are more thermally stable than alkoxy-substituted compounds. The latter completely decompose at 550 °C, whereas aryloxy-derivatives lose only 50% of their weight when the temperature reaches 600 °C (for a heating rate of 10 deg min^{–1}).⁴⁷ The decomposition of poly(aryloxyphosphazenes) affords mostly linear and cyclic oligomers.^{104, 170} Tables 7 and 8 contain thermal characteristics of some poly(diaryloxyphosphazenes) and poly(diarylamino-phosphazenes).

Table 7. Thermal characteristics of some poly(diaryloxyphosphazenes) $[N=P(OAr)_2-]_n$.^{34, 122}

Ar	Decomposition temperature/ °C	
	under argon	under oxygen
C ₆ H ₅	380	400
<i>p</i> -MeC ₆ H ₄	310	310
<i>m</i> -MeC ₆ H ₄	350	340
<i>p</i> -ClC ₆ H ₄	400	385
<i>m</i> -ClC ₆ H ₄	380	375
<i>p</i> -EtC ₆ H ₄	285	250
<i>p</i> -MeOC ₆ H ₄	340	233
<i>p</i> -Bu ^t C ₆ H ₄	350	–
3,4-Me ₂ C ₆ H ₃	315	–
3,5-Me ₂ C ₆ H ₃	340	–

Note. Thermogravimetric analysis was carried out at a heating rate of 10 deg min^{–1}.

Table 8. Thermal characteristics of some poly(diarylamino phosphazenes) [$-\text{N}=\text{P}(\text{NHA}r)_2-$]_n.¹²³

Ar	<i>T</i> /°C	Ar	<i>T</i> /°C
<i>p</i> -MeC ₆ H ₄	250	<i>p</i> -MeOC ₆ H ₄	266
<i>m</i> -MeC ₆ H ₄	262	<i>p</i> -ClC ₆ H ₄	265
<i>p</i> -EtC ₆ H ₄	245	<i>m</i> -ClC ₆ H ₄	253
<i>m</i> -EtC ₆ H ₄	243	<i>p</i> -FC ₆ H ₄	260
<i>p</i> -Bu ⁿ C ₆ H ₄	253	<i>m</i> -FC ₆ H ₄	249

Note. Thermogravimetric analysis was carried out at a heating rate of 20 deg min⁻¹.

The data presented demonstrate that the temperatures of the onset of decomposition of arylamino derivatives are lower than those for poly(aryloxyphosphazenes). According to viscosimetric measurements, destruction of many poly(organophosphazenes) starts in the temperature range 100–200 °C.^{9, 69, 104, 170, 177} Thus a decrease in the molecular masses of poly(diphenoxy- and poly(dim-chlorophenoxy-phosphazenes) can be observed even at 130–160 °C.^{170, 177} Apparently, the destruction processes in poly(organophosphazenes) are strongly influenced by the end groups in the polymer chains as indicated, for example, by the fact that the rate of destruction of poly(dibutoxyphosphazene) at 200 °C *in vacuo* increases with a decrease in the molecular mass of the polymer and with an increase in the concentration of the P=O and P–OH groups.^{9, 180}

Some studies contain results of thermogravimetric analysis and thermal stability of poly(fluoroalkoxyphosphazenes); however, these data are sometimes contradictory.^{3, 70, 171} Thus it has been reported⁷⁰ that the weight loss of poly[bis(trifluoro-ethoxy)phosphazene] starts at ~200 °C, whereas other researchers^{5, 6, 34, 171} give values of 350–360 °C. Molecular-mass characteristics of these polymers have been estimated.^{69, 172–174} It was found that the molecular mass of poly(fluoroalkoxyphosphazenes) decreases relatively rapidly at 150–200 °C, probably due to the presence of defective units in their macromolecules. An attempt has been made to elucidate more precisely the nature of the defective groups and the active sites, which initiate destruction of the polyphosphazene chain in poly[bis(trifluoro-ethoxy)phosphazene].¹⁷⁶ It was shown that thermal depolymerisation of this polymer corresponds to a depolymerisation model with two-stage initiation at which normal phosphazene units are first transformed into defective ones. The latter may be represented by oxophosphazene units like $-\text{P}(\text{O})(\text{CH}_2\text{CF}_3)-\text{NH}-$ and $-\text{P}(\text{O})(\text{CH}_2\text{CF}_3)-\text{N}(\text{Cl})-$. They induce the appearance of active sites for depolymerisation, and, hence, the polymer in question undergoes complete thermal destruction even about 200 °C. Defective oxophosphazene units can arise during the synthesis of the polymer upon hydrolysis of P–Cl bonds and subsequent tautomeric rearrangement; they also can appear upon thermal transformations of normal phosphazene groups at temperatures about 400 °C. It has been suggested¹⁷⁶ that this mechanism of depolymerisation is common to all poly(alkoxy- and aryloxyphosphazenes).

In order to elucidate the possibility of increasing the thermal stability of poly(organophosphazenes), polymers of this type containing carboranyl groups have been synthesised.^{108–111, 141} It was found that a 5% decrease in the weights of these polymers in air is observed at moderate temperatures (200–270 °C). However, the positive influence of the carboranyl groups is manifested at higher temperatures. The coke residue of these polymers in air at 500 °C amounts to 50%–80% and that in a helium atmosphere can be as high as 100% even at 900 °C, whereas the initial poly(dichlorophosphazene) and some poly(organophosphazenes) completely decompose even at 500–570 °C.¹²¹

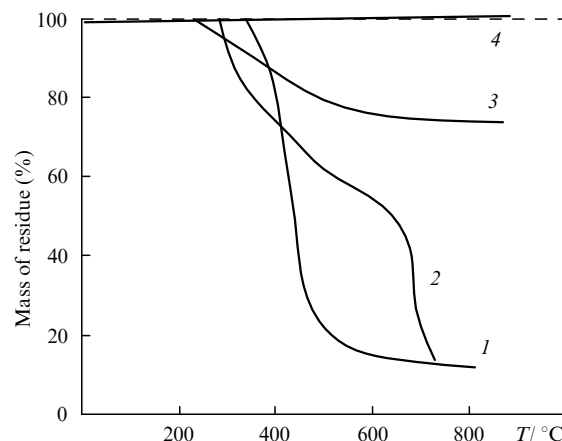
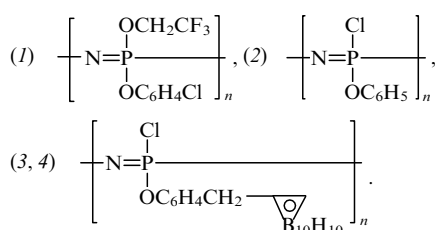
**Figure 2.** Thermogravimetric curves for polyorganophosphazenes with mixed environments recorded in air (curves 1, 2, 3) and under helium (4); heating rate 4.5 deg min⁻¹.

Figure 2 compares thermogravimetric curves for a carborane-containing polyphosphazene (3 and 4) with those for polymers containing no carborane groups (1 and 2). It can be seen that during heating in air, the weight of carborane-containing polymers changes to a much lesser degree than that of the polyphosphazenes $[-\text{N}=\text{P}(\text{OCH}_2\text{CF}_3)(\text{OC}_6\text{H}_4\text{Cl})-]_n$ and $[-\text{N}=\text{P}(\text{OC}_6\text{H}_5)\text{Cl}-]_n$. Heating in a helium atmosphere does not result in any change in the weight of the carborane-containing polymer up to very high temperatures.

Thus, thermal stability of poly(organophosphazenes) depends on a number of factors, namely, on the chemical structure of groups linked to the phosphorus, on the presence of defective fragments in the polyphosphazene chain, on the terminal groups in the macromolecules, and on the molecular mass. The thermal stability of poly(organophosphazenes) can be changed by varying the above factors or by adding special stabilising compounds to materials based on these polymers.^{3, 8, 9, 181–185}

2. Physical properties

Physical properties of poly(organophosphazenes) are intimately connected to their chemical structure. The data of Table 9 give an idea of the influence of chemical structure of poly(organophosphazenes) on their solubility. It can be seen that some poly(organophosphazenes) are readily soluble in ordinary organic solvents, which provides opportunity for investigation of their hydrodynamic, rheological, and molecular-mass characteristics and other properties, which have been dealt with in a number of publications.^{1, 3, 9, 33, 48, 59–63, 87, 91, 121–126, 177, 186–193} Studies of the molecular-mass distribution of polyphosphazenes have led to ambiguous results. Some researchers have noted broad molecular-mass distributions.^{1, 3, 60–62, 121–126, 177} Thus polydispersity factors of about 7–79 have been reported for poly(fluoroalkoxyphosphazenes).^{3, 60–62} However, in relation to poly[bis(tetra-fluoropropoxy)phosphazene], it was shown that the synthesis carried out under controlled conditions can lead to poly(fluoro-alkoxyphosphazenes) with narrow molecular-mass distributions ($M_w/M_m = 1.03, 1.39$).⁶³ A relatively low polydispersity factor, equal to 1.09, has been reported for poly[bis(octafluoropentyl-oxy)-

Table 9. Solubility of polyorganophosphazenes $[-N=PR_2-]_n$.

R	Soluble in	Insoluble in	Ref.
OEt	alcohols, benzene, ethers, ketones	water, ethanol, aliphatic hydrocarbons	1, 32, 44, 92
OBu	hexane, benzene, chloroform, THF, cyclohexane, ethyl acetate	methanol, water	90–92
OCH ₂ CF ₃	acetone, ethyl acetate, THF, dimethyl ether, DMF, ethylene glycol, methyl ethyl ketone	ethanol, diethyl ether, aromatic and aliphatic hydrocarbons	1, 3, 4, 42, 44, 48, 143
OCH ₂ C ₂ F ₄ H	THF, acetone	aliphatic hydrocarbons	1, 3, 16
OCH ₂ C ₇ F ₁₅	no solvents were found		3, 47
OPh	benzene, toluene, DMF, dioxane, chloroform, chlorobenzene, THF	acetone, hexane, ethanol, water, DMSO	1, 32, 44
NHC ₆ H ₁₃	THF	methanol	120

phosphazene].¹³ In another study, it was noted that for poly(aryloxyphosphazenes), the polydispersity factor can be as high as 30.¹²¹ According to the results of gel-permeation chromatography, these polymers are typically characterised by bimodal molecular-mass distributions.^{9, 177, 191} The polydispersity factor of poly[bis(phenylamino)phosphazene] is 13.4.¹²⁴

For a number of poly(fluoroalkoxy- and poly(alkoxyphosphazenes), the parameters of the Mark–Kuhn–Houwink equations and dependences of the sedimentation constants in THF solutions on their molecular masses have been determined (Table 10).^{13, 91, 192}

Table 10. Parameters of the equations $[\eta] = k_\eta M^a$ and $S_0 = k_S M^{1-b}$ for polyphosphazenes $[-N=P(OR)_2-]_n$.

R	k_η	a	$10^{14} k_S$	$1-b$	Range $10^{-3} \times S_0$	Ref.
CH ₂ CF ₃	1.77×10^{-4}	0.59	35.20	0.47	45.0–122.1	13, 192
CH ₂ (CF ₂) ₂ H	6.10×10^{-6}	0.85	1.17	0.39	3.6–63.1	13, 192
CH ₂ (CF ₂) ₄ H	6.74×10^{-7}	1.00	2.95	0.33	7.1–23.7	13, 192
(CH ₂) ₂ CH ₃	2.03×10^{-4}	0.65	27.00	0.45	4.8–20.9	91
(CH ₂) ₃ CH ₃	1.17×10^{-4}	0.70	33.30	0.43	2.7–28.7	91
(CH ₂) ₅ CH ₃	9.36×10^{-6}	0.88	56.00	0.37	4.0–16.1	91

For the same polymers, conformational parameters were calculated and it was shown that the statistical Kuhn segment values increase with an increase in the length of the pendent substituent.^{91, 192} Thus the Kuhn segments for the polyphosphazenes with R = $-(CH_2)_2CH_3$, $-(CH_2)_3CH_3$, and $-(CH_2)_5CH_3$ amount to 53×10^{-8} , 72×10^{-8} , and 110×10^{-8} cm, respectively. The same values for poly[bis(fluoroalkoxy)phosphazenes] with R = $-CH_2CF_3$, $-CH_2(CF_2)_2H$, and $-CH_2(CF_2)_4H$ are equal to 44×10^{-8} , 122×10^{-8} , and 160×10^{-8} cm, respectively. These results permitted the conclusion that the equilibrium rigidity of poly(alkoxyphosphazene) macromolecules is much lower than that of poly(fluoroalkoxyphosphazene) macromolecules, provided that the lengths of the lateral groups are comparable. The replacement of the oxygen atom in the side chain of poly(dihexyloxyphosphazene) by an NH group increases the Kuhn segment by a factor of about three; thus the Kuhn segment of poly(dihexylaminophosphazene) is 350×10^{-8} cm.⁹¹

In several studies^{2, 3, 48, 62, 186, 193, 194} dealing with the concentration dependence of the reduced viscosity of solutions of poly(alkoxy- and poly(fluoroalkoxy-phosphazenes), an abnormal character of this dependence has been observed, namely, the reduced viscosity increases upon dilution, as is normally observed for dilute solutions of polyelectrolytes. Viscosity, electrical conductivity, and dielectric properties of dilute THF solutions of four poly[bis(fluoroethoxy)phosphazene] samples were studied.¹⁹³ The following unusual properties were discovered:

- (1) the reduced viscosity markedly depends on the shear rate;
- (2) the reduced viscosity increases upon a decrease in the polymer concentration in the solution;
- (3) the magnitude of the reduced viscosity of a polymer solution decreases and the pattern of its concentration dependence changes in the presence of various amounts of a salt (KI);
- (4) the magnitude of the reduced viscosity and sedimentation constants S_0 of solutions decrease on passing from a more polar solvent to a less polar one.

This type of combination of hydrodynamic properties is quite typical of linear polyelectrolytes.¹⁹⁵

The polyelectrolyte character of some poly(organophosphazenes), for example, poly[bis(trifluoroethoxy)phosphazene], is caused by anomalous units such as $-P(OCH_2CF_3)=N-$ and $-P(OH)(OCH_2CF_3)=N-$ present in the polymer chain.^{2, 186, 193, 194}

The appearance of ionised groups can be explained by intra- or intermolecular interactions between two different units, for example, by formation of quaternary nitrogen atoms with chloride anions as counter-ions.¹⁸⁶ According to the results obtained by electron microscopy for dilute solutions of polymers in polar and moderately polar solvents such as acetone and tetrahydrofuran, ionised groups in these polymers result mostly from intramolecular interactions.¹⁹⁶

Several studies^{197–200} have been devoted to the Kerr effect in solutions of poly(fluoroalkoxyphosphazenes). Thus investigation of dynamic and electrical birefringence of solutions of the polyphosphazenes $-P[OCH_2(CF_2)_2H]_2=N-$, $-P[OCH_2(CF_2)_4H]_2=N-$, and $-P(OCH_2CF_3)_2=N-$ showed that the specific Kerr constants for these polymers in ethyl acetate are 4.8×10^{-8} , 5.7×10^{-8} , and 7×10^{-8} cm⁵ g⁻¹ (300 V)⁻², respectively. It was shown that polyphosphazene molecules are oriented in an electric field owing to their permanent dipole moment, which is collinear with the vector connecting the ends of the macromolecule. This accounts for the substantial contribution of large-scale motion to the orientation of macromolecules of polyphosphazene in an electric field.

The heat resistance of poly(organophosphazenes) depends appreciably on their chemical structure. Previously, glass transition temperatures for a number of poly(fluoroalkoxyphosphazenes) have been reported; for many of these polymers, these values are fairly low.³ For example, the glass transition temperature of $\{-N=P[OCH_2(CF_2)_2OCF_3]_2-\}_n$ determined by the thermomechanical method is -99°C .⁷⁷

Tables 11–14 contain data on the glass transition and melting temperatures of a series of poly(organophosphazenes) with different substituents. These data show that poly(alkoxy- and poly(fluoroalkoxy-phosphazenes) possess the lowest glass transition temperatures. On passing to aryloxy substituents, glass transition temperatures of polyphosphazenes increase; finally, poly(diarylamino)phosphazenes possess the highest glass transition temperatures (Table 14). It can be seen from Table 13 that the glass transition temperatures of polyphosphazenes with mixed environments can be varied by changing both the chemical nature of substituents at the phosphorus atom and their ratio.

The heat resistance of polyorganophosphazenes with reactive side groups can also be changed by their chemical modification,¹⁶³ which is illustrated by Fig. 3.

Data on the physical state, in particular the phase composition, of poly(organophosphazenes) have been presented in numerous publications (see, for example, Refs 3, 19, 34, 34, 70, 77, 93, 94,

Table 11. Glass transition and melting temperatures of poly(dialkoxyphosphazenes) $[-N=P(OR)_2-]_n$.⁹²

R	Physical state of polymers at 20 °C	$T_{gl}/^{\circ}C$	$T_{melt}/^{\circ}C$
Me	amorphous	-77	does not crystallise
Et	"	-97	—
Pr	mesomorphic	-107	—
Pr	amorphous	-107	—
Bu	mesomorphic	-107	—
Bu	amorphous	-108	—
C ₅ H ₁₁	mesomorphic	-110	—
C ₆ H ₁₃	amorphous	-104	—
C ₇ H ₁₅	"	-96	-17
C ₈ H ₁₇	"	-77	4

Note. Glass transition and melting temperatures were determined by differential scanning calorimetry (DSC).

Table 12. Melting and glass transition temperatures of some poly(diaryloxyphosphazenes) $[-N=P(OAr)_2-]_n$.

Ar	$T_{gl}/^{\circ}C^a$	$T_{melt}/^{\circ}C^b$	$T_{melt}/^{\circ}C^c$
C ₆ H ₅	-1 (5.5)	160	390
<i>p</i> -CH ₃ C ₆ H ₄	3 (0.3)	152	340
<i>m</i> -CH ₃ C ₆ H ₄	-25 (-25)	90	348
<i>p</i> -ClC ₆ H ₄	5 (4)	167	365
<i>m</i> -ClC ₆ H ₄	-37 (-24)	66	370
<i>m</i> -C ₂ H ₅ C ₆ H ₄	-30 (-18)	43	—
<i>p</i> -CH ₃ OC ₆ H ₄	6 (13)	125	—

^a T_{gl} were determined both by DSC and by thermomechanical analysis (values in parentheses);¹²² ^b T_{melt} were determined by DSC at a heating rate of 20 deg min⁻¹ (see Ref. 122); ^c T_{melt} were determined by the penetration method.³⁴

Table 13. Glass transition temperatures of poly[(aryloxy)fluoroalkoxyphosphazenes] $[-N=P(OR')(OR'')-]_n$.

OR'	OR''	Content of groups (%) ^a		$T_{gl}/^{\circ}C$	Ref.
		OR'	OR''		
OC ₆ H ₅	OC ₆ H ₅	100	—	-8	1
OC ₆ H ₅	OCH ₂ CF ₃	41	46	-30 ^b	81
OC ₆ H ₅	OCH ₂ CF ₂ CF ₂ H	37	53	-50 ^b	81
OC ₆ H ₄ Cl- <i>p</i>	OC ₆ H ₄ Cl- <i>p</i>	100	—	-12	121
OC ₆ H ₄ Cl- <i>p</i>	OCH ₂ CF ₃	78	8	-20 ^b	81
OC ₆ H ₄ Cl- <i>p</i>	OCH ₂ CF ₃	52	47	-25 ^b	81
OC ₆ H ₄ Cl- <i>p</i>	OCH ₂ CF ₂ CF ₂ H	59	33	-40 ^b	81
OCH ₂ CF ₂ CF ₂ H	OCH ₂ CF ₂ CF ₂ H	—	100	-60 ^b	81
OCH ₂ CF ₃	OCH ₂ CF ₃	—	100	-66	1

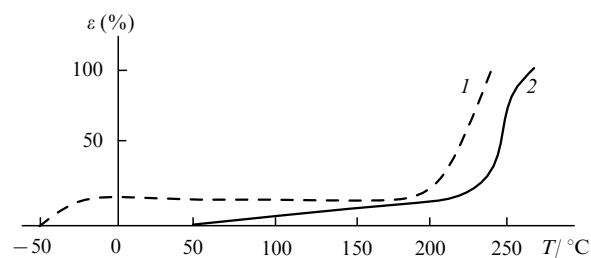
^a According to elemental analysis. ^b According to thermomechanical tests at a load applied to the sample of 0.8 kgf cm⁻² and a heating rate of 1 deg min⁻¹. The T_{gl} was taken to be the temperature of 2% deformation of the specimen.

100, 121, 201–246). Studies of physical transformations of poly(-organophosphazenes) carried out by scanning calorimetry, thermoanalytical methods, nuclear magnetic resonance, and X-ray diffraction^{3, 19, 34, 70, 77, 121, 202–208} demonstrated that some of them exhibit two temperature transitions, despite the fact that they are flexible-chain polymers and contain no mesogenic groups. The lower-temperature transition T_1 corresponds to melting of the crystalline phase with retention of a certain degree of ordering, i.e. at T_1 the polymer passes into a mesomorphic state.

Table 14. Glass transition temperatures of some poly(diarylamino-phosphazenes) $[-N=P(NHAr)_2-]_n$.^{36, 123}

Ar	$T_{gl}/^{\circ}C$	Ar	$T_{gl}/^{\circ}C$
C ₆ H ₆	105	<i>p</i> -Bu ⁿ C ₆ H ₄	53
<i>p</i> -MeC ₆ H ₄	97	<i>p</i> -MeOC ₆ H ₄	92
<i>m</i> -MeC ₆ H ₄	76	<i>p</i> -ClC ₆ H ₄	85
<i>p</i> -EtC ₆ H ₄	88	<i>m</i> -ClC ₆ H ₄	80
<i>m</i> -EtC ₆ H ₄	61	<i>m</i> -FC ₆ H ₄	80

Note. T_{gl} were determined using a thermal analyser at a heating rate of 10 deg min⁻¹.

**Figure 3.** Thermomechanical curves for poly(tetrafluoropropoxy)(*o*-allylphenoxy)phosphazene $-N=P(OCH_2CF_2CF_2H)_{1.96}(OC_6H_4CH_2CH=CH_2)_{0.04}-$.

(1) before curing; (2) after curing with tetramethylhydrodisiloxane in a film at 65 °C for 4 h in the presence of hydrogen hexachloroplatinate. The load applied to the specimen was 0.8 kgf cm⁻², the heating rate was 1 deg min⁻¹.

The upper temperature at which it transforms into an isotropic liquid is the true melting temperature (T_{melt}). For some poly(-organophosphazenes), these two transitions are separated by an unusually broad temperature range; in some cases, it reaches 150–250 °C or even more.^{6, 34} For example, T_1 and T_{melt} for poly[bis(-trifluoroethoxy)phosphazene] are approximately ~90 °C and 240–250 °C;^{13, 34} those for poly[chloro(phenoxy)-phosphazene] are 169 °C and 356 °C.³⁴

The physical state of poly(dialkoxyphosphazenes) has been studied in a number of publications.^{92–94, 244} The influence of the length of the pendent alkoxy groups (ranging from methoxy to octyloxy) in polyphosphazenes on their glass transition temperatures, crystallisation, and the ability to form mesophases has been analysed (see Table 11). For poly(dibutoxyphosphazene), it was found that a mesophase is formed only when the total content of defective units in the polyphosphazene is < 0.1 mol.%.^{93, 94} Thus, the mesomorphic properties of poly(organophosphazenes) are crucially dependent of the chemical homogeneity of their structure. The transition of poly(butoxyphosphazene) from the mesomorphic to the isotropic state occurring at 200 °C is accompanied by a small thermal effect (1.3 J g⁻¹). It was shown for poly(dipentyloxyphosphazene) that the formation of the mesophase depends not only on the content of defective units in the polymer but also on the conditions under which the sample was prepared: when the solvent (benzene, THF, chloroform) is slowly evaporated from a polymer solution, the mesophase is formed, whereas fast evaporation or precipitation of the polymer yields an amorphous phase.⁹⁴

IR and Raman spectra of poly(dialkoxyphosphazenes) $[-N=P(OC_mH_{2m+1})_2-]_n$, where $m = 1–9$, have been studied over a wide temperature range (from -100 to 100 °C).^{247, 248} It was suggested that the backbone has a helical structure. Some temperature-induced spectral changes were attributed to conformation transitions in the side chains. When the temperature is lowered, the content of *trans*-isomers increases, whereas that of *gauche*-isomers decreases.

Various aspects concerning the physical state of poly(fluoroalkoxyphosphazenes) have been studied.^{6, 13, 34, 201, 208, 210–232, 244, 245} For the homologous series of poly(fluoroalkoxyphosphazenes) with various lengths of the pendent groups,^{231, 245} it was shown that the glass transition temperatures of the polymers increase with increase in the length of the side group, whereas the temperatures of the transition to the mesomorphic state, characterised by a hexagonal packing of the macromolecule backbones, scarcely change. The increase in the range of existence in the mesomorphic state for polymers with longer pendent groups is due to higher temperatures at which the polymer passes into the isotropic melt.

It has been noted in a review¹³ that poly(fluoroalkoxyphosphazenes) are characterised by labile structures, which depend on the conditions of preparation of the polymer and its thermal prehistory. The main reason for the formation of the mesomorphic state in these polymers is specific interaction between the backbone and the pendent groups containing a large number of electronegative fluorine atoms. Primary attention was devoted to poly[bis(trifluoroethoxy)phosphazene]. It was noted that a peculiar structure of the mesophase of this polymer accounts for its ability to flow like a liquid in the mesomorphic state. The structure of the isotropic melt of the polyphosphazene retains the main features of the mesophase structure but is distinguished by a coil conformation of macromolecules.²¹² In the 453–493 K temperature range, rheological properties and structural characteristics of the mesophase melt of the polymer substantially change, which is accompanied by a thermal effect.²¹³ It is believed that this change corresponds to a conformational transition of macromolecules into a structure intermediate between one-dimensional layered and two-dimensional pseudo-hexagonal structures. The mesophase in poly[bis(trifluoroethoxy)phosphazene] was found to be highly sensitive to external pressure; when the pressure increases (up to 400 MPa), the temperature (T_1) of the polymer transition from the crystalline state into the mesophase increases, the range of existence of the mesophase is sharply extended, and the mesophase becomes more ordered.²¹¹

Temperature transitions and the orientational order in the near-surface layers of poly[bis(trifluoroethoxy)phosphazene] films have been studied.²³⁰ The glass transition temperature of this polymer is equal to -70°C , the temperature of transition of the mesophase into a new modification is 120°C , and the temperature of isotropisation and transition of the polymer into the amorphous state is 225°C . It was found that the segment optical anisotropy of poly[bis(trifluoroethoxy)phosphazene] in the bulk is twice that in solution. This points to a strong orientational interaction of the macromolecules, resulting in the higher thermodynamic rigidity of polymer chains in the bulk than that in solution. It was noted that the structure of uniaxially oriented fibres of poly[bis(trifluoroethoxy)phosphazene] is fundamentally modified upon annealing at a temperature above the mesomorphic transition. The type of packing changes, namely, non-equilibrium α -phase passes into a thermodynamically stable γ -orthorhombic form.²¹⁶ It has been suggested that macromolecules of this polymer spontaneously straighten out in the mesomorphic state.

The phase transitions in poly(organophosphazenes) with partially fluorinated alkoxy groups $\{-\text{N}=\text{P}[\text{OCH}_2.(\text{CF}_2)_x\text{CF}_2\text{H}]_2-\}_n$, where $x = 1, 3, 5$, from the crystalline phase to the mesophase, which can be regarded as a conformationally disordered crystal, have been studied in detail by various physical methods.^{217–220, 224} The temperatures of phase transitions in these polymers decrease linearly following an increase in the length of the pendent groups. The structure of poly[bis(pentafluoropropoxy)phosphazene] has been studied over a broad temperature range.^{221, 222} It was found that the polymer macromolecules in the mesomorphic state undergo orientation during extrusion. The studies confirmed the condic-crystalline type of the mesophase with a pseudo-hexagonal packing.²²² It was established that poly[bis(heptafluorobutoxy)phosphazene] is capable of existing

in the condic-crystalline and mesomorphic states. The mesophase of this polymer possesses high orientational and positional orders in the basis plane but is conformationally disordered.

The physical structure of poly[bis(halophenoxy)phosphazenes] has been considered in a number of studies.^{208, 233, 243} It was noted that the structures of their mesophases belong to the pseudo-hexagonal type. The physical structures of these polymers are markedly influenced by the thermal prehistory of a particular specimen.²⁴³ The mesophase state can also occur in poly(organophosphazenes) with the following side groups: $4\text{-n-C}_5\text{H}_{11}\text{OOCCH}_2\text{H}_4-$, $4\text{-n-C}_4\text{H}_9\text{OOCCH}_2\text{H}_4-$, and $4\text{-n-C}_{10}\text{H}_{21}\text{OOCCH}_2\text{H}_4-$.²³⁴

Study of the structures and phase transitions of poly(dialkylaminophosphazenes) has demonstrated that linear highly chemically homogeneous polyphosphazenes of this type form thermally reversible, ordered phases.¹¹⁹ An additional driving force for the self-organisation of these polymers is the formation of hydrogen bonds between the NH groups.²⁴⁴

A number of publications contain data on gas permeability of poly(fluoroalkoxyphosphazenes).^{235–240, 246} In particular, it was noted that gas transfer through poly[bis(trifluoroethoxy)phosphazene] is characterised by high selectivity parameters and, hence, this polymer is a promising material for gas separating membranes, for example, for separation of CO_2 -containing mixtures.²³⁵ The penetrability factor of this polyphosphazene in relation to the CO_2/CH_4 pair is ~ 10 . Of particular interest is the mesophase of poly[bis(trifluoroethoxy)phosphazene], which can ensure production of membranes operating reliably at elevated temperatures.²³⁵

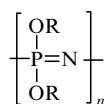
The physical state of poly(organophosphazenes) has a considerable influence on the properties of composite materials based on these polymers. Blends of poly[bis(trifluoroethoxy)phosphazene] with polyethylene^{13, 241, 242} and with the ABS plastic (a ternary copolymer of acrylonitrile, butadiene, and styrene) have been studied.²¹⁵ It was found that the unusual rheological properties of isotropic and mesomorphic polyphosphazenes can be used to modify the technological properties of ultra-high-molecular-mass polyethylenes. Polyphosphazenes added in small amounts sharply decrease the viscosity of polyethylene during extrusion and permit production of extrudates with good surface quality.²⁴¹ A decrease in the melt viscosity by approximately 40% was observed for mixtures of the ABS plastics with 10% of poly[bis(trifluoroethoxy)phosphazene]. The increase in the elasticity of samples, formed from these mixtures, at $225\text{--}240^\circ\text{C}$ (processing temperatures) is presumably due to the orientation effect induced by the mesomorphic character of polyphosphazene in this temperature range.

Many poly(organophosphazenes) possess good film-forming properties; naturally, this requires that these polymers should have high molecular masses and homogeneous chemical structures. In particular, it has been noted⁸³ that high tensile strengths (about 2000 kgf cm^{-2}) of poly[bis(trifluoroethoxy)phosphazene] films are realised only when the molecular mass of the polymer is about 10×10^6 . In addition, the data of Table 6 clearly demonstrate the influence of the unit non-uniformity of the polymer on the strength of polyphosphazene films. Films of poly[bis(trifluoroethoxy)phosphazene] with high molecular masses and chemically homogeneous macromolecules were found to possess long-term climatic stability under conditions of cold (Yakutsk, Russia)²⁴⁹ and tropical²⁵⁰ climates. Thus the service life of these films in the Arctic environment was found to be about 18 years, whereas for polyethylene, this period is only 2 years.

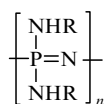
3. Medical and biological properties

The high reactivity of poly(dichlorophosphazene) provides broad opportunities for preparing diverse poly(organophosphazenes) with specific biological properties, which can be used for the development of materials meant for medical purposes. They include thromboresistant,^{14, 251, 252} self-resolvable,²⁵³ biologically inert,^{35, 36} and biologically active materials,^{254–260} medi-

cines,^{35, 254–256} *etc.* In particular, biocompatibility of eight different poly(organophosphazenes) was tested *in vivo* in rat muscles.³⁶



19–22



23–26

R = CH₂CF₃ (19), C₆H₄Me-*p* (20),
C₆H₄Buⁱ-*p* (21),
C₆H₄Buⁱ-*p* (22),
R = Ph (23), C₆H₄Me-*p* (24),
C₆H₄(CH₂)₃Me (25),
C₆H₄C₆H₄Cl-*m* (26)

It was found that the influence of these substances on a living organism is as minor as that of the widely used silicone materials. These poly(organophosphazenes) can be applied as film coatings onto parts to be implanted, or introduced into various compositions.

Especially interesting results have been obtained in a study of medical and biological characteristics of poly[bis(trifluoroethoxy)phosphazene]^{14, 251, 261–263} with a molecular mass of about 16×10^6 and the minimum unit non-uniformity (the concentration of anomalous units with non-substituted P–Cl groups was as low as 5.8×10^{-4} mole fraction).²⁵¹ Thromboresistant properties of more than 100 poly(organophosphazene) samples as films and sutureless tubes have been assayed *ex vivo* by platelet tests and the dynamics of parietal thrombogenesis in dogs.^{14, 262} The results presented in Fig. 4 indicate that in thromboresistance (the number of platelets adhered to the surface of the polymers studied upon contact with blood), poly[bis(trifluoroethoxy)phosphazene] substantially surpasses poly(tetrafluoroethylene) and polyethylene

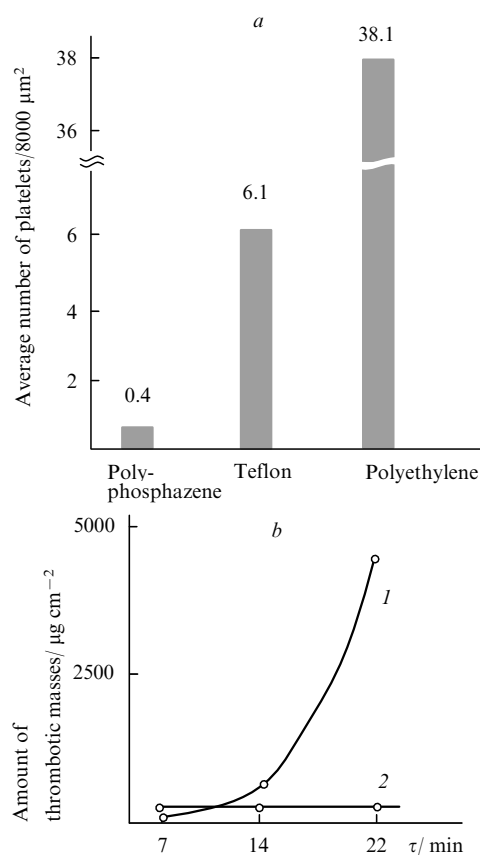


Figure 4. Thromboresistant properties (a) and dynamics of parietal thrombogenesis (duration of the contact of the polymer with blood — 1 min) (b) of 100 samples of poly[bis(trifluoroethoxy)phosphazene] ($M = 16 \times 10^6$, proportion of anomalous units 0.06 mol.%) tested in 10 mongrels.

(1) polyethylene, (2) polyphosphazene.

Table 15. Mechanical properties of nonoriented poly[bis(trifluoroethoxy)phosphazene] films after contact with blood serum at 40 °C.

Duration of the contact (months)	$[\eta]$ / dl g ⁻¹ (acetone)	σ_{tc} / kgf cm ⁻²	σ_{tr} / kgf cm ⁻²	ε (%)	E / kgf cm ⁻²
0	4.00	190	1160	530	725
3	2.90	215	1400	580	910
6	2.70	230	1370	505	1000
8	3.02	170	840	395	1120
12	2.73	160	840	415	1600
16	2.60	140	700	390	1550
24	2.68	146	653	347	1200

Note. σ_{tc} and σ_{tr} are conventional and real tensile stresses related to the initial and ruptured cross-sections of the specimen, respectively; ε is the relative elongation at break; E is elasticity modulus.

meant for medical purposes.^{14, 251} Polyphosphazene is also superior to polyethylene as regards the dynamics of parietal thrombogenesis.

The strength characteristics of poly[bis(trifluoroethoxy)phosphazene] films (Table 15) remain at a good level even after a 2-year contact with blood serum (the results were obtained *in vitro*).²⁶¹ Toxicological assays carried out with an isolated frog heart, male genital cells of animals, and isolated erythrocytes have also demonstrated that films of this polyphosphazene are free from general toxicity; they are highly chemically stable and exert no toxic effect on organs.²⁶²

Biological assays of a polyphosphazene²⁶⁴ as monofilament threads was carried out *in vivo* for 6 months in 12 rats, 4 rabbits, and 2 dogs. Suturing polyphosphazene threads were used in surgical operations in various tissues. These sutures do not cause inflammation in tissues; they are quickly covered by a conjunctive tissue and do not adsorb the tissue liquid. In addition, they are antiseptic and non-toxic and are resolved in living tissues at a controllable rate (from 2 weeks to more than 6 months).²⁶⁴ A fluorinated alcohol, phosphate, and ammonia are the final products of destruction of polyphosphazene filaments. It was concluded that the set of medical and biological properties of polyphosphazene suturing materials permit them to be widely employed in surgery. Polyphosphazene filaments can also be employed to produce a special reinforced jersey fabric for sutureless tubes used in endoprosthetic appliances for the restorative surgery of the upper respiratory tract and for other purposes.

IV. Conclusion

Nowadays, the most widespread method for the synthesis of poly(organophosphazenes) is the polymeranalogous substitution of the chlorine atoms in poly(dichlorophosphazene) by various organic groups. This opens up way for targeted design of polymeric chains and, hence, for the preparation of polymers with diverse properties. However, this synthetic route is characterised by poor reproducibility of experimental results. Nevertheless, these difficulties can be overcome provided that the regularities of the formation of poly(dichlorophosphazene) and polymeranalogous substitution are known. In this case, the method can be used successfully to prepare high-quality poly(organophosphazene) materials with long service lives.

Poly(organophosphazenes) possess a broad range of specific properties and may be of interest for various practical purposes.^{1, 3, 8, 9, 12, 14, 24, 31, 33, 35, 36, 265–276} There are prospects for using them as materials operating at low temperatures (non-freezing elastomers, lubricants, *etc.*). Vulcanisates of poly(fluoroalkoxyphosphazene) elastomers are resistant to fuels, oils, and hydraulic fluids; they are also highly stable with respect to oxygen and ozone and can operate over a wide temperature range, from –65 to 175 °C. Regarding their resistance to repeated low-

temperature deformations, these materials surpass vulcanised materials based on fluorine-containing and fluorosilicone rubbers.²⁶⁶ They can be used to manufacture antivibration and packing gaskets, rings and sleeves, fuel pipes, and other parts for air and space engineering, petrochemical industry, and other branches of industry.^{3, 4, 14, 31, 33, 148, 168, 265, 266, 268} In regions with a cold climate, poly(fluoroalkoxyphosphazenes) can be used both by themselves and as low-temperature modifiers for other materials.²⁴⁹

Some poly(organophosphazenes) can be useful as flame-retardant articles.³³ Thus poly(aryloxyphosphazenes) are highly fire-resistant, and simultaneously they evolve only little smoke. These elastomers appear to be promising as insulating materials for closed spaces such as submarines and planes; they can be used to insulate electric cables and to produce insulating foam plastics.^{265–267}

There are data on using poly(organophosphazenes) as elastic hermetic adhesives for inert materials¹⁶⁴ and for impregnation of textiles in order to impart water- and soil-repelling properties to them.²⁷² Being used to modify other polymers, polyethylene and ABS plastics,^{13, 241, 242} polyvinylphenylsiloxane rubber,^{270, 271} polyesters, phenolic and epoxide polymers,^{10, 24} etc., poly(organophosphazenes) improve in some cases technological properties, elasticity, flame resistance, and thermal stability of these materials.

Poly(organophosphazenes) present considerable interest as polymers used for specific non-trivial purposes, for example, in polymeric catalytic systems,^{14, 113, 254} as solid electrolytes,^{273, 275} or as electrodes in chemical cells.²⁷⁴

Poly(organophosphazenes) are undoubtedly promising for medico-biological purposes, for example, as self-resolvable suture materials meant for diverse purposes in surgery, anaesthetic preparations, and medicines,^{14, 35, 36, 251–264, 276} thromboresistant materials for reliably operating artificial organs (prosthetic blood vessels, heart valves, and ventricles of heart, endoprosthetic respiratory tracts, etc.)

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

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

Natural compounds of the strobilurin series and their synthetic analogues as cell respiration inhibitors

V V Zakharychev, L V Kovalenko

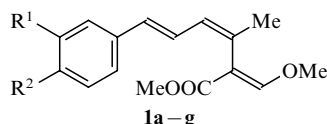
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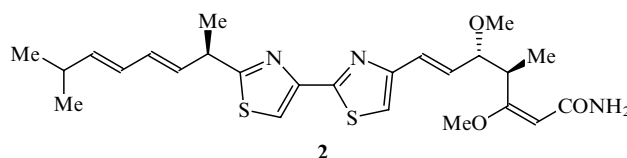
Abstract. A group of fungicidal antibiotics, β -methoxyacrylic acid derivatives (strobilurins, oudemansins, and myxothiazols), their producers, and mechanisms of action are considered. The fungicidal activity of these compounds is based on the suppression of cell respiration of fungi in the bc_1 -complex of cytochromes. They also manifest other biological activities that are not always coupled with inhibition of respiration. Studies of the structure of the natural methoxyacrylates has made it possible to create a novel class of synthetic agricultural fungicides with enhanced stability, high activity, and a broad spectrum of action. The main regularities of the structure–activity relationship and methods of synthesis of these compounds are discussed. The bibliography includes 159 references.

I. Introduction

Some antibiotics produced by various microorganisms (strobilurins, oudemansins, and myxothiazols) were found to inhibit the growth of a broad range of fungi.¹ Mucidin or strobilurin A (**1a**) was the first to be discovered in this group of compounds. Later, several other compounds of similar structure that differed from mucidin only in the number of double bonds and the presence and position of substituents, were identified. These compounds were called strobilurins or oudemansins depending on the structure of their aliphatic chains. All of them are secondary metabolites of various fungi. Myxothiazol **2** has a bacterial origin and its structure differs substantially from that of strobilurin A, although both compounds comprise analogous structural elements.



$R^1 = R^2 = H$ (**a**); $R^1 = OMe$, $R^2 = H$ (**b**), Cl (**c**);
 $R^1 = H$, $R^2 = OMe$ (**d**); $R^1 = OH$, $R^2 = H$ (**e**);
 $R^1 = Me_2C=CHCH_2O$, $R^2 = H$ (**f**);
 $R^1 = OH$, $R^2 = Me_2C=CHCH_2O$ (**g**).



The distinctive feature of this group of compounds is the presence of a fragment of β -methoxyacrylic acid (as methyl ester or amide) linked through an α - or β -carbon atom to the rest of the molecule. They possess identical mechanism of action, which consists in the inhibition of cell respiration at the region of the bc_1 complex of electron-transport cytochromes (complex III). Such an inhibition mechanism made possible wide application of these compounds as a biochemical tool for the study of oxidative phosphorylation. These compounds also served as models for creation of a basically new class of pesticides currently known as 'strobilurin analogues'.

The electron-transport chain of respiratory enzymes plays a crucial role in supplying cells of all aerobic organisms (from bacteria, fungi, and plants to higher animals) with energy. The structure of components of the respiratory chain that are intermediates in the electron transfer from NADH to oxygen, varies insignificantly on passing from species to species. However, substantial differences are observed in the resistance of enzymes of the cytochrome system of various living organisms to specific inhibitors, which is used by certain organisms in the competition struggle.^{2,3}

Natural differences in the structure of respiratory enzymes can be used in the design of agrochemical preparations for achieving their high selectivity with respect to plants and low toxicity for mammals.² Owing to the wide occurrence of redox processes involving the cytochrome system, the respiration inhibitors can be used for suppressing the vital activity of a great variety of organisms. Thus many synthetic strobilurin analogues possess not only fungicidal, but also insecticidal, acaricidal, and nematocidal activities.

Other natural compounds that incorporate a β -methoxyacrylic acid fragment as a structural element are also known. For instance, a β -methoxyacrylate fragment in dihydrokawain (5,6-dihydro-4-methoxy-6-phenylethyl-2H-pyran-2-one), which has been recently isolated from kava *Piper methysticum*⁴ and possesses fungicidal activity, includes a hydroxyranone ring. However, there is no evidence that this compound inhibits respiration.

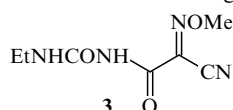
The recently discovered derivatives of mesoxalic acid amidonitrile *O*-methyloxime (e.g., cymoxanil **3**) are structurally similar

V V Zakharychev, L V Kovalenko D I Mendeleev Russian Chemical-Technological University, Miusskaya pl. 9, 125047 Moscow, Russian Federation. Fax (7-095) 200 42 04. Tel. (7-095) 948 54 63 (V V Zakharychev), (7-095) 496 58 37 (L V Kovalenko)

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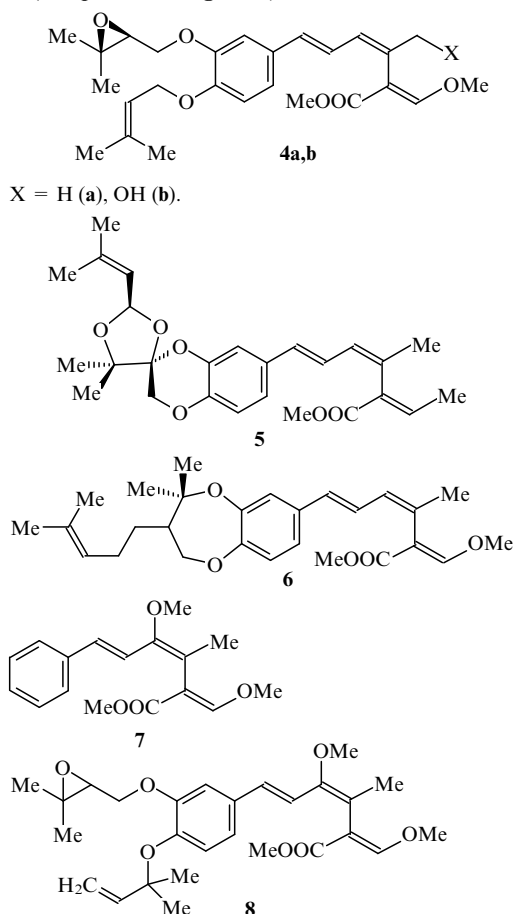
to some strobilurin analogues. However, their fungicidal activity is associated with blocking of RNA synthesis in fungal cells.⁵



II. Natural methoxyacrylate-type inhibitors

The high fungicidal activity of the new antibiotic mucidin (**1a**) isolated from the cultural medium and mycelium of the fungus *Oudemansiella mucida* was first discovered by Musilek *et al.*^{6–8} in the mid-1960's. Two fungicidal antibiotics called strobilurins A and B were isolated from mycelium of the basidiomycete *Strobilurus tenacellus* in 1977.⁹ Structural elucidation of these compounds revealed that strobilurin A and mucidin are identical and represent methyl (2*E*,3*Z*,5*E*)-2-methoxymethylene-3-methyl-6-phenylhexa-3,5-dienoate.^{10,11} The *E,Z,E*-configuration of the double bonds of strobilurins was confirmed by chemical and spectroscopic studies¹² as well as by stereospecific synthesis.¹³ The spectral properties of a synthetic *E,E,E*-isomer of strobilurin A¹³ differed from those of the natural compound.

Later, several other secondary metabolites of various fungi were isolated and characterised. They are strobilurin A derivatives containing substituents in the benzene ring or in the aliphatic chain (compounds **1b–g**, **4–8**).



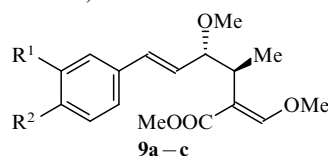
X = H (**a**), OH (**b**).

Table 1. Natural strobilurins and oudemansins.

Struc- ture	Name	Producing organism	Ref.
1a	Strobilurin A (mucidin)	<i>Oudemansiella mucida</i> , <i>Strobilurus tenacellus</i> , <i>Bolinea lutea</i> etc.	6–9, 15–17
1c	Strobilurin B	<i>S. tenacellus</i>	9
1f	Strobilurin C	<i>Xerula longipes</i> , <i>X. melanotricha</i>	16
1d	Strobilurin X	<i>O. mucida</i>	18
4b	Hydroxystrobilurin D	<i>Mycena sanguinolenta</i>	19
5	Strobilurin E	<i>Crepidotus fulvotomentosus</i>	20
4a	Strobilurin D	<i>Cyphellopsis anomala</i>	21
1e	Strobilurin F-1	<i>Cyphellopsis anomala</i>	21
1g	Strobilurin F-2	<i>Bolinea lutea</i>	15, 22
6	Strobilurin G	<i>B. lutea</i>	15, 22
1b	Strobilurin H	<i>B. lutea</i>	15, 22
7	9-Methoxystrobilurin A ^a	<i>Favolaschia</i> spp.	23
8	9-Methoxystrobilurin K ^a	<i>Favolaschia</i> spp.	23
9a	Oudemansin A	<i>O. mucida</i>	24
9b	Oudemansin B	<i>Xerula longipes</i> , <i>X. melanotricha</i>	16
9c	Oudemansin X	<i>O. radicata</i>	25

^a Trivial nomenclature is retained.

aromatic ring and their positions. The same letters are used for the same substitution pattern [cf. the structures of strobilurin B (**1c**) and oudemansin B (**9b**)]. The early name of strobilurin A, mucidin, was preserved in the biochemical literature. Strobilurin X was termed by analogy with oudemansin X,¹ because the investigators who first discovered this compound did not give it any trivial name. Two strobilurins F were identified and named almost simultaneously by independent groups of investigators; therefore, they bear additional numerical indices (in the order of publication).¹



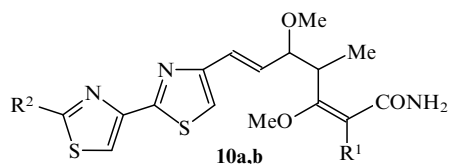
R¹ = R² = H (**a**); R¹ = OMe, R² = Cl (**b**); R¹ = H, R² = OMe (**c**).

Myxothiazol **2** (or myxothiazol A) mentioned above produced by the myxobacteria *Myxococcus fulvus* is also a derivative of β -methoxyacrylic acid.^{14,26,27} In contrast with strobilurins and oudemansins, the β -methoxyacrylate fragment of the myxothiazol molecule is represented by an amide rather than by an ester and is substituted at the β -carbon (but not at the α -carbon) atom. Nevertheless, the mechanism of biological action of this antibiotic is close to that of the natural esters of methoxyacrylic acid.^{28,29}

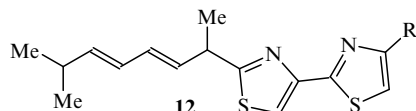
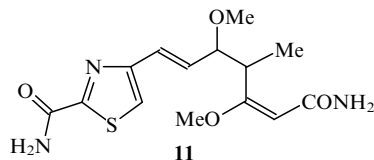
For a long time, myxothiazol had no analogues among β -methoxyacrylate-type compounds. However, a great number of related compounds were discovered recently. At present, 33 myxothiazols have been isolated, and the structures of 24 of them have been given in a review.¹ Unfortunately, comprehensive information about the structure of myxothiazols is still absent in the current literature. It is known only that in myxothiazols B–I, K–O (**10a**) and Q, X, and Y (**10b**), R² = MeCO, MeCH(OH), or an (*E,E*)-nonadienyl residue containing hydroxy, carbonyl, and epoxide groups. Myxothiazol J does not exist. Myxothiazol P (**11**) has only one thiazole ring. In myxothiazols R–W (**12**), the β -methoxyacrylic fragment is absent and R is an oxygenated three-, five-, or six-carbon-atom chain.¹

Oudemansins (**9a–c**) possess similar structure. Formally, they can be regarded as the products of addition of methanol at the C(3)–C(4) double bond of strobilurins. The known strobilurins and oudemansins together with their producers are listed in Table 1.

Considering the trivial names of methoxyacrylate-type antibiotics, it should be noted that the letter symbols A, B, and C in the names of strobilurins and oudemansins refer to substituents in the



R¹ = H (a), Me (b).



Strobilurins A and B, all of oudemansins,¹ and myxothiazol A³⁰ have been synthesised. The generalised data concerning natural methoxyacrylates can be found in a comprehensive review.¹

The conformer of strobilurin A (**1a**) with a minimum energy was calculated using the molecular mechanics method and the molecular orbital theory. It was found that the phenylpentadienyl and methyl β -methoxyacrylate fragments are planar, but are arranged in perpendicular planes. However, according to these calculations, the energy barrier to rotation around the C(2)–C(3) bond is low, therefore enantiomers cannot be isolated at room temperature.³¹

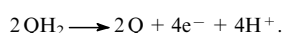
The structure of oudemansin A **9a** in the crystalline state was determined by X-ray diffraction analysis.²⁴ It was found that its conformation closely resembles the conformer of strobilurin A with the minimum energy.³¹ Apparently these conformations of strobilurin and oudemansin are close to the forms of these molecules bound to cytochrome.³¹

III. Biological activity of the natural compounds

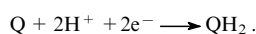
Low concentrations of strobilurins, oudemansins, and myxothiazols inhibit the growth of diverse fungi. Their mechanism of action is associated with violation in electron transport in complex III of the mitochondrial membrane, which results in the inhibition of cell respiration.^{28, 29, 32–34}

Complex III (ubiquinone–cytochrome *c* oxidoreductase or the *bc*₁-complex) is an intermediate link in the chain of respiratory enzymes of bacteria and mitochondria (plant chloroplasts contain a structurally homologous *b*₆*f*-complex). It catalyses the electron transfer from hydroquinone to cytochrome *c*. The energy of the redox reaction is thereby converted into a chemiosmotic membrane potential through the translocation of 2e[−] and 4H⁺ across the membrane.

According to the Mitchell Q-cycle concept,^{3, 35, 36} complex III has two quinone reaction centres localised on opposite sides of the membrane. One of them, the so-called Q_o-centre (also designated as Q_p or Q₂), is the site of hydroquinone oxidation by the reaction:



Two electrons are transferred by a high-potential route via the FeS protein and cytochrome *c*₁ to reduce cytochrome *c*. The other two electrons move to the opposite side of the membrane by a low-potential route formed by cytochromes *b*_H and *b*_L, to the second quinone centre, the so-called Q_i-centre (also designated as Q_n, Q_c, and Q_r) where the quinone is reduced:



The inhibitors binding to the Q_i-centre induce changes in the absorption spectrum of cytochrome *b*_H (*b*₅₆₂). Antimycin is the most specific of these inhibitors. Methoxyacrylates were among

the first to be discovered in a group of compounds that block respiration by binding to the Q_o-centre. This binding results in a shift in the absorption band of cytochrome *b*_L (*b*₅₆₆).^{29, 32, 33, 37–42}

Since all tissue respiration inhibitors of this type contain a residue of *b*-methoxyacrylic acid (MOA) as a structural fragment, which seems to be the key element for manifestation of biological activity, they were termed MOA-inhibitors.³³

The binding site of MOA-inhibitors is not identical with the quinone site, since in the presence of these compounds ubiquinone remains bound with cytochrome *b*. This may be accompanied by changes in the relative position of the ubiquinone molecule at the reaction centre due to a conformational rearrangement of the cytochrome and the resulting violation of the electron transport to the FeS protein.^{43–45} Thus the concentration of myxothiazol required for 50% inhibition of bovine heart cytochrome *b* activity is 0.58 mol per mol of cytochrome.²⁹ At high concentrations, MOA-inhibitors can displace the quinone from the site of its binding with the Rieske FeS-protein.⁴¹ Apparently, the binding of inhibitors is reversible, since they can replace one another in the Q_o-centre.³⁹

Like methoxyacrylates, other compounds can also bind with the Q_o-centre. Pyridine (which inhibits also complex I), 6-hydroxy-5-*n*-undecyl-4,7-dioxobenzothiazole,² dibromothymoquinone,^{2, 41} and the chromone antibiotics stigmatellins A and B^{2, 41, 44, 46} also possess inhibitory activity. Despite the reciprocal competition of these compounds, their binding sites in the Q_o-centre are other than those of MOA-inhibitors.^{1, 2}

The structure of the *bc*₁-complex and the Q_o-centre as well as the mechanisms of resistance to MOA-inhibitors are discussed in a number of publications.^{3, 35, 36, 47}

Strobilurins and oudemansins manifest nearly identical high activity *in vitro* against a wide array of fungi,^{9, 15, 16, 18, 19–21, 23–25, 48, 49} but are inactive against bacteria. Strobilurin F-1 (**1e**), which manifests much lower activity, is an exception.²¹ For example, the minimum inhibitory concentrations of strobilurin A (**1a**) for *Candida albicans*, *C. crusei*, *C. parapsilosis*, *C. tropicalis*, *Cryptococcus neoformans*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Microsporum canis* lie in the range 0.1–12.8 mg ml^{−1}, whereas the inhibitory concentrations for *Aspergillus* spp. and *Scopulariopsis* spp. range from 100 to 1000 mg ml^{−1} (see Ref. 48). Owing to its antimycotic activity, strobilurin A has been used in clinical and veterinary medicine under the commercial name of Mucidermin Spofa.¹

Myxothiazol A **2** is one of the most active MOA-inhibitors.³² It manifests not only fungicidal properties, but inhibits also the growth of some Gram-positive bacteria,¹ reversibly inhibits the late G₁/S phase of the cell cycle of lymphoblastic T-cells,⁵⁰ and possesses insecticidal activity.¹ In addition, myxothiazol **2** can bind to the phyloquinone site in photosystem I (*K*_d = 9.5 × 10^{−6} mol litre^{−1}). However, this inhibitor does not manifest any activity *in vivo* due to the higher affinity of phyloquinone for this site.^{51, 52} Myxothiazol **2** inhibits also complex I of mitochondria.² Other myxothiazols rank below myxothiazol A in fungicidal activity.¹

Oudemansin A (**9a**),²⁴ strobilurins A (**1a**), B (**1c**),⁹ E (**5**),^{20, 49} D (**4a**),²¹ and G (**6**)¹⁵ inhibit the growth of human tumour cells, the latter three compounds manifesting the highest activity. 9-Methoxystrobilurins (**7**, **8**)²³ and strobilurin G (**6**)¹⁵ also display cytostatic activity. Strobilurins D (**4a**)²¹ and E (**5**)^{20, 49} possess antiviral properties. Strobilurins A (**1a**) and B (**1c**) as well as oudemansin A (**9a**) inhibit chitin synthase.⁵³

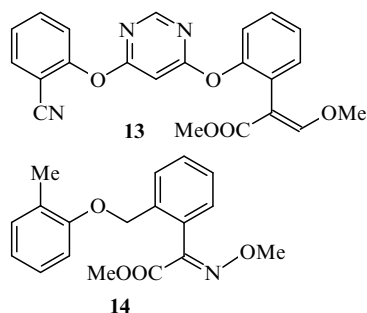
Strobilurins A (**1a**), B (**1c**), C (**1f**), and X (**1d**) as well as oudemansins A (**9a**) and B (**9b**) are relatively non-toxic for mice. According to different data, the peroral lethal dose, LD₅₀, for strobilurin A is 500 mg kg^{−1} (see Ref. 8) or 825 mg kg^{−1} (see Ref. 18). Intraperitoneal LD₅₀ is 250 mg kg^{−1} (see Ref. 8); that for oudemansin A exceeds 300 mg kg^{−1} (see Ref. 31). However, myxothiazol **2** is highly toxic for all animals tested (peroral LD₅₀ for mice is 2 mg kg^{−1}).²⁷

Despite the variety of useful properties, natural MOA-inhibitors have found only limited use as medicinal drugs or biochemical tools for the study of cell respiration. They cannot be used as agricultural pesticides because they have some serious disadvantages. For example, strobilurin A, which possesses high activity against a wide variety of fungi *in vitro*, is fairly inactive in greenhouse studies. This may be due to the low photochemical stability and a relatively high volatility of this compound. Hence, it rapidly evaporates from the surface of leaves of the treated plants. The time of the photochemical loss of the first 50% of strobilurin A in thin film experiments (τ_{50}) is 1 min.³¹ Nevertheless, this group of antibiotics presents substantial interest. The relative simplicity of their structure, their ability to retain high activity irrespective of significant changes in their structure, and a basically new mechanism of their action, which entails the absence of cross-resistance in pathogens insensitive to the currently used fungicides, stimulate the synthesis of biologically active analogues of the natural substances. Although respiration inhibitors may be hazardous for homoiothermal organisms, the low toxicity of individual strobilurins and oudemansins suggests that synthetic analogues may exist which differ substantially in toxicity with respect to fungi and homoiothermal organisms.¹

IV. Synthetic strobilurin analogues and structure – activity relationships

Although the first attempts to synthesise analogues of natural MOA-inhibitors were undertaken only in the early 1980's, over 200 patents for the synthesis of these compounds, their practical applications, and composite mixtures, have been published.^{31, 54, 55}

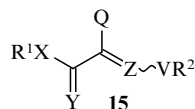
Synthetic analogues of strobilurins have been patented as broad-spectrum agricultural and industrial fungicides, nematocides, insecticides and acaricides, plant growth regulators, antitumour and antiviral preparations. The undeniable leaders in this area are the British company ICI and the German company BASF who have succeeded in creating experimental fungicides ICI-5504 (**13**) and BAS-490F (**14**).



Two fragments can be distinguished in the molecules of natural MOA-inhibitors and their synthetic analogues, *viz.*, a toxophore or a pharmacophore, and a carrier group⁵⁶ (or a ballast group⁵⁴ or backbone⁴⁷). Thus in strobilurins, the β -methoxyacrylate fragment plays the role of a toxophore and a substituted (*E,E*)-phenylpentadienyl residue is the backbone. It is the toxophore that is responsible for the binding with the methoxyacrylate site of the enzyme, although it is inactive if it is not bound with the backbone. In turn, the backbone not only imparts lipophilicity to the compounds, which is needed for the transport of a pharmacophore into the quinone centre, but also enables matching of the shape of the inhibitor molecule and that of the Q_o -centre cavity.⁴⁷

Both factors must be taken into consideration in design of strobilurin analogues. The structure of strobilurins can be modified in two independent ways: (1) substitution of the (*E,E*)-phenylpentadienyl chain of strobilurins for various aryl, heterocyclic, and other groups; (2) substitution of the toxophore element, a β -methoxyacrylic acid fragment, for isosteric fragments

of crotonic, methoxyiminoacetic, and analogous acids. Synthetic analogues of the natural MOA-inhibitors are compounds with the general formula **15**.



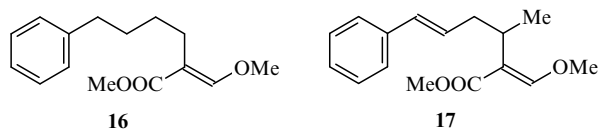
X = O, S, NR³; Y = O, S; Z = CH, N; V = CR⁴, O, S, NR⁵; R¹–R⁵ = H, Alk; Q = Ar, Het, ArX–, HetX–, *etc.*

In synthetic analogues, Q usually stands for a bulky hydrophobic substituent, which mimics a labile phenylpentadienyl residue (the backbone). This largely determines the biological activity, photostability, selectivity, and systemic properties of a compound. The rest of the molecule is a toxophore. The elements V, X, Y, and Z can vary rather independently. More or less active are esters, amides, and thioamides of appropriately substituted acrylic⁵⁷ and crotonic⁵⁸ acids, β -alkoxy-,⁵⁹ β -alkylthio,⁶⁰ β -aminoacrylic acids,⁶¹ *O*-alkyloximes,^{62, 63} *S*-alkylthiooximes,⁶⁴ and alkylhydrazones of glyoxalic acids⁶⁵ and unsaturated acids of analogous structure. Toxophore groups with different structures are also known. For example, compounds **15** devoid of ester or amide groups (R¹ = H, Me, X = CH₂, Y = O, Z = N, V = O, R² = Me) are known to inhibit respiration.⁴⁷ However, these compounds rank below esters and amides of the above-mentioned acids in activity.

After the discovery of a large variety of compounds that are not derivatives of β -methoxyacrylic acid but are able to inhibit cell respiration, the term 'synthetic MOA-inhibitors' is no longer a correct definition for this group of biologically active substances. It was therefore suggested that such compounds be called 'synthetic strobilurin analogues'.⁶⁶

The pioneering studies in the field of synthesis of strobilurin analogues were aimed at increasing their photostability. The effects of structural changes on the photostability of strobilurin analogues were considered by some authors more comprehensively.^{31, 56} Greenhouse studies of oudemansin activity revealed that the presence of a β -methoxyacrylate group did not decrease the photochemical stability of these compounds.^{31, 56}

The simplest strobilurin A analogue **16** with partially hydrogenated double bonds and the oudemansin A analogue **17** did not manifest any useful activity in hothouse studies, although compound **17** shows fungicidal properties on agar cultures of fungi.³¹



One of the first synthetic analogues of natural MOA-inhibitors was the so-called MOA-stilbene **18**.^{57, 67–70} This compound possesses fungicidal and insecticidal properties and surpasses its natural prototypes in activity.¹ X-Ray analysis of a monocrystal of compound **18** showed that the planar methyl β -methoxyacrylate and stilbene fragments are nearly perpendicular to each other as is the case with the strobilurin molecule.³¹ Stilbene **18**, like strobilurin A, is a potent inhibitor of mitochondrial respiration (I_{50} for stilbene is 0.04 μ M, that for strobilurin A is 0.11 μ M³¹). This compound is photochemically more stable than its natural analogue (τ_{50} for irradiation in thin film is 3 min) and less volatile.⁵⁶ The photostability of MOA-stilbene increases considerably in the presence of photostabilisers.⁵⁶

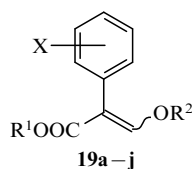
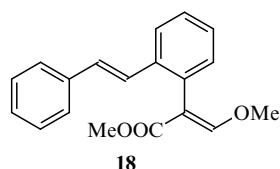
In the series of β -alkoxy- α -arylacrylates **19**, even methyl (*E*)- β -methoxy- α -phenylacrylate **19a** (without substituents in the benzene ring) manifests a pronounced fungicidal activity (Table 2).

Table 2. Comparative activities of acrylates **19**, **20**, and **21**.⁵⁷

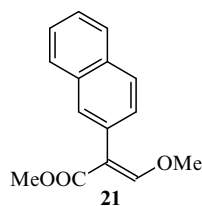
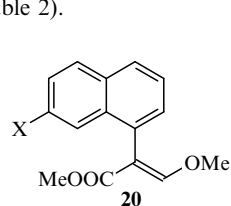
Com-pound	R ¹	R ²	X	Subject of study ^a					
				<i>P.r.</i> ^b	<i>E.g.</i> ^c	<i>V.i.</i> ^d	<i>P.o.</i> ^e	<i>C.a.</i> ^f	<i>P.v.</i> ^g
<i>E</i> - 19a	Me	Me	H	4	4	4	0	2	4
<i>Z</i> - 19b	Me	Me	H	2	0	0	0	0	0
<i>E</i> - 19c	Et	Me	H	0	0	0	0	0	4
<i>E</i> - 19d	Me	Et	H	0	0	1	0	0	0
<i>E</i> - 19e	Et	Et	H	0	0	0	0	0	1
<i>E</i> - 19f	Me	Me	2-(<i>E</i> -PhCH=CH)	4	4	4	3 ^h	4	4
<i>E</i> - 19g	Me	Me	3-(<i>E</i> -PhCH=CH)	0	0	0	0	0	3
<i>E</i> - 19h	Me	Me	4-(<i>E</i> -PhCH=CH)	0	0	0	0	0	2
<i>Z</i> - 19j	Me	Me	2-(<i>E</i> -PhCH=CH)	4	4	4	3 ^h	4	4
<i>E</i> - 19k	Me	Me	2-Cl	0	4	0	0	4	4
20	—	—	H	4	3	4	4	4	4
21	—	—	—	3	0	2	2	—	4

Note. The infected plants were sprayed with emulsions (the concentration of active substance was 100 ppm).

^a Designations: 4 — undamaged plants; 3 — up to 5% damage; 2 — 6%–25% damage; 1 — 26%–59% damage; 0 — 60%–100% damage in comparison with nontreated plants. ^b *P.r.* — *Puccinia recondita* (on wheat); ^c *E.g.* — *Erysiphe graminis* f. sp. *hordei* (on barley); ^d *V.i.* — *Venturia inaequalis* (on apple-tree); ^e *P.o.* — *Pyricularia oryzae* (on rice); ^f *C.a.* — *Cercospora arachidicola* (on peanut); ^g *P.v.* — *Plasmopara viticola* (on grapes); ^h spraying with an emulsion with the concentration of the active substance of 25 ppm.

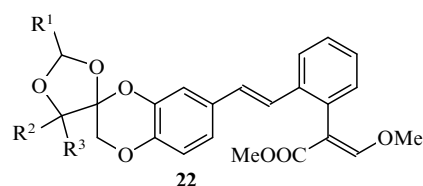


On the whole, phenylacrylates **19** are more active for R¹ = R² = Me than in those cases where R¹ or R² are represented by other alkyl substituents or hydrogen atoms. *E*-Isomers are usually more active than *Z*-isomers; it is probable that the latter, being very weak inhibitors of mitochondrial respiration, acquire the fungicidal activity following isomerisation.³¹ Substituents in the nucleus can both strongly enhance the activity and decrease it. Compounds having a bulky substituent similar to the styryl fragment in the strobilurin molecule at position 2 of the phenyl ring are usually more active. The activity of naphthylacrylates strongly depends on the position of a toxophore: α -naphthylacrylate **20** (X = H) is much more active than the β -isomer **21** (see Table 2).



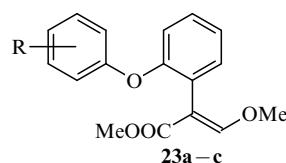
X = H, Ph, Hal, Alk etc.

Although substituted MOA-stilbenes manifest high fungicidal activity in hothouses, in field tests they are moderately active due to their low photostability.¹ However, owing to their availability MOA-stilbenes, together with natural compounds, have found wide use as tools in biochemical studies. Of particular interest are stilbenes **22**, which are analogues of strobilurin E and possess antiviral and antitumour properties.⁷¹



In order to increase the photostability of such compounds, it was suggested to hydrogenate the double bond between two benzene rings⁷² and to replace it by other spacer groups, such as CH₂O, SCH₂, O, S,^{57, 73–75} SO, SO₂,⁵⁷ CH₂SO, CH₂SO₂,⁷⁶ etc.^{56, 77} Methyl (*E*)-methoxyimino-[2-(2-methylphenoxy)methyl]-phenyl]acetate (**14**) (BAS-490F), an experimental fungicide produced by BASF and possessing a protective, curative, and eradicating activities is an example. Its standard doses vary from 50 to 350 g ha^{−1} (see Ref. 66).

Acrylate **23a**, a diphenyl ether derivative, is also highly efficient against a great number of fungi.^{57, 78} This compound is sufficiently resistant to light (τ_{50} for irradiation in thin film is 30 h).⁵⁶ In addition, this compound possesses systemic fungicidal activity.^{1, 54} Compound **23b**, which contains three benzene rings, is even more active,^{54, 77} but is devoid of systemic properties. Besides, a serious disadvantage of this derivative is that it caused severe damages to some cultures in field tests.⁵⁴ The reasons for phytotoxicity of such compounds have not been finally established.⁷⁹ A change in the position of a phenoxy group in the molecule results in a sharp decrease in the fungicidal activity. Thus the isomer **23c** is a weak fungicide. In heterocyclic analogues of the ester **23b**, the high level of fungicidal activity is often associated with their ability to migrate in the plant. However, the biological properties of compounds change in an unpredictable manner depending on the number and position of heteroatoms in the rings: sometimes this activity drops drastically, and the action spectrum is narrowed or the phytotoxicity is enhanced.⁵⁴ Among derivatives of the heterocyclic series, methyl (*E*)-2-[6-(2-cyano-phenoxy)pyrimidin-4-yloxy]phenyl]-3-methoxyacrylate (**13**) (ICI-A5504), turned out to be the most efficient. This compound is an experimental fungicide and exerts systemic and translaminar activities against asco-, basidio-, deuterio-, and oomycetes.^{80, 81}



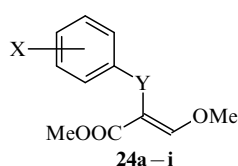
R = H (**a**), 3-PhO (**b**), 4-PhO (**c**).

Table 3. Activities of acrylates **24a–i**.⁸²

Com- pound	X	Y	Object of study ^a					
			<i>P.r.</i>	<i>E.g.</i>	<i>V.i.</i>	<i>P.o.</i>	<i>C.a.</i>	<i>P.v.</i>
24a	2-Ph	CH ₂	1	0	3	0	0	0
24b	3-Ph	CH ₂	4	3	4	0	3	4
24c	4-Ph	CH ₂	0	0	0	2	0	0
24d	H	NMe	0	4	4	4	1	4
24e	3-Ph	NMe	4	4	1	3	4	4
24f	H	O	0	0	2	0	0	0
24g	3-Ph	O	4	0	4	3	3	4
24h	H	S	0	0	0	3	0	3
24i	3-Ph	S	4	4	4	2	4	4

Note. The infected plants were sprayed with emulsions (the concentration of the active substance of 100 ppm).

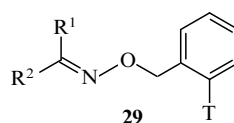
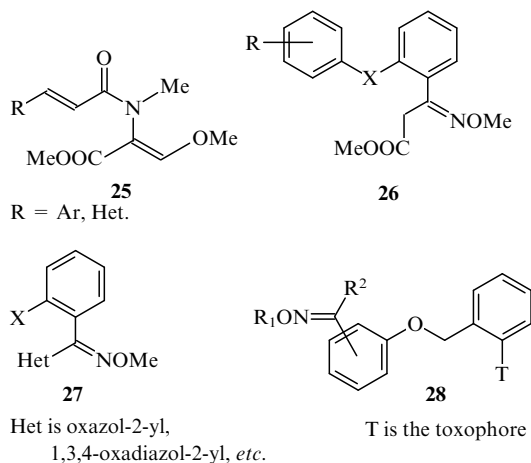
^a For designations see footnote to Table 2.



In a series of compounds of the formula **24** the toxophoric group of which is attached to an aryl or a heterocyclic residue not directly, but through O and S atoms or through NR or CR₂ groups, the derivatives with *meta*-substituents in the aromatic ring display the highest activity (Table 3).

A vast array of structurally diverse synthetic analogues of strobilurin are presently known. Thus biological activities of a great number of compounds with the general formula **15** (where Q designates various substituted carbo- and hetero-cycles), such as derivatives of indole,⁸³ pyrazole,^{84–86} pyrrole^{87–89} (methoxyacrylate derivatives of pyrrole have been described in the review³⁵), triazine,⁹⁰ dibenzo[*b,e*]-1,4-dioxin,⁹¹ thiazole,^{92–94} isoxazole,⁹² pyridine,^{95–98} pyrimidine,⁹⁹ *etc.*, have been assayed. The structure–activity relationships for this group of compounds are nearly the same as those for α -phenylacrylates. Thus the activity of monocyclic compounds increases as certain substituents are introduced at the position adjacent to the toxophoric group. As in the case of α -phenylacrylates, the β -styryl fragment and the radicals having similar bulk and shape, enhance the activity.

Methyl methoxyacrylates derived from amides of aromatic and heteroaromatic acids **25** possess fungicidal properties.^{100,101} In some cases, esters **26** manifested higher activity than the corresponding derivatives of glyoxylic acid.¹⁰² Fungicidal activity was also found in compounds **27** with an unusual structure of the toxophoric group.^{103,104}



Certain oximes **28**^{105,106} and **29**^{107–119} show enhanced fungicidal activity in comparison with their analogues that do not contain an oxime fragment in their backbone. The spatial isomerism about the C=N bond may be crucial for the manifestation of activity of these compounds.¹²⁰

In the series of synthetic analogues of the natural MOA-inhibitors, the experimental fungicides ICI-A5504 (**13**) and BAS-490F (**14**) have been studied in most detail. Like the natural compounds, these analogues bind with the Q_o-centre of cytochrome *b* and actively inhibit cell respiration.^{66,80,81,121,122} Both substances have low toxicity in rats (LD₅₀ > 5000 mg kg⁻¹).

The reason for such a selectivity are the peculiarities of their biokinetic properties rather than their selective affinity for the molecular target. Thus the inhibition constants of complex III from various living organisms were determined using various methoxyacrylates and their analogues.¹²¹ The *pI*₅₀ values for MOA-stilbene (**18**), BAS-490F (**14**), and myxothiazol (**2**) are given in Table 4. The oxidase from cereals was the least sensitive to all of the inhibitors tested. The difference in the *pI*₅₀ values is less pronounced for enzymes from other species. Structural changes in compounds that enhance their activity against fungi, induced analogous changes in the activities against other species.

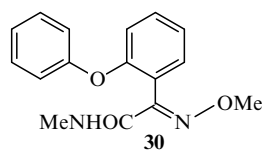
Table 4. *pI*₅₀ Values for inhibitors with respect to complex III of various organisms.¹²¹

Compound	Yeast	Botrytis	Fly	Rat	Corn
MOA-stilbene (18)	7.3	7.4	7.8	7.6	6.3
BAS-490F (17)	7.9	7.8	6.9	6.3	6.0
Myxothiazol (2)	8.0	7.9	8.3	7.8	6.5

Analysis of biokinetic properties of a series of compounds revealed that such properties as absorption, transport, and metabolism are more important for their selective toxicity. For example, the high activity of compound **14** against surface-located powdery mildew is due to its diffusion through the gaseous phase and the low level of its absorption by leaves in which it is rapidly metabolised. In contrast, an analogue of this preparation in which the ester group is replaced by the methylamide group is expected to be highly active against endoparasitic fungi.¹²³

A recent report deals with *N*-methyl-(*E*)-methoxyimino-(2-phenoxyphenyl)acetamide (code SSF-126)¹²⁴ (**30**), a new preparation of this series, which possesses a broad spectrum of fungicidal activities and is being tested. It is assumed that the

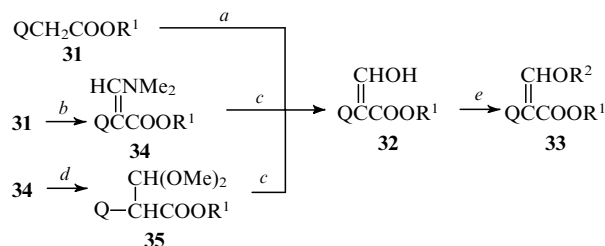
main area of its application is the fight against paddy rice diseases.¹²⁵



Some strobilurin analogues can also bind with the *b*₆*f*-complex of chloroplasts in the Q_o or Q_i centre. Thus compounds **18** and **23a,b** bind with the Q_i centre, whereas compounds **24b,e,g**, with the Q_o centre. No binding was observed for compounds **20** (X = Ph) and **25** (Ar = 2- or 4-ClC₆H₄).¹²⁶

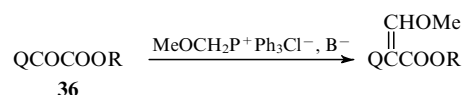
V. Synthesis of strobilurin analogues

Syntheses of β-alkoxyacrylates are usually based on esters of substituted acetic acid **31**. Condensation with formates in the presence of a base gives aldehydoesters **32**.^{31, 54, 56, 81} The reaction with dimethylformamide dimethylacetal gives compounds **34**, which also yield aldehydoesters **32** following hydrolysis or alcoholysis. Alkylation of enolates (compounds **32**) results in β-alkoxyacrylates **33** (Scheme 1).



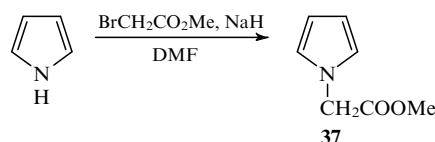
(a) HCOOR, NaH; (b) Me₂NCH(OMe)₂, Py·TsOH; (c) H₂O, H⁺; (d) MeOH, H⁺; (e) B, R²X (X = Hal, SO₃OR²); R¹, R² = Alk; Q = Ar, Het, ArX-, HetX-, etc.

β-Methoxyacrylates are often synthesised from glyoxalates **36** by the Wittig reaction^{31, 56} (Scheme 2).

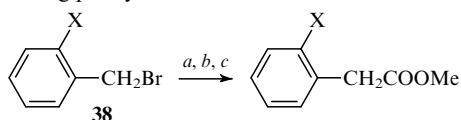


Synthesis of the corresponding derivatives of acetic (**31**) or glyoxylic (**36**) acids is carried out by conventional methods.

Alkylation of nitrogen-containing heterocycles with methyl bromoacetate in the presence of bases was used, e.g., in the synthesis of pyrrole derivatives **37**.^{55, 58}



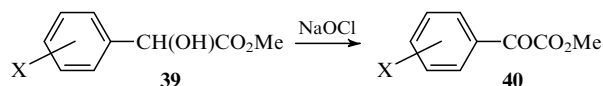
Reaction of benzyl halides and their *ortho*-substituted derivatives **38** with sodium cyanide results in phenylacetonitriles. Their subsequent hydrolysis and esterification yield esters of the corresponding phenylacetic acids.¹²⁸



X = H, Hal, OAr;

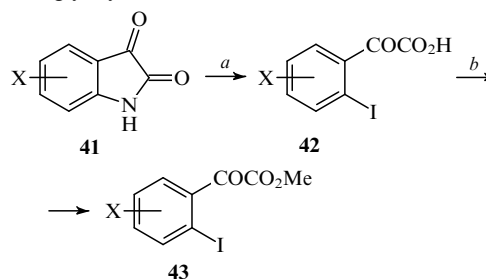
(a) NaCN, EtOH, H₂O; (b) HCl; (c) MeOH.

Esters of glyoxylic acids **40** were obtained by oxidation of alkyl mandelates **39** with sodium hypochlorite.¹²⁹



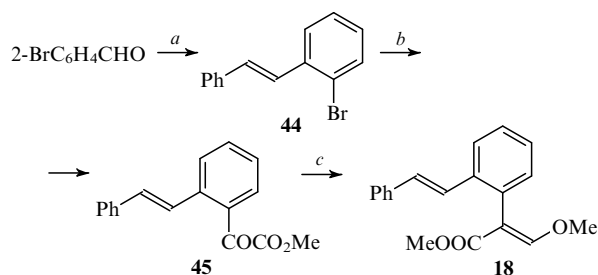
X = Alk, Ar, Het.

Alternatively, they are synthesised from isatins **41**.¹³⁰ To this end, substituted isatins are hydrolysed with a solution of NaOH on heating; the amino group is then substituted for iodine by treatment of the corresponding diazo compound with potassium iodide and copper bronze. The resulting substituted *o*-iodophenylglyoxylic acids **42** are esterified with methyl chloroformate in the presence of triethylamine. In compounds **43**, iodine can be exchanged for other substituents to give a wide range of substituted glyoxylic acids.



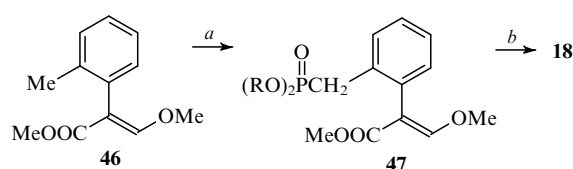
(a) 1. aq. NaOH; 2. NaNO₂, H₂SO₄, H₂O; 3. KI, Cu;
(b) ClCO₂Me, Et₃N, CH₂Cl₂, 10°C;
X = H, Alk, AlkO, Hal, O₂N, NC.

Synthesis of compounds of the type **31** or **36** was also carried out by other methods.^{65, 74, 131–133} Thus MOA-stilbene **18** was synthesised from *o*-bromobenzaldehyde. This was coupled with benzylmagnesium bromide. The resulting alcohol was dehydrated in the presence of an acid to give 2-bromostilbene (**44**). The Grignard reagent prepared from the latter was slowly added to an excess of dimethyl oxalate. The ester arylglyoxylic acid **45** that formed was introduced into the Wittig reaction with (methoxymethylene)triphenylphosphorane. The target product **18** contained a small admixture of the *Z,E*-isomer.⁵⁷

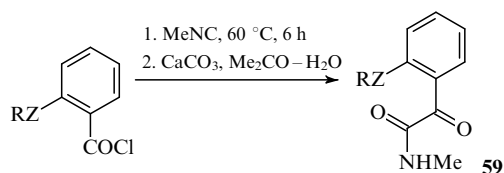


(a) 1. PhCH₂MgCl; 2. aq. HCl; 3. H₃PO₄, Δ;
(b) 1. Mg; 2. (CO₂Me)₂; (c) MeOCH₂P⁺Ph₃Cl⁻, NaH.

Yet another method to obtain compound **18** is the bromination of (*E*)-2-(2-methylphenyl)-β-methoxyacrylate (**46**) with *N*-bromosuccinimide. The reaction of the resulting bromomethyl derivative with trialkyl phosphite and subsequent condensation of methoxyacrylate **47** with benzaldehyde by the Wittig–Horner–Emmons reaction results in stilbene **18**.⁷⁰

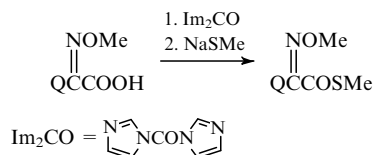


(a) 1. NBS; 2. (RO)₃P; (b) NaH, PhCHO.



R = H, Alk, Hal, Ar, Het; Z = CH₂, O, S, CHOH, CO, CH₂CH₂, CH=CH.

Some *S*-methylmethoxyiminothioacetates that are sometimes more active in trials than compound **14** can be obtained by hydrolysis of methoxyiminoacetic acid esters and subsequent reaction of free acids with sodium methanethiolate¹⁵⁶ in the presence of carbonyldiimidazole.



Methyl *O*-esters and amides of methoxyiminothioacetic acids are obtained by the reaction of esters and amides of methoxyiminoacetic acids with Lawesson's reagent.^{157–159}

VI. Conclusion

The modern approach to the synthesis of pesticides that makes use of the natural compounds for identification of biological targets and for modelling new biologically active substances is well known and has often been employed, *e.g.*, for elaboration of pyrethroid insecticides, nereistoxin analogues, juvenoids, neonicotinoids, 4-hydroxycoumarine derivatives, *etc.* Strobilurin analogues also provide an illustrative example of how bioisosterism can be applied for directed enhancement of properties of natural compounds. Despite high biological and particularly fungicidal activity of methoxyacrylate-type antibiotics, their application for plant protection is impeded due to their high sensitivity to light. Nevertheless, it is on the basis of the natural methoxyacrylates that synthetic agrochemical preparations with a basically new mechanism of action have been obtained.

Analogues of the natural MOA-inhibitors have indisputable advantages over other systemic fungicides because of the lack of natural resistant microbial strains. Thus, ICI-A5504 (compound **13**) efficiently inhibits fungi that are resistant to inhibitors of C-14-demethylase, phenylamides, dicarboximides, and benzimidazoles.⁸⁰

Strobilurins and their analogues constitute a large group of compounds that are hardly inferior to triazole fungicides in structural diversity. They represent a new class of plant-protecting agents that meet all the demands that are made nowadays for pesticides. Intensive studies aimed at a search for novel biologically active pesticides are currently under way by different manufacturers. However, these studies are still in their infancy and so far only three fungicides have been produced by ICI, BASF, and Shionogi. Probably, original products will be offered very soon by Bayer and Roussel UCLAF.

Interest in this group of compounds is increasing with every passing year as can be evidenced from the number of patent applications. The place occupied by strobilurin analogues on the world pesticide market will be evident in due course.

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^a — *Biochemistry (Engl. Transl.)*

Some peculiarities of synthesis of cysteine-containing peptides

E V Kudryavtseva, M V Sidorova, R P Evstigneeva

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Abstract. Data on protective groups for the thiol function of cysteine and methods of disulfide bonds formation used in modern peptide chemistry are considered and systematised. The advantages and disadvantages of protective groups, of reagents used for cyclisation, and possible side reactions associated with them are described. The bibliography includes 119 references.

I. Introduction

Among other peptides and proteins occurring in nature, those containing cysteine constitute a separate group. Disulfide bridges formed between pairs of cysteine residues play an essential role in the stabilisation of tertiary and quaternary structures of the protein molecules by determining their rigid spatial orientation and giving them a unique shape required for the fulfilment of their biological functions. In low-molecular-mass peptides, all types of noncovalent contacts are weakened; therefore, disulfide bonds are of crucial importance for the structural stabilisation of a molecule and reproduction of its biological activity.

Many peptides are known that contain one, two, or more disulfide bridges and take part in the regulation of physiological processes occurring in the organism.^{1,2} Synthetic peptides including those with S–S bonds are widely employed in many areas of medicine and pharmacology.^{3,4} Therefore, the methods used for the formation of disulfide bridges are of great practical significance.

Modern peptide chemistry possesses a wide range of methods for synthesis, purification, and analysis, which allow one to obtain virtually any kind of peptides, their analogues, and even mini-proteins. However, the synthesis of peptides containing disulfide bonds still presents a challenge because of low yields at the stage of their closure. Very often, all efforts spent to synthesise linear precursors come to an overall negative result. Elucidation of the reason for such failures often goes beyond the scope of synthetic studies. The reviews devoted to the synthesis of peptides having

disulfide bridges are very few in number and are often limited to particular aspects of the general problem.

The present review considers modern approaches to the synthesis of cysteine-containing peptides, the groups employed for protection of the thiol function, the methods for their removal, and most popular reagents used for the closure of the disulfide bonds.

II. Protective groups for the thiol function

It is necessary that the strongly nucleophilic thiol group of cysteine be protected in the course of peptide synthesis. The protective groups for the SH function of cysteine should meet the same demands as those for the protective groups of the side-chain functions of other amino acids, *viz.*, stability in the reactions of peptide chain elongation and deblocking of α -amino groups and retention of configuration of the asymmetric centre in the course of synthesis. The protective groups for the thiol function that have been successfully used in peptide syntheses are listed in Table 1. The choice of a protective group is determined by the procedure of subsequent cyclisation. Depending on conditions of cysteine deblocking, one may obtain free thiols or disulfides. The protective groups should possess different chemical stability, which would enable the selective formation of two or more disulfide bonds if required.

In order to characterise protective groups for the thiol function of cysteine used in modern peptide chemistry, Hiskey^{5,6} has proposed to classify them according to the structure of the protected derivatives, *viz.*, sulfides, thioacetals, *S*-acylamido-methyl thiazolidine derivatives, thioesters, and disulfides.

1. Protective groups that form sulfides and related compounds

Protective groups that form this type of compounds (RSR'), are the most well-known, numerous, and popular. The benzyl group proposed by Sifferd and du Vigneaud is an example of a classical protective group that forms sulfides (see Ref. 1). Rather drastic conditions necessary for the removal of the protective benzyl group (Na in liquid ammonia or HF at 25 °C) impose certain limitations on its application. It has been observed^{1,43} that HF results in desulfurisation of the cysteine residue, which may also occur with Na/NH₃. In addition, deprotection with Na/NH₃ is sometimes accompanied by the cleavage of the peptide bonds; the bonds formed by the amino group of proline appear to be the most labile under these conditions.¹ In this connection, it was necessary to design acid-labile protective groups by introducing electron-donor substituents into the aromatic ring of benzyl alcohols. A great number of such protective groups have been synthesised. In

E V Kudryavtseva, M V Sidorova Russian Cardiological Scientific Centre, Ministry of Health Care and Medical Industry of the Russian Federation, 3-ya Cherepkovskaya ul. 15a, 121552 Moscow, Russian Federation. Fax (7-095) 414 67 86. Tel. (7-095) 414 67 16

R P Evstigneeva M V Lomonosov Moscow Academy of Fine Chemical Technology, prosp. Vernadskogo 86, 117571 Moscow, Russian Federation. Fax (7-095) 430 79 83. Tel. (7-095) 434 86 78

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Table 1. The protective groups for the thiol function of cysteine employed in peptide synthesis.

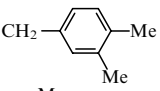
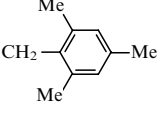
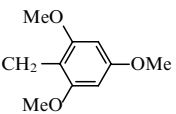
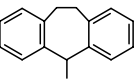
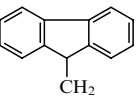
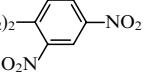
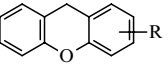
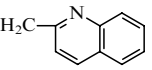
Name ^a	Formula of the protective group	Conditions where the protective group is stable ^b	Conditions for removal of the protective group	Ref.
Benzyl (Bzl)	CH ₂ Ph	HF, 0 °C; Tl(III); B RSCl; H ₂ /Pd; HBr/AcOH TFA; Ag(I); RSCl; B	Na/NH ₃ (liq); HF, 25 °C, 30 min HF/MeOPh, 0 °C, 60 min; ^c Tl(III)	2, 6–8
Methylbenzyl (Meb or Mbzl)	CH ₂ C ₆ H ₄ Me- <i>p</i>			6–9
3,4-Dimethylbenzyl (Dmb)		TFA; Ag(I); B; RSCl	HF/MeOPh, 0 °C, 10 min	8
2,4,6-Trimethylbenzyl (Tmb)		TFA, 23 °C, 2 h	HF/MeOPh, 0 °C, 30 min; TFA, Δ, 1 h	10
4-Methoxybenzyl (Mob)	CH ₂ C ₆ H ₄ OMe- <i>p</i>	B; RSCl; I ₂	HF, 0 °C; Hg(II); Ag(I); Tl(III); (BrC ₆ H ₄) ₃ N; TFA : CH ₂ Cl ₂ (1 : 1), 25 °C ^c	6–8, 10–13
2,4,6-Trimethoxybenzyl (Tmob)		B; Nu	30% TFA/scavengers, ^d I ₂ ; Tl(III), HF	2, 7, 14, 15
<i>tert</i> -Butyl	Bu ^t	TFA; HF, 0 °C; B; I ₂ ; Ag(I)	HF, 20 °C; HF/scavengers, ^d 0 °C; Hg(II); NpsCl; Tl(III)	2, 12, 16
Diphenylmethyl (or benzhydryl) (Dpm)	CHPh ₂	TFA; I ₂ ; ^c Hg(II); ^c Ag(I) ^c	TFA/MeOPh, Δ; HF; Na/NH ₃ (liq); HBr/AcOH; (SCN) ₂ ; NpsCl	5, 17
Di(4-methoxyphenyl)methyl (Ddm)	CH(C ₆ H ₄ OMe- <i>p</i>) ₂	HCl/AcOH; ^c B; Tl(III)	TFA, 70 °C, 2 h; TFA/MeOPh, 10 min; TFA : PhOH (85 : 15), 25 °C, 2 h	1, 5, 8
Triphenylmethyl (Trt)	CPh ₃	B; Nu	TFA/scavengers; ^d Hg(II); Ag(I); I ₂ ; Tl(III); RSCl	1, 2, 5–8, 18
4,4',4''-Trimethoxytriphenyl- methyl (TMTr)	C(C ₆ H ₄ OMe- <i>p</i>) ₃	B; Nu	TFA (dilute); I ₂ (1–2 equiv.), 25 °C, 15–30 min	2, 7
Pyridyldiphenylmethyl	(Ph) ₂ C- 	B	Hg(II) pH 4; Zn/AcOH; electrolytic reduction	19
Dibenzosuberyl		HCl(gas) in organic solvents; TFA; B	HBr/AcOH; ^c HF	6
Fluorenylmethyl (Fm)		HF; TFA; Tl(III) or I ₂ (stable for 1 h)	NH ₃ /MeOH; Pip	5, 20
2-(2,4-Dinitrophenyl)ethyl (Dnpe)	(CH ₂) ₂ - 	HF; I ₂ ; Tl(III); TFA; TFMSA	Pip	21
β,β-Diethoxycarbonylethyl (Dce)	CH ₂ CH(COOEt) ₂	HBr/AcOH	1 M KOH, 20 °C, 5–10 min	1
Adamantyl (Ad)		TFA ⁱ	Tl(III); 1 M TFMSA/PhSMe in TFA, 0 °C	13, 22, 23
Xanthenyl, R = H (Xan), R = 2-MeO (2-Moxan), R = 3-MeO (3-Moxan)		B	dilute acids in the presence of scavengers; ^d I ₂ ; Tl(III)	24
2-Quinolylmethyl	H ₂ C- 	AH	FeCl ₃ /DMF/H ₂ O; FeCl ₂ /DMF/H ₂ O; CuCl ₂ /DMF/H ₂ O	25
Ferrocenylmethyl (Fcm)	C ₅ H ₅ FeC ₅ H ₄ CH ₂	NaOH; NaOMe; I ₂ ; N ₂ H ₄ ; Pip	TFA; (SCN) ₂ ; RSCl; Hg(II); Ag(I)	26

Table 1 (continued).

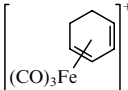
Name ^a	Formula of the protective group	Conditions where the protective group is stable ^b	Conditions for removal of the protective group	Ref.
2-Ferrocenylpropan-2-yl (Fc)	C ₅ H ₅ FeC ₅ H ₄ CMe ₂	NaOH; NaOMe; I ₂ ; N ₂ H ₄ ; Pip	TFA; (SCN) ₂ ; RSCl; Hg(II); Ag(I)	26
(η^5 -Cyclohexa-3,5-dienyl)tri-carbonyl iron		NaOH/Me ₂ CO	HBFe ₄ /CHCl ₃	27
Tetrahydropyranyl (Thp)		B	0.5 M AgNO ₃ , 0 °C; TFA; HBr/TFA; (SCN) ₂	5, 6, 8
Isobutoxymethyl (<i>i</i> -Bom)	CH ₂ OBu ^t	B	TFA; HCl/AcOH; Hg(II)	5, 6, 8
<i>p</i> -Chlorophenoxymethyl	CH ₂ OC ₆ H ₄ Cl- <i>p</i>	B	TFA	5
Benzylthiomethyl (Btm)	CH ₂ SCH ₂ Ph	B	HF; Hg(AcO) ₂ /HCOOH (80%), 25 °C, 20 min	5, 6, 8
Phenylthiomethyl	CH ₂ SPh	B	HF; Hg(II)	5
Acetamidomethyl (Acm)	CH ₂ NHCOMe	HF, 0 °C; B; H ₂ /Pd	Ag(I); Hg(II); I ₂ ; Tl(III); AgBF ₄ ; RSCl	2, 5, 6, 8, 18, 28, 29
Trimethylacetamidomethyl (Tacm)	CH ₂ NHCOBu ^t	HF; TFA; 1 M TFMSA; B	Hg(AcO) ₂ ; TFA/MeOPh; I ₂ (10 equiv.) in AcOH; AgBF ₄	28–31
Phenylacetamidomethyl (Phacm)	CH ₂ NHCOCH ₂ Ph	HF; B	Hg(II); I ₂ ; Tl(III); penicilline aminohydrolase	2, 32, 33
Benzamidomethyl (Bam)	CH ₂ NHCOPh	AH, B	Ag(OTf); Hg(II)	6, 18
(2-Oxo-1-pyrrolidino)methyl (Pym)		B	Hg(II); I ₂ /MeOH	34
Acetyl (Ac)	COMe	TFA (boiling); HBr/AcOH	0.1 M NaOMe/MeOH, 25 °C, 5–10 min; N ₂ H ₄ /MeOH	1, 5, 8
Benzoyl (Bz)	COPh	TFA (boiling); HBr/AcOH	0.1 M NaOMe/MeOH, 25 °C; N ₂ H ₄ /MeOH; 0.2 M NaOH	1, 5, 8
Benzylloxycarbonyl (Z)	COOCH ₂ Ph		0.1 M NaOMe/MeOH, 25 °C; aqueous alkali; NH ₃ ; Na/NH ₃ (liq); TFA/PhOH, Δ; HBr/AcOH	1, 5, 8
<i>p</i> -Methoxybenzylloxycarbonyl (pMZ)	COCH ₂ C ₆ H ₄ OMe- <i>p</i>		TFA, 20 °C; 0.2 N HBr/AcOH; HCl/AcOH; 0.5 N NaOMe in DMF; Na/NH ₃ (liq)	1, 8
<i>tert</i> -Butoxycarbonyl (Boc)	COOBu ^t		AH (TFA)	8
<i>p</i> -Nitrophenoxycarbonyl	COOC ₆ H ₄ NO ₂ - <i>p</i>		AH(TFA); Na/NH ₃ (liq)	5
Phenylthiocarbonyl	COSPh		AH	5
Butylthiocarbonyl	COSBu		AH	5
Ethylcarbamoyl (Ec)	CONHEt	4.5 M HBr/AcOH; 1 M HCl; TFA, Δ	Na/NH ₃ ; 4 M NH ₃ ; NH ₃ (liq); MeOH (1 : 1); 1 M NaOH; NaOMe; N ₂ H ₄ /MeOH; Hg(II) (pH 7); Ag(I) (pH 7)	5, 6, 8
<i>N</i> -Methoxymethylcarbamoyl	CONHCH ₂ OMe	AH	Na/NH ₃ (liq); NaOMe/MeOH; aqueous buffers (pH 9.5), 25 °C	8
<i>N</i> -[β-(<i>N</i> -Acyl- <i>N</i> -methylamino)-ethyl]carbamoyl	CONHCH ₂ CH ₂ N(R)Me R = PhCH ₂ OCO, Bu ^t OCO		AH	6
Alkylthio (SEt, SPr ⁱ , STrt)	SR R = Et, Pr ⁱ , CPh ₃	AH; NH ₄ OH; NaOH	β-mercaptoethanol; benzenethiol (pH 7.5–9); dithiothreitol; Bu ₃ P; oxidative sulfitolysis	6, 8, 35
<i>tert</i> -Butylthio (SBu ^t)	SBu ^t	HCl/dioxane; Pip; TFA; RSCl; B	Na/NH ₃ ; RSH; Bu ₃ P; 2-pyridinesulfonyl chloride; <i>o</i> -nitrobenzenesulfonyl chloride	2, 6, 8, 17, 35–37
Methoxycarbonylthio (Scm)	SCOOMe	HF; AH	RSH; mild alkaline reagents (pH 10.6)	1, 6, 8, 35, 36
(<i>N</i> -Methyl- <i>N</i> -phenylcarb-amoyl)thio (Snm)	SCON(Me)Ph	HF	RSH (especially dithiothreitol and 2-pyridinethiol)	2

Table 1 (continued).

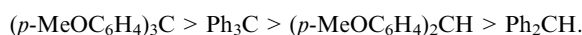
Name ^a	Formula of the protective group	Conditions where the protective group is stable ^b	Conditions for removal of the protective group	Ref.
3-Nitro-2-pyridylthio (Npys)		HF, 0 °C (in the absence of thiols); TFA, 25 °C; ^c HOBT/DCC	RSH or other reducing agents	2, 38–41
<i>tert</i> -Butoxycarbonylthio (SCB)	SCOOBu ^t		B and AH	36
Benzoyloxycarbonylthio (SZ)	SCOOCH ₂ Ph	TFA; weak bases	40% HBr/AcOH; strong bases	36
Sulfonates	SO ₃ Na	B	Bu ₃ P; β-mercaptoethanol, dithiothreitol	42

^a The abbreviations of protective groups cited in Ref. 8 are given; ^b the following notations are adopted: B are bases; TFA is trifluoroacetic acid; Nu are nucleophiles; NpsCl is 2-nitrobenzenesulfonyl chloride; Pip is piperidine; TFMSA is trifluoromethanesulfonic acid; AH are acids; HOBT is *N*-hydroxybenzotriazole; DCC is dicyclohexylcarbodiimide; ^c partial removal; ^d scavengers are compounds that neutralise carbocations formed upon splitting of protective groups; ^e low stability.

Table 1, they are listed in the order of the increase in their acid lability. The most acid-labile group is *S*-2,4,6-trimethoxybenzyl protection,^{5, 7, 14} which is easily removed with 30% trifluoroacetic acid (TFA) in CH₂Cl₂ in the presence of phenol, thioanisole, or water (the so-called scavengers whose purpose is to neutralise the carbocations formed upon cleavage of protective groups) as well as with 5% TFA in CH₂Cl₂ in the presence of 3% triethylsilane or tri(isopropyl)silane. Scavengers are necessary to prevent the reverse addition of the trimethoxybenzyl group to the SH group.¹⁴ The distinctive feature of methoxy- and trimethoxybenzyl protective groups is the possibility of their removal with heavy metal salts, *e.g.*, Ag(I) and Hg(II), which makes it possible to selectively deblock cysteine.^{7, 11, 15} The mechanism of this reaction is analogous to that of splitting of trityl and acetamidomethyl groups and will be considered in more detail in subsequent sections.

S-tert-Butyl protection is extremely acid-resistant. Its removal can be accomplished with HF or Hg(AcO)₂ in TFA.^{2, 12} Quantitative removal of the *tert*-butyl group can be achieved with the use of strongly electrophilic reagents, such as 2-nitrophenylsulfenyl chloride, which binds two cysteine residues through intermediate mixed disulfides² (this reaction will be considered below). However, this reagent cannot be used if the peptide chain contains tryptophan because side reactions may occur in the indole ring.¹⁶

The next type of protective groups includes di- and triarylmethyl groups. In Table 1, they are also presented in the order of the increase in their acid lability:

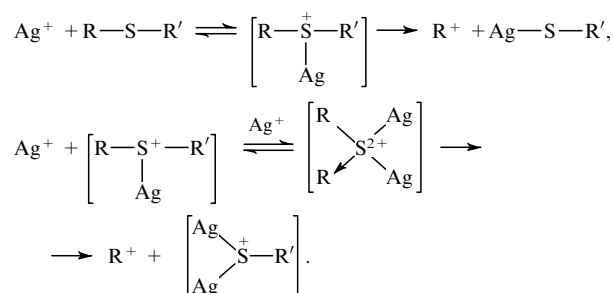


The ease of removal of these protective groups under mild acidic conditions makes them attractive for solid-phase peptide synthesis, which makes use of *N*⁹-9-fluorenylmethoxycarbonyl derivatives of amino acids (the Fmoc-technique).^{4, 44, 45} Cleavage of these sulfides occurs faster than that of their *tert*-butyl and benzyl analogues. This is due to the greater stability of the carbocations formed; however, their higher reactivity can result in the reverse alkylation reaction of cysteine. Thus in the case of the triphenylmethyl protection, an equilibrium between the protected and free cysteine is established in TFA in 30 min and in most cases the degree of *S*-detritylation does not exceed 60%.^{1, 8} The reaction equilibrium can be shifted to the right by addition of scavengers (especially, sulfur-containing ones) or water to the reaction mixture.^{1, 5, 16}

In terms of its reactivity, the Ddm group occupies an intermediate position between the Trt and Dpm groups⁵ and is much more acid-labile than the triphenylmethyl group. This permits selective removal of the Ddm group without affecting the Trt

group.^{1, 5, 8} On the other hand, the resistance of Ddm protection to heavy metal salts allows selective splitting of the Trt group in the presence of Ddm deprotection.

Cleavage of the Trt group can be carried out with Hg(II) or Ag(I) ions.⁵ The mechanism of cleavage of sulfides with metal ions is similar to the mechanism of the acid-catalysed reaction: the difference between these mechanisms is that in the case of metal ions the last stage is irreversible and leads to a stable carbocation, which can be formed by two routes:



In some cases, silver salts are more efficient than mercuric salts, because mercuric derivatives of peptides (mercaptides) are sometimes difficult to cleave.⁵ Metal mercaptides are usually destroyed by thio alcohols. To this end, the reaction product is treated *in situ* with a 20–50-fold excess of a reducing reagent in an appropriate buffer, such as dithiothreitol or β-mercaptoethanol.^{2, 18} The reduced product is purified by gel filtration, ion-exchange chromatography, or HPLC to remove the excess of the reducing reagents. Hg(II) ions are usually removed with hydrogen sulfide.

Owing to the stabilising effect of three electron-donor methoxy groups, the TMTr protective group produces a more stable carbocation than the Trt group, which determines its specificity. The distinctive feature of this protective group is its extremely high acid lability. Deprotection is performed with dilute solutions of TFA.⁷ The tris(methoxyphenyl)methyl carbocation formed, like the trityl carbocation, can enter into the reverse reaction, *viz.*, alkylation; therefore, the use of scavengers is obligatory in this case. Both Trt and TMTr protective groups may be split off together with simultaneous closure of the disulfide bonds with iodine or thallium trifluoroacetate (see Section III).

The *S*-pyridyldiphenylmethyl group is not so popular in peptide synthesis. Only a few examples concerning this protective group are documented.¹⁹ The *S*-dibenzosuberyl protective group is also used rather seldom. In its chemical properties and deblocking conditions, it is similar to the Ddm group.⁶ The *S*-9-fluore-

nylmethyl protective group^{5,20} is one of the few groups that is removed under basic conditions, as a rule, this is performed by treatment with piperidine in DMF. The stability of this protective group under conditions of TFA treatment and in anhydrous HF makes possible its application in solid-phase syntheses, whereas its resistance to Ti(III) and I_2 allows its selective removal in the presence of such protective groups as Acm , Trt , Meb , *etc.*, and selective formation of disulfide bonds. Yet another example of a base-labile protective group is the 2-(2,4-dinitrophenyl)ethyl group.²¹ The electron-acceptor nitro groups in *ortho*- and *para*-positions make this group similar to Fm as regards its stability in the presence of strong acids and splitting by bases by a β -elimination mechanism. The presence of nitro groups allows one to increase the solubility of Dnpe derivatives in polar solvents. Like Fm , this group is completely stable under conditions of classical and solid-phase syntheses, which employ *N*²-*tert*-butoxycarbonyl derivatives of amino acids (Boc-technique)^{4,45} as well as under conditions of splitting of a peptide from the polymer with HF or trifluoromethanesulfonic acid.

Yet another alkali-labile protective group is S - β , β -di(ethoxycarbonyl)ethyl group.¹ It is easily split off by the β -elimination reaction upon treatment with 1 M KOH .¹

The advantages of the S -adamantyl (Ad) protective group,²² although it is used rather seldom, are best manifested in comparison with Mob protection. The adamantyl protective group is more resistant to TFA: the degree of cleavage is only 10% over 2.5 h at 0 °C. It is quantitatively removed with a mixture of 1 M $\text{CF}_3\text{SO}_3\text{H}$ and PhSMe in TFA (60 min, 0 °C) or $\text{Ti}(\text{CF}_3\text{COO})_3$ in TFA.^{13,22,23}

Xanthenyl and its 2(3)-methoxy derivatives are new protective groups for the thiol function of cysteine.²⁴ These acid-labile groups are eliminated by dilute acids in the presence of appropriate scavengers. An alternative procedure for their removal is the treatment with I_2 or $\text{Ti}(\text{F}_3\text{CCOO})_3$, which allows direct synthesis of cyclic disulfides.²⁵

The use of a novel quinolin-2-ylmethyl protective group has been reported.²⁵ A new procedure for the direct conversion of its derivatives into symmetrical disulfides includes treatment with FeCl_3 , FeCl_2 , and CuCl_2 .²⁵

Two new protective groups (Fc and Fcm) containing a ferrocenylmethyl fragment also deserve special mention.²⁶ These groups are rather stable under basic conditions and in the presence of reducing reagents, such as NaBH_4 and Zn in AcOH , although the Fc group is partly eliminated under these conditions. Both protective groups are rapidly split off by electrophilic reagents, *e.g.*, thiocyanogen ($\text{SCN})_2$, methoxycarbonylsulfonyl chloride, and TFA. The Fc group can be also cleaved with formic acid. Iodine only partly destroys the Fc and Fcm protective groups. Removal of both these protective groups by acids is efficient only in the presence of scavengers (*e.g.*, benzenethiol), which capture the ferrocenylcarbenium ion formed. Fcm protection, which was used in combination with *N*²-Boc or *N*²-Fmoc protections, is of greatest importance for the peptide synthesis. In this case, *p*-toluenesulfonic acid was used for selective removal of Boc protection.²⁶

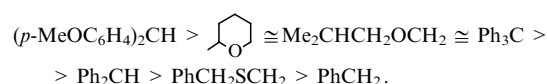
The $(\eta^5\text{-cyclohexadienyl})\text{tricarbonyl iron}$ complex $\{[(\eta^5\text{-C}_6\text{H}_7)\text{Fe}(\text{CO})_3]^+\}$ was successfully used to protect the thiol function of cysteine in the synthesis of a model peptide $\text{Ac-Cys-Gly-Ala-OEt}$.²⁷ Owing to the high affinity of this complex for the SH group of cysteine, the formation of the corresponding adduct occurs rapidly and without side reactions. Protected derivatives are bright yellow coloured, which facilitates monitoring of their purification on silica gel.²⁷

2. Protective groups that form mono- and di-thioacetals

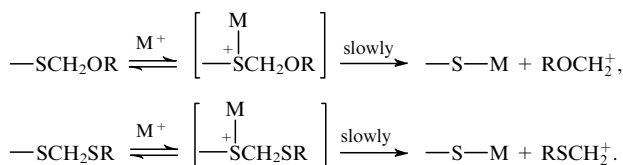
Protective groups that form mono- ($\text{S}-\text{C}-\text{O}$) and di-thioacetals ($\text{S}-\text{C}-\text{S}$) are not numerous and seldom used for cysteine protection.

The protective groups of the thioacetal type, *viz.*, tetrahydropyranyl, isobutoxymethyl, *p*-chlorophenoxymethyl, benzylthio-

methyl, and phenylthiomethyl groups, are stable under alkaline conditions and can be removed by acids. The ease of their cleavage with acids decreases in the following order: acetals $\gg$ monothioacetals $\gg$ dithioacetals, and is determined by the same factors as for sulfides, *viz.*, the ease of protonation, the stability of the cation formed, and the possibility of irreversible reactions that shift the equilibrium towards the cleavage products.⁵ S -Monothioacetal derivatives of cysteine react with acids at the same rates as do trityl sulfides, whereas S -dithioacetal derivatives resemble $\text{Cys}(\text{Bzl})$ and $\text{Cys}(\text{Bu}^t)$ under acidolysis conditions. According to the ease of their acidolysis, the protective groups are arranged in the following order:⁸



Cleavage of mono- and di-thioacetals is more efficient with Hg(II) and Ag(I) salts.⁵ The conditions for selective cleavage have been established for virtually each protective group.⁸ The mechanism of cleavage of mono- and di-thioacetals by metal ions seems to be analogous to the mechanism of cleavage of sulfides. The formation of the $\text{M}-\text{S}$ bond weakens the $\text{C}-\text{S}$ bond. The formation of a cation is the rate-determining step of this reaction. The rate of cleavage depends of the cation stability.⁵

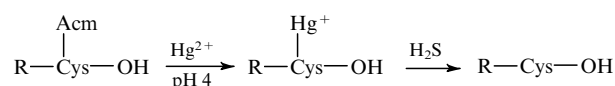


As with sulfides, regeneration of free thiols is achieved by treatment with a great excess of mercaptoalcohols or hydrogen sulfide. It is still uncertain whether selective cleavage of S -monothioacetals can be performed in the presence of S -dithioacetals, disulfide bonds, and other protective groups that are sensitive to heavy metal ions.⁵

Direct oxidation of monothioacetals into disulfides by halogens is inapplicable to cysteine derivatives. However, there is evidence of removal of the S -Thp group from the A-chain of synthetic insulin by its direct conversion into a symmetric disulfide using $(\text{SCN})_2$.^{5,6}

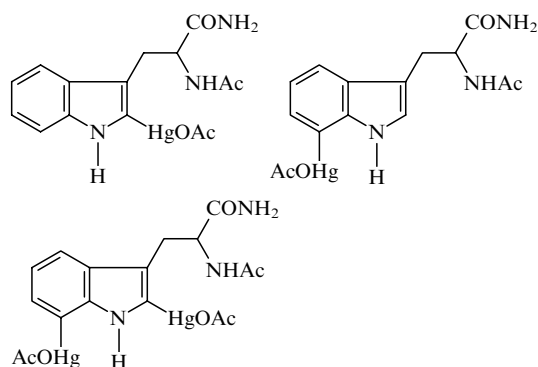
3. S -Acylamidomethyl protective groups

The acetamidomethyl protective group the introduction of which can be accompanied by the formation of thiazolidine derivatives is widely employed in the synthesis of cysteine-containing peptides owing to its high stability in acidic and alkaline media and under conditions of catalytic hydrogenolysis. It is used in combination with Boc, Fmoc, and benzyloxycarbonyl protections of the α -amino group in classical and solid-phase syntheses of peptides. However, there are a few reports on the partial loss of the Acm protective group on repeated treatment of the peptide chains with HF needed for their splitting from the polymer.³⁰ The Acm protection is stable under conditions of acid-catalysed removal of Meb , Mob , Trt , and Tmob groups. Specially selected conditions of deprotection of the thiol function of cysteine with heavy metal salts in appropriate solvents ensure selective removal of the S - Acm group in the presence of Bzl and Bu^t groups. Reaction with Hg(II) salts yields an intermediate peptide-metal compound. When Hg(II) salts are used in acidic aqueous solutions, the reaction is completed within 1–2 h.⁶ Deblocking can also take place in organic solvents, *e.g.*, in DMF .²



R is the peptide residue.

As in the case of removal of Trt protection, subsequent treatment with hydrogen sulfide or mercaptoalcohols yields free thiol groups. If Hg(II) salts are used for removal of Acm protection from the SH group of cysteine in tryptophan-containing peptides, side reactions can occur.⁴⁶ Thus treatment of a bis-Acm derivative of somatostatin with a large excess of Hg(AcO)₂ (5–20 equiv. per one Acm group) in 1%–10% acetic acid results in substitution of hydrogen in positions 2 and 7 by the HgOAc group to form mono- and bis-mercuriacetates of tryptophan.

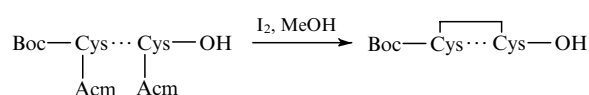


Treatment of these derivatives with β -mercaptoethanol results in the substitution of the Hg(AcO)⁺ group by HOCH₂CH₂S to yield undesirable side products. Acetoxymercuration can be avoided by decreasing the amount of Hg(AcO)₂ to 1–2 equiv. and by using 50% acetic acid.⁴⁶

There is evidence of the possibility of S $\rightarrow$ N and S $\rightarrow$ O migrations of the Acm protective group to the side carboxamide groups of asparagine and glutamine^{2,47} and to the hydroxy groups of serine and threonine.^{2,48,49} The migration of the Acm protective group to the side chain of glutamine (S $\rightarrow$ N migration) was observed in the deprotection of the thiol function of cysteine with I₂ in MeOH. This side reaction is inhibited by an excess of glutamine as a scavenger.⁴⁷ S $\rightarrow$ O Migration was observed in the deprotection of cysteine with Tl(III) and Hg(II) salts in a peptide containing several serine and threonine residues.⁴⁸ This reaction is efficiently inhibited by three-carbon alcohols (e.g., glycerol) as scavengers.^{2,48}

The anion plays an important role in the removal of the Acm group with Ag(I) salts. The reaction occurs with silver nitrate,⁵ trifluoromethanesulfonate,¹⁸ trifluoroacetate,¹⁸ and tetrafluoroborate.²⁸ Silver acetate does not remove the Acm protection. Deprotection of cysteine with silver trifluoroacetate requires that the excess of the deblocking reagent to be twice as high as that with silver trifluoromethanesulfonate. The reaction time is also twice as long;¹⁸ therefore the use of AgOTf is preferable. Silver salts are removed by large (up to 50 equiv.) excess of β -mercaptoethanol or dithiothreitol.¹⁸ Then, the reaction mixture is purified by gel filtration. This deblocking procedure does not affect such highly sensitive amino acids as methionine, tryptophan, and tyrosine.

Direct conversion of di-Acm substituted peptides into disulfides upon treatment with iodine is an attractive method for the removal of the Acm protective group.



This method will be considered in more detail in Section III.

Recently, trimethylacetamidomethyl, phenylacetamidomethyl, and benzamidomethyl protective groups, which can be regarded as derivatives of acetamidomethyl protection, have gained wide acceptance. The properties of benzamidomethyl protection are identical with those of the Acm group.^{6,18} It is also sensitive to AgOTf. However, the removal of the Bam group takes more time than the removal of the Acm protection.¹⁸

Yoshida *et al.*^{28–31} have proposed to use the trimethylacetamidomethyl group to protect the SH function of cysteine. It was found that under conditions of post-synthetic deblocking of the side functional groups of peptides with HF or NaOH, the Tacm and Acm groups, unlike the Bam group, were sufficiently stable. The authors³⁰ attribute the ease of introduction of the protective group and high yields of protected cysteine derivatives to salient advantages of Tacm protection. It should be mentioned that the formation of a side product (thiazolidine-4-carboxylic acid) cannot be avoided in the synthesis of *S*-acetamidomethylcysteine.³⁰

The phenylacetamidomethyl protective group^{32,33} is stable and is split off under the same conditions as the Acm group. Its distinctive feature is the possibility to be cleaved by penicillin aminohydrolase.² Therefore, the Phacm group is orthogonal with respect to Acm protection. First, it is possible to remove the Phacm group enzymically and then the Acm group is removed by treatment with heavy metal salts or iodine.^{2,33}

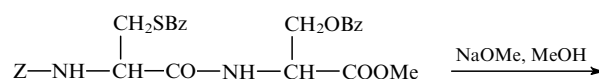
The 2-oxopyrrolidinomethyl group is resistant to reagents of peptide synthesis in a broad range of pH (from 0.5 to 13). In its resistance to alkalis, it surpasses the Bam group.³⁴ Cleavage of the Pym protection with simultaneous formation of the disulfide bond is achieved by treatment with I₂ in MeOH.³⁴

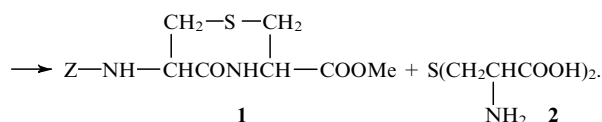
4. Protective groups that form thioesters and related compounds

Protective groups that form thioesters (RCOSR') include acetyl, benzoyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *tert*-butoxycarbonyl, and *p*-nitrophenoxycarbonyl groups. Dithiocarbonates (RSCOSR') are represented by derivatives with phenylthiocarbonyl and butylthiocarbonyl protective groups and *N*-(alkyl)thiocarbamates (RNHCOSR'), with *N*-ethylcarbamoyl, *N*-methoxymethylcarbamoyl, and *N*-[β -(*N*-acyl-*N*-methylamino)ethyl]carbamoyl protective groups.

A characteristic feature of thioesters (acetyl and benzoyl protections), thiocarbonates (benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrophenoxycarbonyl protections), and thiocarbamates (*N*-ethylcarbamoyl and *N*-methoxymethylcarbamoyl protections) is their sensitivity to nucleophiles and bases. Similarly to the corresponding esters and urethanes, thiocarbonates containing a benzyloxycarbonyl group and its analogues as well as Boc-protection are also cleaved in acidic media and with even greater ease.⁸ Dithiocarbonates (phenylthiocarbonyl and butylthiocarbonyl protections) and thiocarbamate (*N*-[β -(*N*-acyl-*N*-methylamino)ethyl]carbamoyl protection) are cleaved only with acids. Alkaline treatment of thioesters can induce base-catalysed disulfide exchange, which can result in the formation of polymer mixtures and peptide parallel and antiparallel dimers. The side reaction of β -elimination, which is accompanied by elimination of thiobenzoic acid from the corresponding Cys(Bz) derivatives in peptides, can also take place.⁵ The occurrence of this reaction depends on the solvent polarity; therefore one must avoid the addition of DMF to the reaction mixtures in the treatment of cysteine-containing peptides with bases, such as NaOMe.⁵ Cleavage of *S*-acyl groups can be achieved by treatment with hydrazine in methanol. Under these conditions, Ac protection is split off rapidly as the corresponding acethydrazide without β -elimination.

A peculiar side reaction was observed when the protected peptide Z-Cys(Bz)-Ser(Bz)-OMe was treated with NaOMe in MeOH.¹ The serine residue was converted into an α -aminoacrylic acid residue, and the addition of the deblocked SH group to the double bond yielded products 1 and 2:



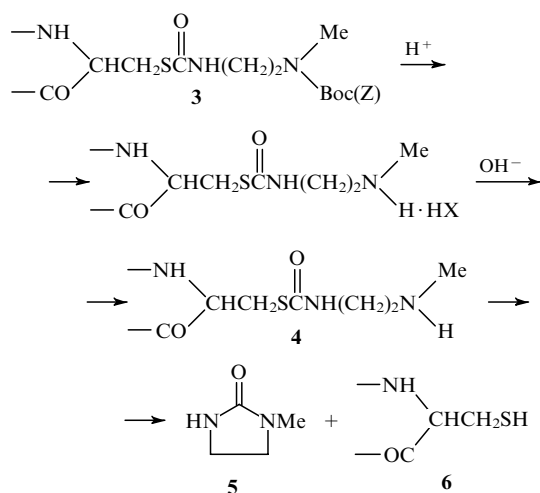


A serious limitation to the use of Ac, Bz, Z, pMZ, Boc, nitrophenylthiocarbonyl, butylthiocarbonyl, *N*-methoxymethyl-carbamoyl, Ec-, and $[\beta$ -(*N*-acyl-*N*-methylamino)ethyl]carbamoyl acyl protective groups is their proneness to S $\rightarrow$ N acyl migration. Such migration takes place in the course of elongation of the peptide chain as soon as a free amino group appears.^{5,8} This side reaction has been observed both in the classical and solid-phase peptide syntheses.⁶ When acetyl and benzoyl protective groups were used in solid-phase synthesis for protection of the thiol function of cysteine, a nearly quantitative chain growth termination occurred due to the interaction of the deblocked SH group with the residual chloromethyl groups of the polymeric support after S $\rightarrow$ N migration.⁶ Nevertheless, Ac and Bz groups are used to protect cysteine residues in solid-phase syntheses of protected peptide fragments designed for fragment condensation. The S $\rightarrow$ N acyl migration can be suppressed if highly reactive derivatives (*e.g.*, mixed anhydrides with pivalic acid) are used for the formation of the amide bond.⁵ In this case, the rate of aminolysis significantly exceeds the rate of S $\rightarrow$ N migration. The benzyloxycarbonyl group also undergoes S $\rightarrow$ N migration, but this reaction proceeds at a much slower rate. The formation of side products can be avoided in this case if condensation is carried out with pivaloyl chloride or diphenyl phosphorochloridate.⁵

The *p*-methoxybenzyloxycarbonyl protective group is distinguished by higher stability of the cation formed on its splitting and can therefore be removed not only by alkalis, but also by acids. However, its application is limited due to the difficulty of its introduction (the yields are about 30%) and high lability with respect to acids and alkalis.⁵

The *N*-ethylcarbamoyl and *N*-methoxymethylcarbamoyl protective groups are resistant to acids and easily removed by basic reagents (as a rule, without racemisation and desulfurisation), they do not undergo S $\rightarrow$ N migration. Thus, they present substantial practical interest.^{6,8} The possibility of partial splitting of the Ec group with an excess of triethylamine during solid-phase synthesis with the use of the Boc-technique (at the stage of neutralisation of the peptidyl polymer or on repeated condensation) restricts the application of this protective group.

The use of *S*-[*N*-β-(*N*-alkoxycarbonyl-*N*-methylamino)ethyl]-carbamoyl protective group, yet another group of the ethylcarbamoyl type, has been reported.⁶ In order to deblock compound **3** in which the thiol function of cysteine is protected by this group the alkoxycarbonyl (*Z* or *Boc*) group is removed by acid treatment. The resulting *N*-β-(methylamino)ethylcarbamoyl derivative **4** is cyclised to yield 1-methyl-2-imidazolidone **5** and the target thiol-containing peptide **6**.⁶



5. Protective groups that form disulfides

Disulfide derivatives (R-S-S-R') obtained after blocking of the SH group include symmetrical and asymmetrical cysteine disulfides, *S*-sulfonates, *S*-alkyl(aryl)thio, *S*-alkoxycarbonylthio derivatives, and sulfamides. Symmetrical disulfides are very seldom used in modern peptide chemistry for synthetic purposes. Ethylthio, isopropylthio, triphenylmethylthio, *tert*-butylthio, methoxycarbonylthio, (*N*-methyl-*N*-phenylcarbamoyl)thio, and 3-nitro-2-pyridinethio protective groups that form asymmetrical disulfides are good alternatives to the protective groups described above owing to their lability with respect to aliphatic and aromatic thiols. A specific feature of some of these groups (Scm, Snm, Npys) is their ability to form intra- and intermolecular disulfide bonds as soon as cysteine is deblocked. Here, the SH groups of peptide thiols play the role of a deblocking reagent (this problem will be considered in detail in Section III).

S-Methoxycarbonylthio derivatives of cysteine are highly reactive compounds.^{6,35,36} Their reactivity with respect to thiols is greater than that of *S*-sulfonates and is comparable with that of sulfenyl thiocyanates or sulfenyl iodides, which are intermediates in the closure of disulfide bonds by the corresponding reagents (see Section III). The advantages of the Scm group are the stability of protected derivatives and the irreversibility of their reaction with thiols, unlike the reaction of sulfenyl iodides and sulfenyl thiocyanates.⁶ Owing to its stability in acidic media, the Scm group can be used in solid-phase syntheses using the Boc-technique.

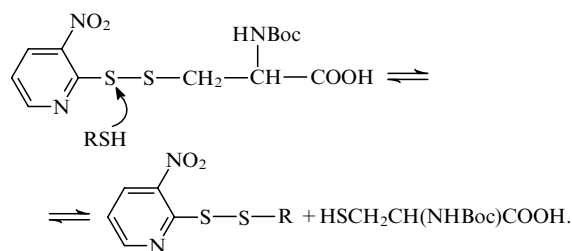
Cleavage of disulfides is performed in aqueous solutions (pH 7.5–9.0) with thiols, such as β -mercaptoethanol or benzenethiol, which is a stronger nucleophile.⁸ The reaction with thiols is based on the thiol–disulfide exchange. In order to shift the equilibrium in the direction of the target product, thiol must be employed in a large excess. Deblocking can also be achieved with a small excess of dithiothreitol, where the equilibrium is shifted due to the intramolecular cyclisation of the reagent, or with 1 equiv. of tributylphosphine at pH 8.⁸ Phosphines are specific reagents for cysteine and reduce only disulfide bonds; this reaction is selective.¹⁷ Disulfides may also be cleaved by oxidative sulfitolysis. The resulting *S*-sulfonates are reduced with thiols or aqueous solutions of thio acids with gentle heating.⁸

It is known that disulfide derivatives are relatively resistant to acids. Their stability decreases in the following order: $\text{RSSBu}^t > \text{RSSPr}^i \sim \text{RSSEt}$. Thus the SBu^t group is cleaved by treatment with liquid HF for 1 h at 0 °C.^{2,6} The SPr^i and SEt groups can be split off with hydrogen chloride in AcOH .⁶ Only the SBu^t group is of practical value and has been successfully used in solid-phase synthesis using the Boc and Fmoc techniques.^{36,37} The majority of mixed disulfides (Table 1) are resistant to ammonia and alkalis, which are used to split the peptides from the polymeric supports with phenolic and phenacyl anchor groups.⁸

Alkoxy-carbonylthio (*tert*-butoxycarbonylthio and benzyloxycarbonylthio) protective groups were proposed by Nokihara and Berndt.³⁶ Unfortunately, SCB derivatives proved to be not very stable on storage. Thus the cysteine derivative ZCys(SC-B)OMe turned into its cysteine analogue within 3 months. In addition, the high lability of SCB protection with respect to alkalis restricts its application in peptide synthesis.³⁶ The benzyloxycarbonylthio protective group is stable in TFA. It is more resistant to alkalis than the methoxycarbonylthio (Scm) group and can be removed by treatment with strong alkalis, though this is preserved for 2 h at pH 10.6, which results in complete removal of the Scm protection. Therefore, the SZ group can be used both for the protection of the SH group of cysteine and for the selective formation of cystines.³⁶

The *N*-methyl-*N*-phenylcarbamoylthio protective group is resistant to acids and can therefore be used in peptide syntheses with the Boc-technique. The possibility of removal of this protective group by alkaline treatment has not been finally clarified.²

Like Scm protection, the 3-nitro-2-pyridylthio and *N*-methyl-*N*-phenylcarbamoylthio protective groups may selectively generate disulfide bonds in the presence of free SH groups. These groups are removed by thiolysis, which occurs in accordance with the Scheme:^{38, 39}



It has been found³⁹ that Npys protection is the most efficiently split off with aliphatic thiols, such as β -mercaptoethanol or mercaptoacetic acid: when the thiols are taken in a 10-fold excess over 3-nitro-2-pyridylthio derivatives, the reaction is completed within 10 min. The S–Npys bond is rather resistant to the action of aromatic thiols, 1-methylimidazole-2-thiol, and pyridine-2-thiol. In this case, selective cleavage of the O–Npys and N–Npys bonds may occur.³⁹ Albericio *et al.*⁴⁰ have shown that the Npys group is more stable under standard conditions of peptide synthesis using the Boc-technique (HF, TFA, and tertiary amines) in comparison with the methoxycarbonylthio group. The Npys protection for the thiol function of cysteine is absolutely stable in solvents and reagents used in solid-phase syntheses using the Boc-technique, *e.g.*, CH_2Cl_2 , DMF, *N,N*-dimethylacetamide, *N*-methylpyrrolidone, MeOH, trifluoroethanol, dioxane, in a mixture of 40% TFA and CH_2Cl_2 , this also withstands treatment with HF (to which 10% anisole or *p*-cresol is added) for 1 h at 0 °C. Thus, the Npys group is virtually resistant under conditions of HF cleavage by the high technique.⁴⁰ The low-high technique is inapplicable in this case, since the use of *p*-thiocresol and dimethyl sulfide results in the loss of lateral Npys groups.⁴⁰ The data on the resistance of Npys protection to *N*-hydroxybenzotriazole are contradictory.^{40, 41} Partial (12%) cleavage of the Npys group was observed in the treatment with 0.1 M solution of this reagent in DMF.⁴¹ Therefore, the method of activated *p*-nitrophenyl and pentafluorophenyl esters was employed to form the amide bond (condensation).^{4, 40, 50} Matsueda *et al.*⁴¹ have successfully used *N,N'*-dicyclohexylcarbodiimide with *N*-hydroxybenzotriazole to attach Boc-Cys(Npys)-OH in the synthesis of a series of peptides. The protective Npys group was found to be very labile under conditions of solid-phase synthesis using the Fmoc-technique, but was sufficiently stable in the photolytic cleavage of peptides from the polymer.⁴⁰

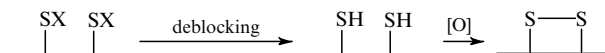
Of interest is the report on the use of base-resistant *S*-sulfonates [Boc-Cys(SO_3Na)-ONa] and [Fmoc-Cys(SO_3Na)-ONa] in peptide synthesis.⁴² Deblocking of cysteine may be achieved by treatment with tributylphosphine, β -mercaptoethanol, and dithiothreitol.⁴² Splitting of the peptide from the polymer with TFA–*p*-cresol systems leads to partial loss of sulfonates.

III. Methods for the formation of disulfide bonds

Despite the intensive progress in methodology of peptide chemistry, the formation of disulfide bonds still presents a serious problem. Its solution involves: (1) the choice of a protective group for the thiol function of cysteine and (2) the selection of a method for the formation of a disulfide bridge. These two aspects are closely interrelated, for the choice of a protective group is the principal factor that predetermines the selection of the method for the formation of the S–S bonds. This problem becomes more complicated in the case where several disulfide bonds are to be formed. The so-called ‘orthogonal’ scheme of synthesis allows selective closure of disulfide bonds between definite cysteine

residues without involvement of other protected residues or the preformed disulfide bridges. In this case, the choice of protective groups that can be selectively split off and the cyclisation procedure are of crucial importance.⁸ In any case, the cyclisation process is very complicated and its successful outcome depends on many factors, such as the correct choice of the solvent, temperature, pH of the reaction medium, concentration of reagents, type of the oxidant, and so on. The methods for cyclisation can be arbitrarily classified into three groups:²

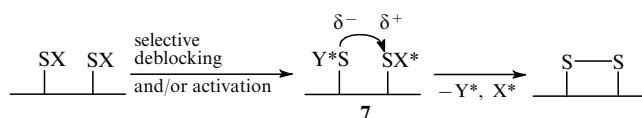
A. Deprotection and formation of a disulfide bond starting from the corresponding SH-derivatives of peptides.



B. Deprotection with simultaneous closure of the ring.



C. Closure of the disulfide bond by thiolysis. This entails two possibilities: (1) The protective group of one of cysteine residues (X^*) enhances the electrophilicity of the sulfur atom (activation). This facilitates the cleavage of the bond between the sulfur atom and the protective group in the thiolysis. The free SH group of the other cysteine residue is the necessary thiol. In this case, $\text{X}^* = \text{X} = -\text{SCOOMe}$, $-\text{SCON}(\text{Me})\text{Ph}$, 3-nitro-2-pyridylthio, *etc.* (2) The protective groups $\text{X} = \text{CPh}_3$, CH_2NHCOMe , Bu^t , *etc.*, are split off with $(\text{SCN})_2$, 3-nitro-2-pyridinesulfonyl chloride, 4-nitrobenzenesulfonyl chloride, and other reagents to form activated asymmetrical disulfides ($\text{X}^* = \text{SCN}$, 3-nitro-2-pyridylthio, 4-nitrophenylsulfonyl) that can enter into the reactions of thiol–disulfide exchange:



1. Formation of disulfide bonds in SH-derivatives of peptides

Group A methods envisage the blocking of two cysteine residues by identical protective groups that are removed under identical conditions, purification of linear polythiols, and oxidation of SH groups with any appropriate reagent providing the formation of intra- or intermolecular disulfide bonds. Oxidation of free thiols is usually carried out in highly dilute solutions at the peptide concentration 10^{-4} – 10^{-5} M in order to avoid intermolecular coupling and side reactions.^{2, 8} Direct formation of the S–S bonds in dilute solutions strongly depends on the peptide structure, particularly on the nature of the amino acids separating two cysteine residues and the number of amino acids between them.^{51, 52} If the number of amino acids between two cysteine residues (*n*) is from 4 to 20, the intramolecular S–S bonds are predominantly formed under conditions of high dilution (10^{-3} – 10^{-4} M). At $n < 3$, the limited chain flexibility results in dimers and polymers that are formed in addition to the peptides with the intramolecular S–S bonds.⁵¹ The formation of the disulfide bond between the neighbouring cysteine residues demands very strong oxidants, such as thallium(III) trifluoroacetate.⁵³ The ability to form intrachain disulfide bonds depends also on the structural stability of the disulfide loop. Thus the oxidation of peptides is facilitated by the presence in the amino acid sequence of Pro-Gly residues involved in the formation of β -folds of proteins and peptides. Many peptides (*e.g.*, oxytocin) can be readily oxidised by atmospheric oxygen. Peptide fragments of proteins having the Pro-Pro sequence between two cysteine residues are difficult to oxidise and can form only symmetrical dimers.⁵¹

a. Oxidation with atmospheric oxygen

Atmospheric oxygen is often used to oxidise thiol groups of cysteine to yield disulfides. This reaction is usually carried out in weakly alkaline solutions at pH 7.5–8.5 with vigorous stirring or by bubbling air through the reaction mixture. The required level of pH is usually maintained by adding ammonia,^{54,55} or other reagents, such as ethyldiisopropylamine.^{55,56} In some cases, cyclisation occurs much faster when ethyldiisopropylamine is used instead of ammonia.⁵⁵ The oxidations may also be carried out in 0.1 M NH_4HCO_3 (pH 8.0)⁵⁷ or 0.1 M ammonium acetate buffer (pH 6.8–7.0).⁵¹ Passage of pure oxygen (instead of air) through a solution of a peptide in 0.1 M NH_4HCO_3 did not increase the rate of cyclisation.⁵⁷ In the case of peptides that aggregate in aqueous solutions, 0.5–8.0 M urea or 0.1–1.5 M guanidine hydrochloride are added.^{2,58,59} As a rule, the oxidation is performed at 5–25 °C. The reaction time varies from several hours to several days.^{54–57} Most probably, this reaction occurs by a free-radical mechanism. The cyclisation is usually monitored by HPLC or by a reaction for the presence of a free SH group using Ellman's reagent, 5,5'-dithiobis(2-nitrobenzoic acid).⁶⁰ The yields of cyclic disulfides in this oxidation are usually small (9%–15%).^{54–56}

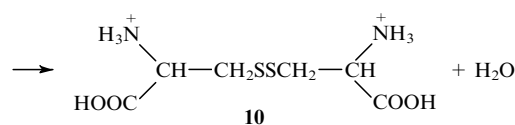
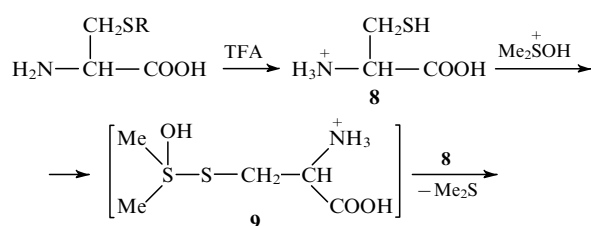
There are some examples of preparation of synthetic toxins, growth factors, and enzyme inhibitors by this method. That this process is lengthy and the product yields are low are serious limitations of this method. However, its simplicity makes it an attractive procedure despite the advent of new efficient reagents.

b. Oxidation with potassium ferricyanide

Potassium ferricyanide is a popular cyclisation reagent. Laloo and Mahanti⁶¹ have studied the kinetics of cysteine oxidation with potassium ferricyanide and proposed a mechanism for this reaction. Using ESR spectroscopy they have found that this reaction occurs *via* an intermediate radical, $[-\text{SCH}_2\text{C}^+(\text{NH}_2)\text{COO}^-]$.⁶¹ Depending on the solubility of a peptide, the oxidation is carried out in aqueous or aqueous-ethanolic solutions with high dilution (pH 8–10).^{60,62} Haskell-Lecevano *et al.*⁶³ performed this oxidation in a saturated solution of NH_4OAc containing methanol and acetonitrile. The termination of the reaction is judged from the appearance of a persistent yellow colouration. Inorganic impurities are removed by ion-exchange chromatography. This method mainly yields homogeneous reaction mixtures. Oxidation of sulfhydryl groups occurs virtually quantitatively.⁵⁵ This procedure has been used to obtain oxytocin,^{2,64} vasopressin analogues,⁶² somatostatin,^{2,65} and peptides with two S–S bridges (endothelin-1,⁵⁸ a bee venom peptide of mast cell degranulation,⁶⁶ *etc.*).

c. Oxidation with dimethyl sulfoxide

Dimethyl sulfoxide (DMSO) was used to oxidise peptide thiols for the first time in 1988.⁶⁷ This compound has a number of indisputable advantages: it can be used in a wide range of pH (from 3 to 8), ensures higher reaction rates (in comparison with oxidation with atmospheric oxygen), and increases solubility of peptides.^{2,59,67–71} This reaction is catalysed by acids or primary and secondary amines. The mechanism of oxidation in an acidic medium was proposed by Otaka *et al.*⁶⁸



R = Trt, Mbzl, Dpm.

The limiting step of this reaction is the formation of the intermediate compound **9**, which rapidly yields the disulfide **10** on reaction with the free thiol **8**. The optimum pH range for the reaction with DMSO is 3–8.⁶⁹ In this case, the reaction rate does not depend on pH, because in this pH range both the protonation of DMSO and the formation of a thiolate anion may take place. At pH < 3, methionine can undergo oxidation into the corresponding sulfoxide, whereas at pH > 8 the rate of disulfide exchange increases. However, there are some exceptions. For example, the oxidation of peptides with an N-terminal cysteine should be conducted at pH 6–7. If the amino groups of cysteine are acetylated, the pH is unimportant. Tam *et al.*⁶⁹ interpret this phenomenon by the fact that the weakly positive α -amino group of cysteine facilitates the formation of the unstable intermediate adduct **9**. In more acidic media, the α -amino group is protonated and does not exert such an effect.

Oxidation with dimethyl sulfoxide is carried out at its concentration in the reaction mixture from 10% to 50%. An increase in DMSO concentration increases the reaction rate. Thus complete oxidation of a linear precursor of a human growth factor fragment with 10%–30% DMSO requires 2–3 h, whereas with 40%–50% DMSO it takes only 0.5 h. The oxidation-sensitive amino acid residues of tryptophan, tyrosine, and methionine are not modified under these conditions.^{69,71}

A 10% DMSO solution in TFA has been used for simultaneous splitting of acid-labile cysteine protective groups (Trt, Mbzl, Dpm) and the closure of disulfide bonds.^{68,70} However, in this case the oxidation lasted several hours. Over this time, the unprotected tryptophan was strongly modified and methionine was oxidised into the corresponding sulfoxide. Oxytocin, which has no tryptophan or methionine in its amino acid sequence, was obtained in 73.5% yield from a bis(methoxybenzyl)cysteine derivative by treatment with 10% DMSO in TFA in the presence of anisole (12 h, 25 °C). Human calcitonin (α -hCGRP) was obtained from a bisadamantyl derivative of cysteine under identical conditions (1 h, 17%).⁶⁸

The resistance of the oxytocin derivatives [1,6-Cys(Acm)] and [1-Cys(Acm), 6-Cys(SH)] with respect to 10% DMSO in TFA has been studied.⁷⁰ The former proved to be stable for 12 h, whereas the monosubstituted derivative [1-Cys(Acm), 6-Cys(SH)] was converted into oxytocin under identical conditions within 1 h (69%); the product was contaminated with a dimer.

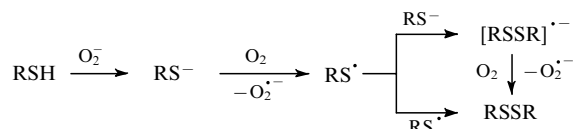
Tamamura *et al.*⁵⁹ reported on the closure of the S–S bonds upon action of 10% or 50% DMSO in 1 M HCl. The thiol groups of cysteine protected with Acm of Mbzl groups had been deblocked beforehand with silver trifluoromethanesulfonate in TFA. Two chemical reactions occurred simultaneously in the DMSO–HCl system: conversion of Cys(Ag) derivatives into cysteine and oxidation of cysteine residues with DMSO. This approach was used to obtain oxytocin, urotensin II, tachiplensin I, and endothelin I in 72%, 80%, 79%, and 62% yields, respectively (as calculated per bis-Acm derivatives). No side reactions that could affect methionine, tyrosine, or tryptophan residues were observed under these conditions.⁵⁹

Oxidation by DMSO is especially efficient in cyclisation of basic peptides that are insoluble in weakly alkaline solutions, which are required for oxidation with oxygen or $\text{K}_3[\text{Fe}(\text{CN})_6]$. This problem appeared in the synthesis of basic hydrophobic growth factors that remained insoluble in weakly alkaline solutions even after addition of 8 M urea.^{69,71} The advantages of this method have been also exemplified in the synthesis of a natriuretic peptide (pBNP) and tachiplensin I having two S–S bonds.⁶⁷

However, despite the obvious merits of this method, it has certain disadvantages, which are connected with the difficulty of removal of the excess of DMSO and dimethyl sulfide formed in this reaction.

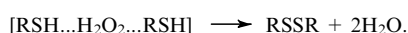
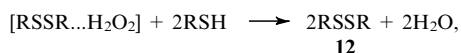
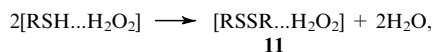
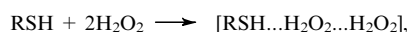
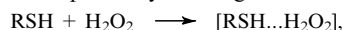
d. Oxidation with hydrogen peroxide

Hydrogen peroxide is a common component of biological systems and participates in physiological oxidation processes.⁷² Therefore, the use of this oxidant in peptide synthesis is fully justified. Oxidation of thiols with H_2O_2 may occur in two ways: *via* generation of a thiolate anion (RS^-) or a radical ($\text{RS}^\cdot$):⁷³



The oxidation performed under alkaline conditions accelerates the generation of the thiolate anion; therefore in this case the formation of the disulfide occurs at higher rate.⁷⁴

Using oxidation of *N*-acetylcysteine and glutathione as examples, it was shown that this reaction proceeds *via* several thiol and disulfide complexes with H_2O_2 .^{75, 76} The important role of H_2O present in the reaction mixture was emphasised, since it stabilises these complexes by creating a solvate shell around them.^{75, 76}



The dependence of the rates of these reactions (in a phosphate buffer, pH 7.0) on the concentration ratio, $K = [\text{RSH}]/[\text{H}_2\text{O}_2]$, has been studied. The formation of the complex **11** takes place at $K < 2.5$, while that of the free disulfide **12** at $K > 2.5$, *i.e.*, where the concentration of the residual thiol is $< 10^{-2}$ mol litre⁻¹.

A systematic study of the applicability of hydrogen peroxide for the closure of disulfide bonds has been carried out by Kudryavtseva *et al.*^{77, 78} Table 2 lists the yields obtained in the formation of disulfide bonds in peptides of various lengths and structures under the action of both iodine and hydrogen peroxide.⁷⁸ Syntheses of some biologically active peptides, such as antigenic determinants of HIV proteins (compounds **13–16**, Table 2), atrial (vasodilator) (compounds **18–20**, Table 2) and vasoconstrictor peptides, containing oxidation-sensitive tryptophan, tyrosine, and methionine residues demonstrate that the oxidation with H_2O_2 enables the preparation of the target disulfides within only 15–20 min and in high yields (60%–85%) without formation of side products.⁷⁸ The oxidation was carried out in aqueous media at pH 6.5–8.0. It was also shown that H_2O_2 can be used for the synthesis of preparative (gram-scale) amounts of antigenic determinants of HIV proteins (**13–16**) and oxytocin (**17**).⁷⁸

There are other reports concerning the use of H_2O_2 in the synthesis of oxytocin and vasopressin.^{3, 79} Hydrogen peroxide was used for cyclisation of methionine-containing peptides (pH 8–11), human natriuretic peptide (α -hNAP), and somatostatin in phosphate buffer (pH 8.5, 10 min). The reaction products were obtained in more than 90% yields and with high purity.

Apparently, the use of hydrogen peroxide in cyclisation has limitations of its own. It is known, for example, that H_2O_2 may induce more profound oxidation of disulfides to sulfones.⁷²

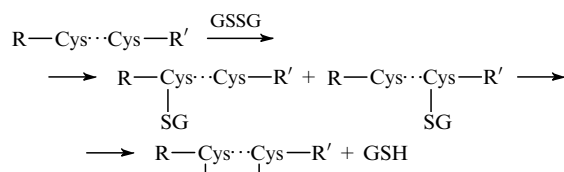
Table 2. Comparative yields of cyclic peptides during the closure of the S–S bridge with iodine (in ACOH or MeOH) and hydrogen peroxide.

No. of compound	Structure	Yields (%)	
		I ₂	H ₂ O ₂
13	H-LGLWGCSGKLIIC-NHEt	51	75–85 ^a
14	H-LGIWGCSGKHIC-NHEt	56	85–90 ^a
15	H-NSWGCAFRQVC-NHEt	66	80–87 ^a
16	H-WGCSGKLICTTAVPWNA-OH	25	85–90 ^a
17	H-CYIQNCPLG-NH ₂	50	70–75 ^b
18	H-SSCFGGRIDRIGAQSGLGCNSFR-OH	23	83
19	H-SSCFGGRIDRIGAQSGLGCNSFRY-OH	26	50
20	H-SLRRSSCFGGRIDRIGAQSGLGCNSFRY-OH	20	62

^a The scatter in yields on oxidation of 0.1–1.5 g of the corresponding bis-Acm derivatives of peptides; ^b the scatter in yields on oxidation of 2.0–20.0 g of bis-Acm derivatives of oxytocin.

e. Oxidation with glutathione

Yet another way to close S–S bonds is the use of buffers that simulate physiological conditions. Since *in vivo* disulfide bridges are formed under reductive conditions, and the reducing medium in cells is maintained by the glutathione system (5 mM reduced and 0.1 mM oxidised glutathione),⁸¹ buffer solutions containing reduced and oxidised glutathione at a 10:1 ratio are most often used for the formation of S–S bonds.² Other ratios of reduced and oxidised forms, *e.g.*, 1:1 (Ref. 82) or 2:1 (Ref. 83) are also employed. The reaction of peptide polythiols is conducted in dilute solutions at pH 7.3–8.7 and 0.1–0.5 M Tris–HCl buffer is used for dissolution.^{83, 84} The oxidation of thiols with glutathione occurs in two steps.⁸⁵ At first, a 'reduced' peptide having free SH groups reacts with the oxidised glutathione (GSSG) to give mixed disulfides, which undergo intramolecular thiol–disulfide exchange to form disulfide bonds in peptides and the reduced glutathione.⁸⁵



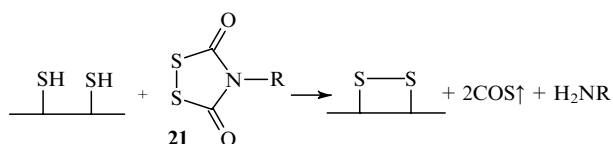
The limiting step of this reaction is the reaction of the peptide with GSSG; therefore, the reaction rate depends on the concentration of the latter. The oxidation is normally carried out for 16–72 h at 25–35 °C.^{82, 83} The reaction product is purified by affinity chromatography² or by HPLC.^{83, 84} This method was used to obtain a 48-membered neurotoxin of sea anemone (yield 22.8%),⁸⁴ the trypsin inhibitor CMTI III (yield 10%),⁸² human epidermal growth factor (h-EGF) peptides,⁸³ and ω -conotoxin.⁸⁶ All these peptides contain three disulfide bonds; their closure was performed simultaneously. This method yields predominantly natural, thermodynamically favourable structures.^{82–86} However, the procedure that employs a mixture of oxidised and reduced glutathiones is mainly limited by large molecules with a thermodynamically favourable physiologically active conformation and is hardly suitable for the synthesis of short peptides containing disulfide bonds.

f. The use of polymers

Clarc and Pai have proposed an original procedure for cyclisation of linear SH-containing peptides using an EkathioxTM polymer.⁸⁷ The resin (40–80 μ , pore diameter 100 Å) contains 0.2–0.4 mmoles of oxidising functional groups per gram. The oxidising polymer was removed by filtration after 4 h at 20 °C. The efficiency of the polymer was evaluated by the formation of oxytocin (yield 92%). The authors⁸⁷ note that the high yield and the absence of dimeric side products were due to pseudo-dilution (see Section III.4), where the reaction was performed on a solid phase.⁸⁷ The polymer EkathioxTM does not modify tryptophan, tyrosine, or methionine residues. Moreover, it allows one to conduct oxidation in both aqueous and organic media. It is difficult to evaluate the advantages of this method, because the nature of the functional groups was not specified by the authors.

An alternative approach to cyclisation using polymeric reagents was proposed by Lin Chen and Barany.⁸⁸

N-Substituted 2,3-dithiasuccinimides **21** were used as oxidants to produce intramolecular disulfide bridges in the synthesis of oxytocin and deaminoxytocin performed under different conditions.



R = CH₃, CH₂CO₂H, CH₂CO₂-(P),
(P) is the insoluble polymer.

One procedure consisted in the reaction of soluble peptides with a dithiasuccinimidoacetyl polymer, and the other, the reaction of a peptidyl polymer with a soluble derivative of 2,3-dithiasuccinimide. The rate of this reaction depends on the pH of the reaction medium. The reaction kinetics has been studied in aqueous, organic, and aqueous-organic media. The disadvantage of this method is the high reactivity of dithiasuccinimide derivatives, which irreversibly oxidise functional side groups of amino acids.⁸⁸

g. Miscellaneous reagents

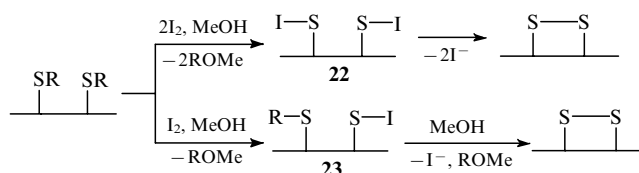
Other reagents, such as 5,5'-dithiobis(2-nitrobenzoic acid) (Ellman's reagent⁸⁹) and a CCl₄-NEt₃ mixture,^{2,7} have been used to oxidise free thiol groups of cysteine residues. Although these compounds did not gain wide acceptance for oxidation in solution, they have been used for solid-phase cyclisation and therefore will be considered below.

2. Removal of protective groups with simultaneous closure of an S–S bridge

Direct conversion of S-protected peptides into the corresponding disulfides is one of the most attractive methods of disulfide bond formation. A number of reagents are now available that can be used for such conversions.

a. Iodine

Iodine is the most popular reagent used in the formation of the disulfide bonds. The reactions of cysteine with Trt, Acm, Tmob, Mob, and other protective groups with iodine have been studied in great detail. Two mechanisms have been proposed to explain the conversion of a sulfide into a disulfide.⁵ One of them implies the formation of an intermediate sulphenyl iodide **22**, and the other, of alkyl(aryl)thiosulphenyl iodide **23**.



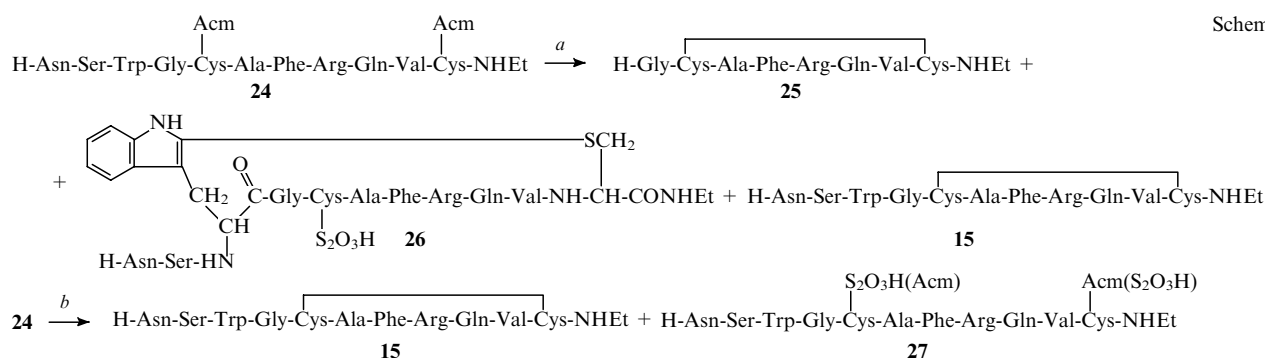
R = Acm, Trt, Tmob, Mob.

Neither of these mechanisms has been favoured, although both routes have been confirmed by several authors.⁵ Since the intermediate sulphenyl iodides are highly reactive, the efficiency of oxidation strongly depends on the amino acid sequence of a peptide.

Several procedures for oxidation of protected peptides with iodine exist, which differ in the ratios of the reaction components, solvents, reagents used to remove the excess of iodine, etc. The oxidation is carried out in both neutral solvents (MeOH or aqueous MeOH, trifluoroethanol, dioxane, CHCl₃, DMF) and in acids (acetic, propionic, trifluoroacetic) or their mixtures with water. Depending on the type of the thiol function protection and the nature of the solvent, the reaction rates may vary considerably. Thus the rates of oxidation of Cys(Trt) in MeOH, acetic acid, and their mixtures with H₂O are from 4 to 500 times as high as that of oxidation of Cys(Acm) in the same solvents. If oxidation is carried out in chloroform, dichloromethane, and trifluoroethanol, this difference is much higher. This allows selective oxidation of Cys(Trt) in the presence of Cys(Acm). On the contrary, the rate of oxidation of Cys(Acm) in DMF and its mixtures with water is 5–10-fold higher than that of Cys(Trt).²

The excess of iodine plays an important role in this process. With equimolar amounts of the oxidant with respect to the [Cys(Acm)]₂ derivative of gramicidin S, the reaction in methanol was completed within 3 h and the yield of gramicidin S was 67%.⁹⁰ The use of 5–15-fold excess of I₂ in AcOH made it possible to obtain cyclic disulfides of various lengths and structures and in sufficiently good yields.^{66,91,92} The use of 40- and 50-fold excess of I₂ in AcOH was reported to result in low yields (10%) of the target products.^{93,94}

Using the synthesis of the cyclic disulfide **15** from the bis-S-Acm-protected fragment 593–603 of HIV-2 gp41 (**24**) as an example (Scheme 1), the effect of the excess of iodine and of the solvent on cyclisation has been studied.^{55,78,95} With 2–13-molar excess of I₂ in AcOH, the yields of the target product **15** did not exceed 39%.^{55,78,95} The highest yield (66%) was obtained when



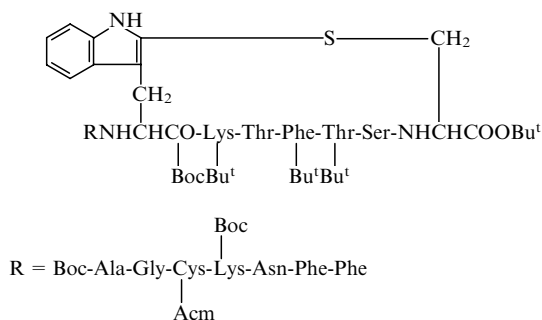
(a) 13 moles of I₂ per 1 mole of the peptide in AcOH; (b) 5 moles of I₂ per 1 mole of the peptide in AcOH.

oxidation was performed in aqueous methanol using 2 moles of I_2 per 1 mole of the peptide.^{78, 95, 96}

The excess of iodine is removed with sodium thiosulfate, ascorbic acid, zinc dust, and by extraction with carbon tetrachloride.^{2, 55, 78, 91–95} Removal of the excess of iodine with sodium thiosulfate was accompanied by modification of the cysteine residue with the thiosulfate ion^{55, 78, 95, 96} (compounds **26** and **27**, the exact positions of the Acn and S_2O_3H groups in compound **27** were not determined) (Scheme 1).

The limitation of the use of iodine for the disulfide formation is the possibility of side reactions affecting oxidation-sensitive amino acid residues, *e.g.*, iodination of the benzene ring of tyrosine,⁸ oxidation of methionine to the corresponding sulfoxide,⁸ and scission of the indole ring of tryptophan with subsequent cleavage of the peptide chain.^{8, 55, 78, 95–97} Thus the formation of a shortened peptide **25** (Scheme 1) was a result of oxidative degradation of tryptophan by iodine.^{78, 95} Since these reactions are catalysed by acids, the cleavage of the peptide chain at the tryptophan residue can sometimes be avoided if oxidation is conducted in neutral organic solvents.^{55, 95, 96, 98}

Oxidation of tryptophan-containing peptides with iodine sometimes results in tryptophan-2-yl sulfides as a side product of the type **26**. Apparently, one of the reasons for this side reaction is the formation of highly reactive intermediate sulfenyl iodides. Tryptophan-2-yl sulfides were obtained under various conditions.^{42, 95, 98} For example, in the synthesis of somatostatin from a precursor with different protective groups at cysteine residues (Acn in position 3 and Trt in position 14), treatment with iodine in 10% aqueous trifluoroethanol resulted in the formation of a side product in 65% yield.⁹⁸



According to Sieber *et al.*,⁹⁸ this reaction occurs due to the different lability of Acn and Trt groups in trifluoroethanol.^{2, 98} When oxidation was carried out in a MeOH/DMF mixture, tryptophan-2-yl sulfide was not formed. The distance between the cysteine and tryptophan residues plays a significant role in the formation of tryptophan-2-yl sulfides. Oxidation of model tryptophan-containing peptides with iodine shows that only disulfide dimers are formed if tryptophan and cysteine are separated by one or two glycine residues. If this distance is four glycine residues, the yields of tryptophan-2-yl sulfides are 40% and 70%, respectively.⁹⁸

Alternatively, tryptophan-2-yl sulfides were formed when sodium thiosulfate was used to remove iodine in the synthesis of a fragment of the HIV-2 protein gp41 (if $Na_2S_2O_3$ is replaced by ascorbic acid, this side reaction does not take place). Blocking of the thiol function of one of cysteine residues with the thiosulfate ion (compound **26**) triggers the reaction of the thiol function of the other cysteine residue on position 2 of the indole ring of tryptophan.^{55, 78, 95}

No side reactions involving the indole ring of tryptophan took place during cyclisation with iodine when its N^{im} -formyl derivative was used.⁵⁸

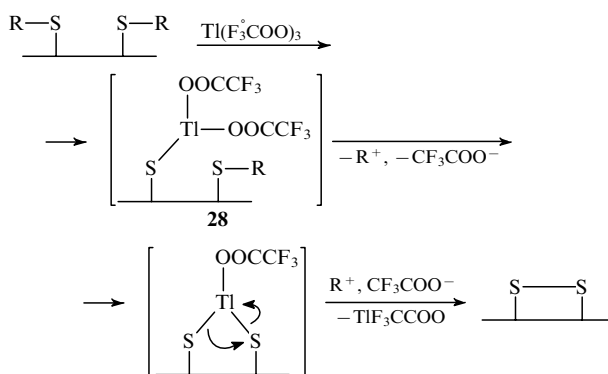
Despite the obvious limitations of this method, there are many examples of its successful application in the synthesis of compounds with several disulfide bonds in particular.^{54, 58, 66}

b. Cyanogen iodide and *N*-iodosuccinimide

These compounds also serve as a source of the I^{2+} ion. The mechanism of oxidation with these reagents is identical with that of iodine. Good solubility of ICN in aqueous-organic solvent systems has been reported.⁹⁹ The utility of ICN was demonstrated in the cyclisation of several Cys(Acn) peptide derivatives in aqueous methanol. A comparison of oxidation with cyanogen iodide and iodine showed that although large excess of the oxidant (from 25- to 80-fold) is required in the former case and the duration of these reactions was 24–48 h, the yields were about twice as high as with I_2 . *N*-Iodosuccinimide was used in the synthesis of oxytocin and vasopressin on a polymer,¹⁰⁰ therefore this reagent will be considered below in more detail.

c. Thallium(III) trifluoroacetate

A new, rather efficient oxidant, $Tl(CF_3COO)_3$, was first used in 1987 for removal of certain cysteine protective groups with simultaneous formation of the disulfide bond.^{9, 101} Thallium trifluoroacetate removes many protective groups of the sulfide type (Mob, Tmob, Bu^t, Trt, Xan, Ad, Meb) and acylaminomethyl derivatives (Acn, Phacm). The oxidation occurs through the formation of a highly reactive intermediate compound **28**, *viz.*, thallium(III) thiolate. At the final step of this reaction, the protective group is split off from the thiol group of the second cysteine residue with concomitant disulfide bond closure.



The oxidation is carried out in trifluoroacetic acid (1–2 h, 0 °C) in the presence of 2 equiv. of anisole to bind the carbocations formed^{9, 101} or in DMF.^{2, 7} The use of aqueous solvents is excluded in this case, since the presence of water can bring about the formation of small quantities of cysteic acid.⁹ Thallium salts are readily soluble in ether and their removal does not present any problem.⁹

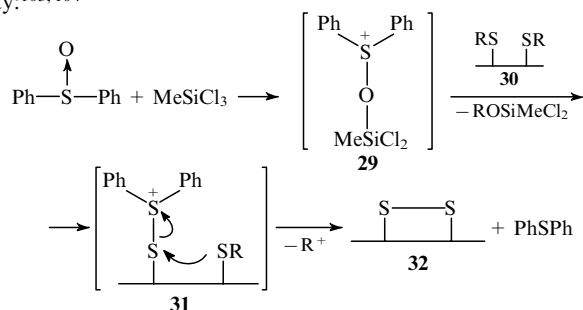
The use of $Tl(CF_3COO)_3$ gave satisfactory results in the synthesis of oxytocin, urotensin II, and human calcitonin. The yields of the products purified by gel filtration were 45%, 35%, and 11%, respectively.¹⁰¹ In the latter two cases, the decrease in the product yields can be explained by the presence of a tryptophan residue in the amino acid sequences of these peptides, which undergoes considerable modification. It was shown that only 38% of tryptophan remains intact under these conditions. The use of a Trp(Mts) derivative allows one to preserve tryptophan for 60 min on treatment with $Tl(CF_3COO)_3$ at 0 °C. Methionine is partly oxidised (by ~ 38%) to the corresponding sulfoxide with $Tl(III)$ salts.⁹

The use of this reagent is efficient in the case of difficulty oxidisable thiols, where cysteine residues are adjacent as in the peptide fragment of the acetyl choline nicotine receptor (alpha 185–196).⁵³

A comparison of efficiencies of atmospheric oxygen, potassium ferricyanide, and thallium(III) trifluoroacetate as oxidants in some syntheses revealed that $Tl(CF_3COO)_3$ gave the highest yields.^{17, 53} It has been widely employed for the closure of disulfide bonds on a polymer.^{7, 17, 102} The high toxicity of thallium salts imposes certain restrictions on their application, which will hardly go beyond the scope of laboratory experiments.

d. Sulfoxides in the presence of silyl chlorides

This cyclisation method was proposed in 1991 independently by Kiso^{103, 104} and Fujii.¹⁰⁵ In the presence of silyl chlorides in trifluoroacetic acid, aryl(alkyl) sulfoxides may split off Ac^m, Tac^m, Bam, Bu^t, Meb, and other cysteine protective groups with simultaneous closure of the S–S bridges in 10–30 min at 4 °C. The mechanism of this reaction can be presented in the following way:^{103, 104}



The closure of the disulfide bond occurs through the generation of the sulfonium cation **31** upon treatment of the protected peptide **30** with diphenyl sulfoxide and silyl chloride. Further, electrophilic attack of the second substituted sulfur atom in compound **31** results in the formation of an S–S bridge and the splitting of the protective group, which is similar to the reaction of sulfonyl iodide with S-protected cysteine in the oxidation with iodine. The nature of silyl chloride seems to play a key role in the reactivity of the intermediate compound **29**. The ability of the protective group split off to form stable structures similar to the immonium ion derived from the Ac^m group is also important. These two factors determine the rate of the reaction.¹⁰⁴

The efficiency of various silyl chlorides (SiCl₄, MeSiCl₃, Me₃SiCl), and Me₄Si in combination with sulfoxides [PhS(O)Ph, MeS(O)Me, and MeS(O)Ph] has been studied.¹⁰⁴ SiCl₄ and MeSiCl₃ were found to be the most efficient silylating reagents. There was no difference in reactivities of different sulfoxides.¹⁰⁴ The Ph₂SO–MeSiCl₃ system or SiCl₄ removes Ac^m, Mob, Meb, Bzl, and Bu^t protective groups with equal efficiency.¹⁰⁵

Tryptophan is subject to side reactions under these conditions. Chlorination of the indole ring is the predominant reaction in the treatment of tryptophan-containing peptides with silyl chloride.^{104, 106} The addition of scavengers (anisole and 3-methylindole) routinely used to prevent tryptophan modification was inefficient.¹⁰⁴ It is therefore recommended to use tryptophan in the form of a formyl derivative.^{103, 104, 106} Nevertheless, successful application of this reagent has been demonstrated in the synthesis of somatostatin (yield 60%),^{104, 106} oxytocin (yield 56%–69%),¹⁰⁴ and human natriuretic peptide (hBNP) (yield 50%).¹⁰⁴ This method was also used for regioselective formation of disulfide bonds in the synthesis of conotoxin M1 and human insulin.¹⁰⁷

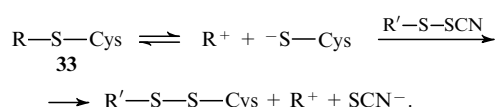
3. Closure of disulfide bonds by thiolysis or thiol–disulfide exchange

Implementation of the route C requires that the two protective groups of two cysteine residues be different in stability. This enables selective removal of one of the protective groups (Y), whereas the other group (X*) activates the sulfur atom of cysteine, thus facilitating the formation of a disulfide bond. In this case, the intermediate electrophilic derivative (–S–X* in compound **7**) undergoes a nucleophilic attack by the sulfhydryl group of the second cysteine residue. This approach is used for the closure of both intra- and intermolecular S–S bonds and is particularly widely employed for the preparation of asymmetrical disulfides. Methods A and B are less efficient to this end. The reason is that simultaneous oxidation of two cysteine residues, when the formation of the S–S bonds between two different peptide chains is needed, gives predominantly dimers, whereas asymmetrical disulfides are the minor products. The peptide thiols are activated by

introducing electron acceptor substituents, which enhance the ability of sulfur for the nucleophilic substitution. Activation may be accomplished either *in situ*, or as an individual stage with the isolation and characterisation of the intermediate product, or by selection of appropriate protective groups. In the latter case, the protective groups (*e.g.*, of the disulfide type) must be sufficiently stable under conditions of elongation of the peptide chain and simultaneously ensure the formation of a disulfide bond by thiol–sulfide exchange.

a. Thiocyanogen (SCN)₂

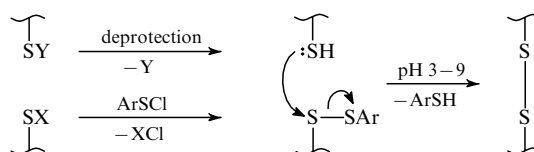
Thiocyanogen^{2, 6} reacts both with free and protected thiols. The resulting activated peptide (X* = SCN in compound **7**) reacts with the thiol group of the same or another peptide *in situ* to form a disulfide bond. It has been established that this reagent selectively reacts with Thp and Trt derivatives of peptides in the presence of Dpm and Bzl protections.^{5, 6} The reaction of thiocyanogen with sulfides can be presented as a reaction of an electrophile with a dissociated form of a sulfide.⁵



The rate of this reaction is determined by the degree of dissociation of the corresponding protected derivative **33**, which, in turn, depends on the stability of the cation R⁺ formed upon splitting. Therefore, the cyclisation of Trt and Mob derivatives of peptides occurs rapidly and specifically even in nonpolar solvents, whereas Dpm sulfides react slowly and are converted into the corresponding disulfides in 60%–75% yields.⁵ The degree of dissociation of derivatives **33** may be enhanced by acid catalysis. Cleavage of Dpm and But sulfides requires stronger acids than that of Trt and Mob derivatives. If the reaction with thiocyanogen occurs at a slow rate (as is the case with Bzl derivatives), the formation of homodimeric side products is more probable.^{2, 5} High electrophilicity of thiocyanogen favours the occurrence of side reactions.² Thiocyanogen is decomposed by amines (including free bases of arginine and histidine), the corresponding reactions may be carried out only in acidic or neutral media.

b. Aromatic sulfonyl halides

2-Nitrobenzenesulfonyl chloride (Nps-Cl) or 2-pyridinesulfonyl chloride (PyS-Cl) activate free or protected cysteine residues. The closure of the disulfide bonds by these reagents may be illustrated by the following general scheme:²



In the case of intermolecular closure of the S–S bonds, Y is a protective group of any type, and X is hydrogen or a protective group that can be removed by aromatic sulfonyl halides, *e.g.*, Trt, Dpm, Bu^t, SBU^t, and Ac^m.

Nps-Cl and PyS-Cl are extremely reactive, they decompose in the presence of moisture. PyS has been proposed for deprotection of cysteine protected with Trt, Dpm, Ac^m, Bu^t, and SBU^t groups and subsequent preparation of asymmetrical disulfides.¹⁰⁸ Reactions with this reagent are carried out in glacial acetic acid. The reactive mixed disulfide formed reacts with a free SH group to give the target disulfide. The mixed disulfide Cys(PyS) is resistant to acids. Removal of the Boc group in the derivative Boc-Cys(PyS)-OH by treatment with acid is not accompanied by splitting of the PyS group. The activation of thiols and formation of disulfide bonds occur without removal of protective groups, such as Boc, Z, and Bzl. The PyS derivatives of peptides are formed in quantitative yields and can be isolated in a crystalline state. The mixed

disulfides Cys(PyS) and the respective peptides are unstable in alkaline solutions and rapidly decompose to yield symmetrical disulfides and di(2-pyridyl) disulfide, (PyS)₂. Free SH groups may be liberated by the action of an excess of thiols (*e.g.*, β-mercaptoethanol).¹⁰⁸

Nps-Cl was used to remove Trt, Dpm, Ddm, and Acn protections¹⁰⁹ and intermediate mixed disulfides can be isolated. Free SH-derivatives can be obtained under the action of an excess of a thiol (*e.g.*, β-mercaptoethanol or dithiothreitol). Deprotection and formation of disulfide bonds using Nps-Cl occur much more slowly than with PyS-Cl.¹⁰⁸

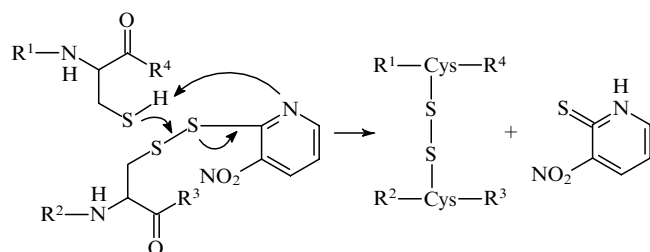
The use of aromatic sulfonyl halides is limited because of difficulties associated with their synthesis and isolation (these compounds are easily hydrolysed even in humid air) and due to the fact that tryptophan can undergo side reactions under the action of these compounds.

Peptides containing cysteine with free SH groups can be activated directly in solution or on a solid phase with di(2-pyridyl) disulfide, (PyS)₂. Highly specific conversion of a Cys(Snm) derivative into a Cys(PyS) derivative under the action of 2-mercaptopyridine in chloroform is an alternative procedure for obtaining stable S-arylsulfonyl derivatives.² And, finally, cysteine-containing peptides may react with Ellman's reagent in buffer solutions at pH 7.4 to give intermediate disulfides. The interaction of the latter with a free SH group of the other cysteine residue also results in the closure of S—S bridges.²

c. Disulfide derivatives

The characteristic feature of this method is that disulfides play a dual role. On the one hand, they are used for protection of the thiol functions of cysteine because they are stable under conditions of a multistep peptide synthesis. On the other hand, being strong electron acceptors, they activate the thiol groups in reactions of thiol–disulfide exchange and thiolysis and thus facilitate the closure of the S—S bonds. These groups include alkoxycarbonylthio (Scm, Sce), Snm, and Npys protections.

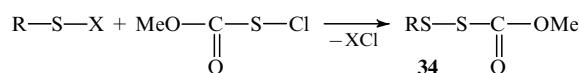
Asymmetrical disulfides have been synthesised from peptides containing Cys(Npys) derivatives.^{17, 110}



R¹, R², R³, R⁴ are amino acids.

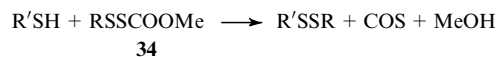
Derivatives containing Npys protective groups are also used to form intramolecular disulfide bonds.² This reaction is carried out over a rather broad pH range. The reaction time varies from several hours at pH ~ 4 to 30 min at pH 8–9. However, at pH > 9, disproportionation of disulfides may occur, which shifts the reaction equilibrium towards the formation of symmetrical homodimers. The probability of disulfide exchange between asymmetrical cysteines formed and the free SH groups present decreases at low pH. The optimum pH values are 4.45–9.35. The stability of the Npys protective group in acidic media (TFA at 25 °C and HF at 0 °C in the absence of thiols) makes it possible to use these cysteine derivatives in solid-phase syntheses using Boc-technique. This protection was successfully used for the formation of S—S bridges in the synthesis of insulin, its analogues, and relaxin.¹⁷

Methoxycarbonylsulfonyl chloride (Scm-Cl), like aromatic sulfonyl halides, removes such protective groups as Trt, Acn, Bu^t, Ddm, and Dpm to form Cys(Scm) derivatives.¹¹¹



X is Trt, Acn, Bu^t, Ddm, Dpm.

Compound **34** reacts with free thiols to produce the disulfide bonds.



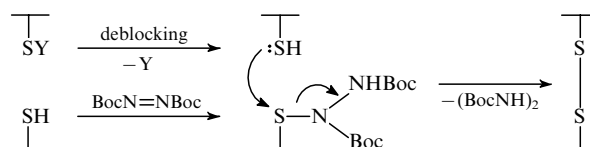
The latter reaction is catalysed by mild bases, such as triethylamine.¹¹¹ Sulfonylthiocarbonates are unstable in the presence of alkalis; therefore, experiments with these compounds must be carried out in neutral or acidic media. However, undesirable modification of tryptophan is possible. Conversion of Acn derivatives into Scm derivatives or the reaction of free SH groups with Cys(Scm) may also be carried out on a solid phase² with formation of both inter- and intramolecular disulfide bonds.

Ethoxycarbonylsulfonyl chloride (Sce-Cl) was proposed for the formation of intramolecular disulfide bonds. This reagent is identical in structure and mechanism of action with Scm-Cl.¹¹¹ The activated cysteine derivatives thus formed react with free thiol groups of cysteine to yield intramolecular disulfide bridges. The optimum results were obtained with ammonium-acetate buffer, pH 7.0. However, this reaction may also be carried out in weakly acidic solutions, but in this case the yields are lower. The rate of this reaction is very high: cyclisation is completed within 10 min, but the reaction conditions could not be found where the yields exceeded 20%–30%.¹¹¹ The application of Sce-Cl to tryptophan-containing peptides is problematic.¹¹¹ Nevertheless, this reagent was used in the synthesis of somatostatin, urotensin IIA,¹¹¹ and a trypsin inhibitor.⁵⁶

d. Bis(*tert*-butyl) azodicarboxylate

The closure of the disulfide bond using bis(*tert*-butyl) azodicarboxylate (Boc—N=N—Boc) occurs *via* thiolysis. Boc—N=N—Boc has not gained wide acceptance despite its successful application in the synthesis of asymmetrical disulfides.^{112, 113}

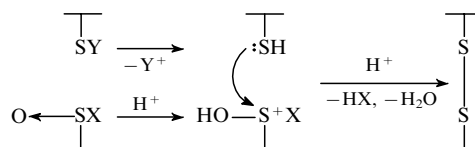
The synthesis of an activated peptide derivative was carried out in DMF with 2–3 equiv. of bis(*tert*-butyl) azodicarboxylate under argon (4–12 h, 25 °C).^{112, 113} The resulting compound is rather stable and can be isolated. The activated derivative is dissolved in an appropriate solvent, after which the second peptide containing a free sulfhydryl group is added to form a disulfide heterodimer.



BocN = NBoc is bis(*tert*-butyl) azodicarboxylate.

e. The use of cysteine sulfoxide

This method is used for the closure of both intra- and intermolecular S—S bonds. One of the cysteine residues is used in the form of a sulfoxide.¹¹⁴ The reaction occurs in a strongly acidic medium (TFA or a trifluoromethanesulfonic acid–TFA mixture). Under these conditions, the sulfoxide is protonated, and the resulting electrophilic derivative readily reacts with the nucleophilic thiol.



Y is Mbzl, Ad, Bu^t; X is Acn or Mob.

Methods of direct conversion of cysteine-protected peptides into disulfides [I_2 , $Tl(CF_3COO)_3$] have proved to be very efficient in oxidation on a solid phase. Standard conditions of this oxidation include treatment of cysteine-protected (Acn, Trt, Tmob) peptidyl polymers with 3–10 equiv. of I_2 in an appropriate solvent (TFA, AcOH, DMF, *etc.*) (1–2 h, 25 °C) or with 1.2 equiv. of $Tl(CF_3COO)_3$ (1–2 h, 0 °C). The yields of cyclic products are 60%–90%.^{89,117} Treatment of peptidyl polymers with acid-labile anchor groups [*p*-alkoxybenzyl or tris(alkoxy)-benzylamide] with solutions of I_2 or $Tl(F_3CCOO)_3$ in TFA or AcOH results in simultaneous closure of S–S bridges and splitting of the peptide from the polymeric support. This approach was used by Barlos *et al.*¹¹⁸ for cleavage of the acid-labile

2-chlorotrityl anchor group with an AcOH:trifluoro-ethanol:CH₂Cl₂ mixture (1:2:7). When this mixture was used in combination with 10 equiv. of I₂ (10–15 min, 20 °C), cyclic disulfides were obtained in ~60% yields. Protective groups of the *tert*-butyl type were not removed under these conditions.¹¹⁸

The advantage of direct conversion of Cys(Acm) and Cys(Trt) peptide derivatives into the corresponding disulfides by treatment with Tl(III) salts over iodine has been demonstrated by several authors.^{89, 102, 116} Treatment of S-Acm or S-Trt derivatives of the model peptide Ac-Cys(Acm)-Pro-D-Val-Cys(Acm)-NH₂ with Tl(CF₃COO)₃ in TFA:anisole (21:1) with subsequent cleavage from the polymer with HF gave a cyclic product in 91% yield, whereas after treatment with 10 equiv. of I₂ in aqueous AcOH the yield was 52%.^{89, 116} In the latter case the decrease in the yield is unrelated to the nature of the oxidant but rather is due to the application of the AcOH–water mixture (1:4, v/v), which prevents swelling of the polystyrene-peptidyl polymer.

Cyclisation on a solid phase was highly efficient in the synthesis of parallel dimers of oxytocin and deaminoxytocin.^{7, 119} The attempts to obtain these compounds in solution failed, because in dilute solutions it was monomeric products that were predominantly formed, whereas at high concentrations polymers were formed.¹¹⁹ Rigid fixation of peptides on a polymer has made

it possible to obtain target dimers in good yields. The synthesis of a parallel dimer of deaminoxytocin is shown in Scheme 2.

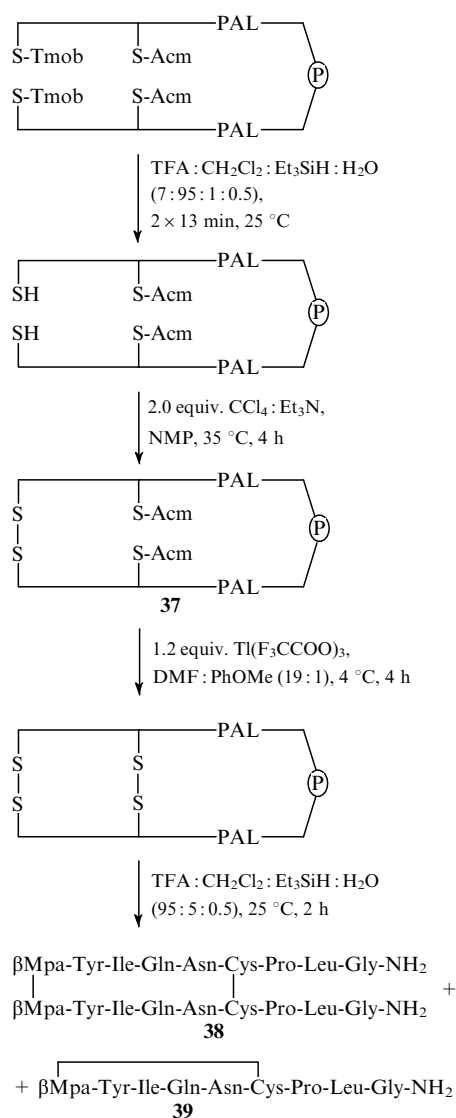
The CCl₄–NEt₃ mixture was used for the closure of the S–S bond between Tmob-blocked N-terminal residues of β-mercaptopropionic acid (βMpa) after preliminary treatment of the peptidyl polymer with dilute TFA and scavengers. This procedure gave an intermediate product **37** in more than 90% yield. A mixture of the target parallel dimeric product **38** and deaminoxytocin **39** was obtained in 3:1 ratio after closure of the second disulfide bond with Tl(CF₃COO)₃ and cleavage of the reaction product from the polymer. Whether deaminoxytocin **39** results from the oxidation of an intermolecular side reaction product with Tl(F₃CCOO)₃ or from the dimer–disulfide exchange still remains unclear.¹¹⁹ A scheme with an alternative combination of protective groups [Cys(Tmob) and βMpa(Acm)] has also been tested. At the first step of this synthesis, the disulfide bond was closed between cysteine residues. It is of note that in this case the yield of the intermediate product having only one disulfide bridge was as low as 20%.

The closure of S–S bonds with *N*-iodosuccinimide in a DMF–CH₂Cl₂ mixture (1:1) in the synthesis of the (1–29) fragment of the human growth hormone having one disulfide bond (yield 15.6%) and an 18-membered peptide apamine having two S–S bonds (yield 11%) was reported.¹⁰⁰ In this case, the closure of S–S bridges did not follow the conventional procedure, *viz.*, oxidation after the completion of the linear peptide synthesis, but was rather included into the protocol of a solid-phase synthesis on an automatic peptide synthesiser using the Boc-technique. After attachment of the appropriate pair of cysteine residues, the disulfide bond between them was closed and the elongation of the peptide chain was continued. Acm and MbzI protections were used for the blocking of the thiol functions of cysteine. The use of an analogous procedure for the synthesis of oxytocin resulted in extremely low yields of the cyclic product (~1%), although [8 Arg]vasopressin was obtained in 41% yield under identical conditions. The question about the reason for such a low yield of oxytocin is still obscure. In our opinion, the authors' attempts¹⁰⁰ to interpret this phenomenon in terms of intermolecular aggregation of Cys(Acm) derivatives of oxytocin contradicts the results obtained by Albericio *et al.*^{89, 116} according to which it is cyclisation leading to oxytocin on a polymer under various conditions that occurs in sufficiently high yields, which often exceed those obtained by cyclisation in solution.

IV. Conclusion

The methods of formation of disulfide bonds considered above usually give compounds having one or two S–S bonds. However, each of the above-described methods has limitations of its own. Most often, they are related to oxidation-sensitive amino acids: tyrosine, tryptophan, and methionine. Despite the explosive development of methods and techniques of modern peptide chemistry, no versatile cyclisation procedure exists, and each time when an S–S bond is to be formed in a new compound, special experiment is required for the selection of the most adequate protection for the thiol function of cysteine and cyclisation reagent. In this context, further development of protective groups for the thiol function, elaboration of selective methods for deblocking of SH groups and specific activation of the thiol groups, and a search for new mild reagents suitable for the formation of S–S bridges are currently central tasks. Their solution assumes special importance in the synthesis of compounds with several intra- and intermolecular S–S bonds. At present, only few syntheses of such compounds have been carried out. Synthesis of complex molecules is a challenge of the nearest future. In this respect, methods of closing S–S bonds on a solid phase hold especially great promise. Further development and improvement in these techniques might facilitate laborious and sometimes unpredictable processes of cyclisation and make them

Scheme 2



Ⓟ is the styrene copolymer with 1% divinylbenzene, PAL is the tris-(alkoxy)benzamide anchor group, NMP is *N*-methylpyrrolidone, βMpa is β-mercaptopropionic acid.

automatic by including this stage into the program of a peptide synthesiser.

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^b — *Russ. J. Bioorg. Chem. (Engl. Transl.)*

Catastrophic oxidation of metals

V V Belousov

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Abstract. The review deals with the current state of the problem of catastrophic oxidation of metals ('hot corrosion') caused by formation of a liquid corrosion product in a multi-component system. The kinetics, thermodynamics, and mechanisms of the two stages of accelerated oxidation of metals, namely, fast and super-fast stages, are considered with the copper–bismuth oxide system as an example. It is shown that the fast stage is caused by the formation of a liquid-channel grain boundary structure in the corrosion product, while the super-fast stage is caused by the high rate of dissolution of the oxide layer. The results of studies of the interaction of liquid phase with two-dimensional defects (grain boundaries) in solids are generalised. A model of catastrophic oxidation of metals is proposed. The bibliography includes 104 references.

I. Introduction

The creation of high-temperature corrosion-resistant materials intended for prolonged exploitation under extremely drastic conditions is a current task of materials science. Such materials are used in nuclear and fuel-based power industries, in space technology, and in other branches of industry. In most cases, composite materials based on metals, such as metal-ceramics, sintered powder compositions of metals with oxides, nitrides, and borides, as well as amorphous alloys are employed. The practical solution of problems involved in the creation of corrosion-resistant materials depends largely on the development of theoretical concepts in the field of high-temperature oxidation of metals.

By now, it has been reliably established that the rate of high-temperature oxidation of metals leading to the formation of dense scale is controlled by diffusion processes. The rate of metal oxidation is determined by bulk diffusion of the reacting ions and electron transfer through the growing scale. These aspects are described by the Wagner model^{1,2} which makes it possible to find quantitative relationships between the rate of metal oxidation, the type and extent of oxide disordering, and the partial pressure of oxygen as a function of the type of conductivity of the scale (ionic or electronic).

However, in certain cases the rate of metal oxidation exceeds that predicted by the Wagner model by several orders of magnitude. This phenomenon referred to as catastrophic oxidation of metals (COM)^{3,4} may be caused by the following.

1. The loss of isothermicity in the oxidation zone. The rate of metal oxidation increases continuously with temperature. This occurs if the liberated heat of the exothermic reaction cannot dissipate efficiently. Hence, the temperature of the metal surface increases, and the oxidation accelerates continuously. At a sufficient rate of oxygen supply, this process can result in inflammation of the metal. Inflammation of niobium, tantalum, titanium, and some other metals has been observed under extremal conditions.^{5,6}

2. The formation of volatile oxides. For example, tungsten, molybdenum, vanadium, rhenium, and osmium form volatile oxides but no protective oxide films.^{7–10}

3. The formation of a small amount of a liquid phase in the oxidation product. This may be exemplified by oxidation of alloys the components of which form low-melting oxides; oxidation of metals in an atmosphere containing vapour of low-melting oxides; direct contact of metals and alloys with low-melting oxides. Even the appearance of a small amount of a liquid phase in the scale can lead to the COM.^{11–27}

In the latter case, two stages of COM, namely, fast and super-fast ones, can take place.^{28–30} The fast stage is caused by the formation of a liquid-channel grain-boundary structure (LGBS) in the oxidation product^{31,32} and occurs by an electrochemical mechanism. The super-fast stage is caused by the high rate of dissolution of the protective oxide layer and occurs by a fluxing mechanism.

The term 'COM' has been first introduced by Leslie and Fontana^{3,4} for an abrupt (by several orders of magnitude) increase in the rate of metal and alloy oxidation under isothermal conditions in a medium containing low-melting oxides (oxides of molybdenum, vanadium, lead, *etc.*). This phenomenon is also named 'hot corrosion'.^{33–38} Strictly speaking, this definition of COM refers only to the third case discussed above. The other cases do not fit the definition completely. In the first case, metal oxidation occurs under non-isothermal conditions (a continuous increase in temperature in the reaction zone; the theory of this process has been suggested by Zel'dovich^{5,6}) and is related mainly to the physics of burning. In the second case, the oxidising medium does not contain a foreign low-melting oxide.

In the present work, only the third case is considered in detail with the copper–bismuth oxide system as an example.

To date, some progress has been achieved in the investigation of COM. However, many key questions remain debatable or unclear. For example, the mechanism of anomalously fast mass

V V Belousov Open Joint Stock Venture 'Research Institute of Steel'
Dubninskaya ul. 81a, 127411 Moscow, Russian Federation.
Fax (7-095) 485 43 95. E-mail: nsteel@dol.ru

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transfer in solids involving the liquid phase and the mechanism of formation of a distributed structure (LGBS) are obscure; the interaction of a liquid phase with two-dimensional defects of a solid have been studied insufficiently.

In this review, the author attempted to discuss, from common viewpoints (thermodynamic, kinetic, structural), the mechanism of the COM caused by the formation of a liquid corrosion product in a multi-component system.

II. Fast stage of catastrophic oxidation of metals

1. Oxidation kinetics, structure and composition of the reaction products

Let us consider COM with the copper–bismuth system as an example, which most fully reflects the general features characteristic of other systems. It is known^{26,27} that copper coated with a thin film of bismuth (10–100 µm) undergoes catastrophic oxidation in air at 770 °C (Fig. 1). The rate of copper oxidation does not depend on the starting state of bismuth but depends on its quantity (Fig. 2). It has been found^{28,29} that the rate of copper oxidation increases with the thickness of the coating to reach a maximum at ~100 µm thickness (Fig. 3). The process of COM is determined by a parabolic time law, which indicates that the process is diffusion-controlled.

$$\left(\frac{\Delta m}{S}\right)^2 = kt \quad (1)$$

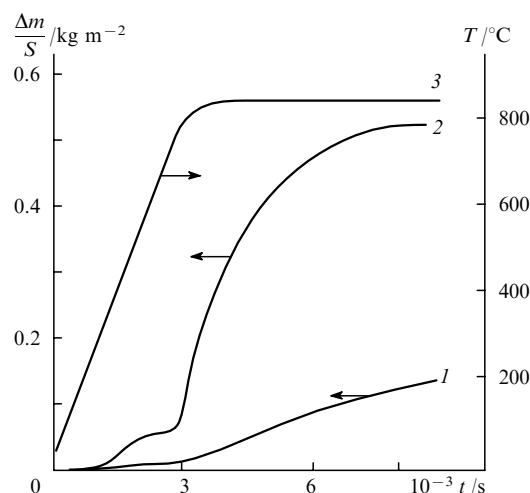


Figure 1. Kinetics of copper oxidation (1, 2) and temperature change (3); 1, without coating; 2, coated with a 30 µm-thick bismuth film.

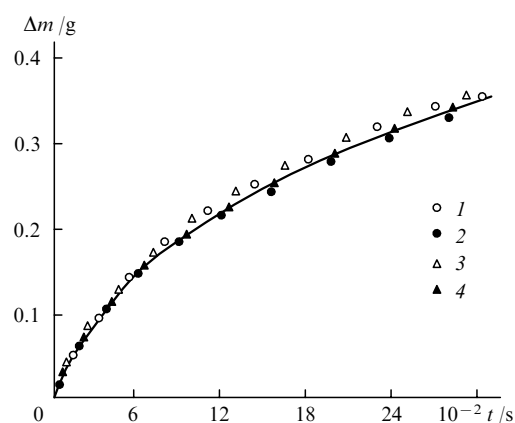


Figure 2. Kinetics of oxidation of copper with different coatings; (1), Bi₂O₃ + Bi₂CuO₄; (2), Bi; (3), Bi₂CuO₄; and (4), Bi₂O₃. In all cases, the amount of bismuth per unit area of copper is the same, $T = 800$ °C.

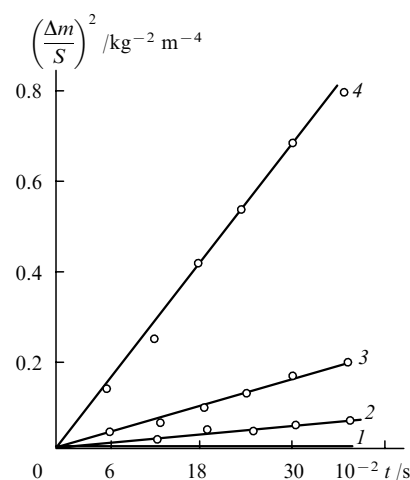


Figure 3. Kinetics of oxidation of copper coated with Bi₂O₃ films of different thickness at $T = 800$ °C. Film thickness $\times 10^5$ /m: (1), 0; (2), 3; (3), 6; (4), 9; $10^5 k / \text{kg}^2 \text{ m}^{-4} \text{ s}^{-1}$: (1), 0.012; (2), 1.6; (3), 4.9; and (4), 21.

Here Δm is the change in the mass of the specimen, S is the area of the surface that undergoes oxidation, k is the oxidation rate constant, and t is time. The k value depends on the coating thickness and exceeds the scale-formation constant on copper by a factor of over 1000. The temperature of 770 °C (threshold temperature for catastrophic oxidation of copper in the phase diagram of CuO–Bi₂O₃, see Refs 39–47) corresponds to the melting of the eutectics between Bi₂O₃ and Bi₂CuO₄. The COM process is associated with the formation of a liquid phase in the reaction products.

The scale on copper consists of two layers,^{26–29} viz., the inner dark layer and outer light layer with a distinct interface (Fig. 4). The outer layer is formed of Bi₂CuO₄ with minor amounts of Bi₂O₃, Cu₂O, and CuO. The inner layer is built of CuO with minor Bi₂CuO₄, Bi₂O₃, and Cu₂O. The concentrations of the latter two compounds increase abruptly near the copper surface. The distribution of elements across the scale is in quantitative and qualitative agreement with the phase distribution shown in Fig. 4.

The position of layers in the scale shows that copper is oxidised predominantly due to oxygen diffusion.

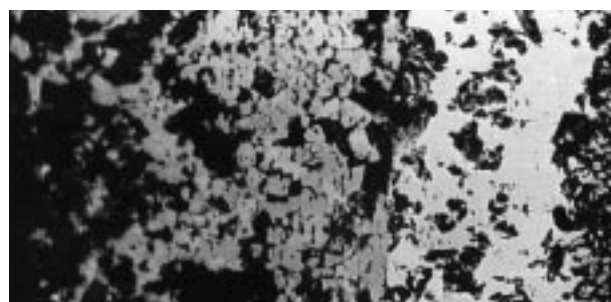


Figure 4. Microstructure of the scale on copper coated with a Bi₂O₃ film and oxidised in air at 800 °C; magnification is $\times 400$.

2. Interaction of liquid phase with grain boundaries of the solid

Model experiments carried out in order to reveal the specific features of penetration of Bi₂O₃ and Bi₂CuO₄ into the bulk of CuO formed upon copper oxidation show that intense penetration of Bi₂O₃ or Bi₂CuO₄ (in liquid state) along CuO grain boundaries occurs at 770 °C (Fig. 5). The width of intergranular layers depends on the quantity of compound that has penetrated and can vary from fractions of a micron to several microns. The

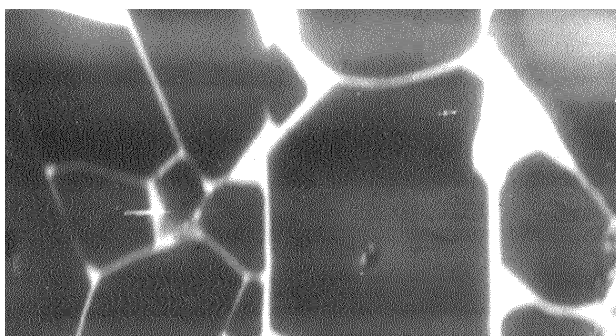


Figure 5. Microstructure of a CuO ceramics following thermal treatment in contact with Bi₂O₃ in air (cross-section).

penetration rate is high and reaches a few centimetres per minute (Fig. 6). The dependence of the penetration depth on time is linear. The activation energy of the process is $87 \pm 20 \text{ kJ mol}^{-1}$.

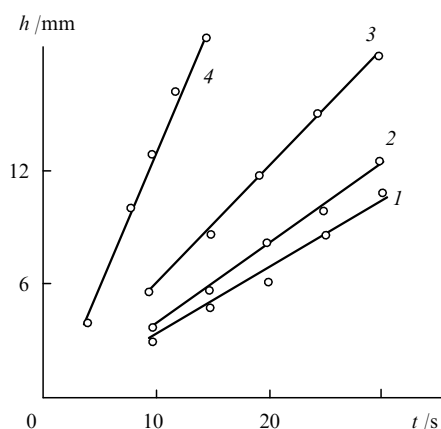


Figure 6. Dependence of the depth of penetration of the liquid phase (h) along CuO grain boundaries on time at different temperatures. $T/^{\circ}\text{C}$: (1), 860; (2), 900; (3), 950; and (4), 1050.

The linear time dependence of the depth of penetration of the liquid phase along grain boundaries and its high rate indicate that the process is not diffusion-controlled.

3. Phase formation

According to the phase diagram, only one compound, namely, Bi₂CuO₄, is formed in the CuO–Bi₂O₃ system.^{39–47} The amount of this compound decreases upon heating above 730 °C (Fig. 7).³²

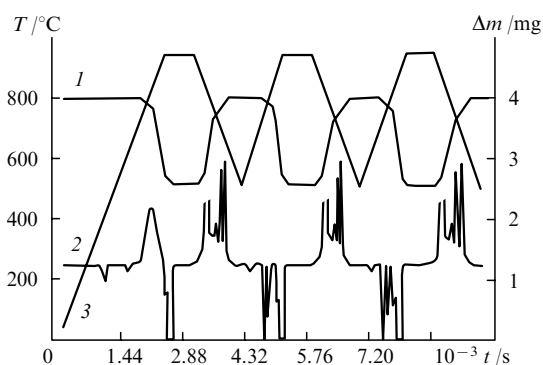
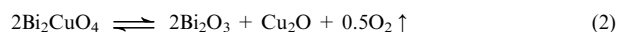


Figure 7. TGA (1), DTA (2), and T (3) curves for Bi₂CuO₄ exposed to cyclic heating and cooling in air.

The weight loss is accompanied by an exothermic effect on the DTA curve (2) and increases with temperature. The original weight is restored on cooling, but a small hysteresis appears on the TGA curve (1). The weight recovery is accompanied by additional exothermic effects corresponding to the reverse polymorphic transformation of Bi₂O₃, $\delta \rightarrow \gamma \rightarrow \beta \rightarrow \alpha$.^{48–58} The weight loss is caused by partial dissociation of bismuth cuprate according to the reaction



The decomposition of polycrystalline Bi₂CuO₄ occurs both from the outer and inner surfaces (grain boundaries). A liquid phase is formed at grain boundaries (Fig. 8). The figurative point of the system in the phase diagram of Bi₂O₃–Cu₂O (Fig. 9) with composition $2\text{Bi}_2\text{O}_3 + \text{Cu}_2\text{O}$ and a temperature of 730 °C is above the liquidus line, which corresponds to the liquid state. The volume fraction of the liquid phase increases with temperature. Hence, the equilibrium at the ternary diagram of Bi–Cu–O is shifted from the Bi₂O₃–CuO cross-section to the Bi₂O₃–Cu₂O cross-section. The liquid phase forms a connected network of channels along Bi₂CuO₄ grain boundaries (see Fig. 8), thus forming an LGBS.^{31,32} This implies that the thermodynamic condition of wetting, $\sigma_{\text{gb}} > 2\sigma_{\text{sl}}$ (where σ_{gb} is the surface tension of grain boundaries and σ_{sl} is the surface tension of the crystal–melt interface) is fulfilled. The exothermic effect at the DTA curve (first cycle, see Fig. 7) is probably related to wetting of grain boundaries with the liquid.

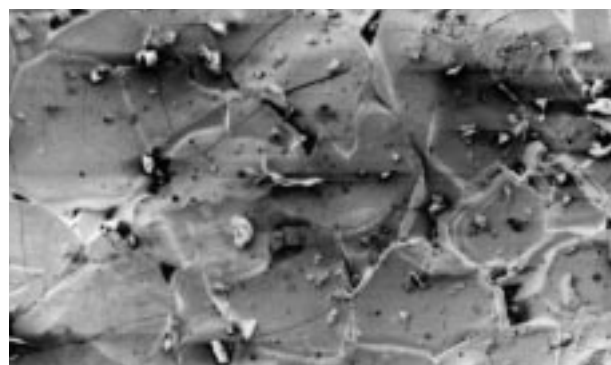


Figure 8. Microstructure of Bi₂CuO₄, quenching from 820 °C (fractured surface).

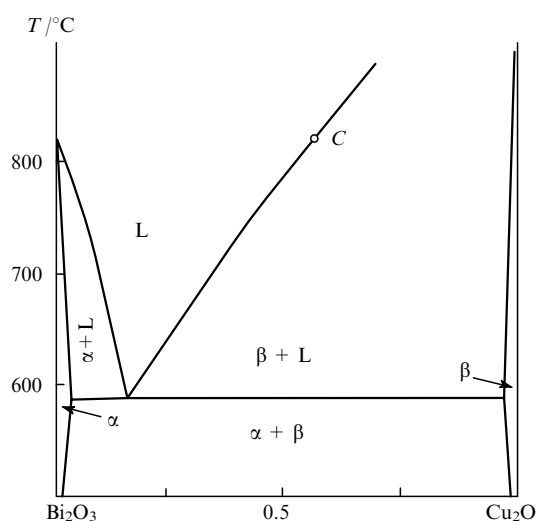


Figure 9. Cross-section of the phase diagram of Bi₂O₃–CuO, $p_{\text{O}_2} = 10^{-2} \text{ Pa}$. Point C corresponds to 60 mol.% of Cu₂O and 40 mol.% of Bi₂O₃, $T = 816^{\circ}\text{C}$.

4. Liquid-channel grain-boundary structures

Experimental results^{26–29, 31, 32} provide a reason to believe that the liquid phase plays an important role in the COM. This phase interacts with two-dimensional defects (grain boundaries) to form an LGBS, which affects considerably the mass transfer in the solid.

In some instances, the contact of solids with liquids results in the formation of grooves where grains outcrop at the outer surface;^{59–85} these grooves are characterised by a definite dihedral angle θ (Fig. 10). The value of θ is related to the surface tensions at the grain boundary and at the crystal–melt interface by a mechanical equilibrium at the groove apex:

$$\sigma_{gb} = 2\sigma_{sl} \cos \frac{\theta}{2}. \quad (3)$$

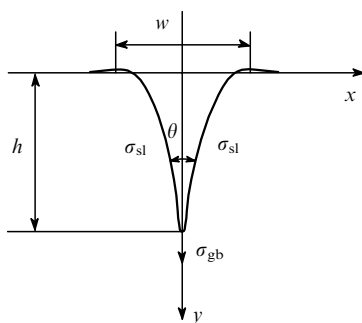


Figure 10. Profile of a grain boundary groove of liquid-phase etching.

A theoretical description of changes in topography of grain-boundary grooves and various transfer mechanisms is given by Mullins.^{60, 61} Let us briefly consider the Mullins theory of the development of a grain-boundary groove with a thermally etched groove as an example. Let a flat grain boundary outcrop at a flat surface (Fig. 10). The problem is to determine the surface profile at time t . The dependence of the chemical potential of an atom at a curved surface on the surface curvature is described by the Gibbs–Thomson equation

$$\mu_i(L) = \mu_i(\infty) + \Omega_i \sigma L, \quad (4)$$

where $\mu_i(L)$ and $\mu_i(\infty)$ are the chemical potentials of the i -th component at a surface of curvature L and at a flat surface, respectively, Ω_i is the partial volume of the i -th component, and σ is the surface tension. Hence, the chemical potential of an atom is determined by the surface curvature at this point

$$L = y'' [1 + (y')^2]^{-3/2}. \quad (5)$$

The value

$$\Delta\mu = \mu_i(L) - \mu_i(\infty) \quad (6)$$

reaches a maximum at $x = 0$ and decreases at $x > 0$ and $x < 0$. At the same time, $\nabla\mu$ is not equal to zero, causing a flux of atoms from the region with a higher potential (groove tip and banks) to that with a smaller potential (plateau), hence the groove should deepen and widen.

The dependence of the groove dimensions on time (t) is determined by the mechanism of the atom transfer. For example, for surface diffusion the groove width (w) and depth (h) are proportional to $t^{1/4}$:

$$\begin{aligned} w &= 4.6(At)^{1/4}, \\ h &= 0.97(At)^{1/4} \cotg \frac{\theta}{2}, \\ A &= \frac{D_s \sigma \Omega^2 n_s}{kT}, \end{aligned} \quad (7)$$

where D_s is the surface diffusion coefficient, n_s is the atom surface density, k is the Boltzmann constant, and T is temperature.

For bulk diffusion

$$\begin{aligned} w &= 5(Bt)^{1/3}, \\ h &= (Bt)^{1/3} \cotg \frac{\theta}{2}, \\ B &= \frac{D\sigma\Omega^2\rho}{kT}, \end{aligned} \quad (8)$$

where D is the bulk diffusion coefficient and ρ is the bulk density.

Quite a different physical picture appears if a fast diffusion pathway, such as liquid-phase diffusion, is possible. An analysis of the role of this process requires that the cases of saturated and unsaturated solutions are distinguished. The growth of a groove in a saturated solution occurs under the action of capillary forces. This process can be described using the Mullins theory, *i.e.* by the bulk diffusion of atoms through the liquid phase. This approach has been used repeatedly (see *e.g.*, Refs 76–78) to find that the groove width and depth change proportionally to $t^{1/3}$. Calculations agree satisfactorily with experimental data,⁷⁶ which shows that the maximum growth rate of the groove in this mode is as high as $\sim 0.5 \text{ mm h}^{-1}$. This value is considerably lower than that in the case of COM, where the liquid phase interacts with the grain boundaries of a solid (see Fig. 6).

Groove growth in unsaturated solution occurs under concentration gradient. Two extreme cases are possible. First, the process can occur in a kinetic mode ($h \sim t$, $w \sim t$), where the groove growth rate is controlled by dissolution, and diffusion transfer in the liquid phase occurs fast. Second, the process can occur in a diffusion mode ($h \sim t^{1/2}$, $w \sim t^{1/2}$), where the groove growth rate is controlled by diffusion through the liquid phase, and dissolution occurs rapidly. Calculations and experimental data⁷⁵ show that the maximum groove growth rate in the diffusion mode can be as high as several millimetres per hour, which is also much slower than in the case of COM.

The possibility of attainment of high rates of the groove deepening in the kinetic mode was considered by Fradkov.⁸¹ It was shown that in narrow grooves the groove tip moves much faster than the banks, resembling the movement of scissors. The groove deepening rate (v) is related to the rate of dissolution of a flat solid surface (v_0)⁸¹

$$v = \frac{v_0}{\sin(\theta/2)}. \quad (9)$$

However, an estimate of v using this formula showed that it is physically unreal to reach rates of several centimetres per minute. Such a rate can only be obtained at $\theta \approx 0.2^\circ$. Hence the Fradkov model is not applicable, as also noted by the author. The situation changes if v_0 increases. For example, this can occur if the groove deepening rate is controlled by the kinetics of channel opening at the tip rather than by that of the banks' expansion. It has been established experimentally that in the case of COM, where a liquid phase interacts with grain boundaries of a solid, the rate of the channel opening at the tip is controlled by the chemical reaction



It was noted above that Bi_2CuO_4 is thermally unstable and undergoes partial dissociation according to reaction (2). At grain boundaries, reaction (10) occurs, which [according to Eqn (2)] does not require any diffusion-controlled supply of the reagent, Bi_2O_3 , or diffusion-controlled withdrawal of the product, Bi_2CuO_4 . The oxygen evolved at the groove tip favours convective mixing (as the width of liquid channels exceeds considerably the free path of molecules).

Thus, fast penetration of a liquid along the CuO grain boundaries occurs due to acceleration of a chemical reaction at the grain boundaries rather than in the bulk. The most significant factors that favour the development of this process are the following: the chemical potential of atoms at the grain boundaries is higher than in the bulk; a chemical reaction occurs which does not require a diffusion-controlled supply of reagents (or diffusion-controlled withdrawal of products); a liquid, thermally unstable

product is formed; reaction is accompanied by gas evolution; a local temperature gradient appears due to a local chemical reaction; and the liquid is supplied to the channel by capillary forces.

The development of liquid channels occurs in the kinetic mode (see Fig. 6), hence equation (9) is still valid. However, v_0 acquires the meaning of the chemical reaction rate on a solid flat surface. Estimates show that the kinetic mode of the liquid channel growth controlled by a chemical reaction can result in narrow deep channels with a dihedral angle at the tip $0 < \theta < \pi$ at $v \sim 1 \text{ cm min}^{-1}$ and with v_0 values $0.001\text{--}1 \text{ cm min}^{-1}$, which are characteristic of topochemical reactions.^{86,87} The activation energy of the process, 87 kJ mol^{-1} , is also typical of topochemical reactions.⁸⁶

As a result of fast liquid penetration along the CuO grain boundaries, a continuous network of intergranular liquid channels is formed, eventually resulting in the LGBS formation.

Liquid-channel grain boundary structure can also be formed in different ways, *e.g.*, by topochemical decomposition of thermally unstable Bi_2CuO_4 . In both cases, the LGBS formation manifests itself as a sharp increase in electric conductivity caused by the onset of high ionic conductivity due to the oxygen ions.^{31,32} It has been shown^{28,29} that an LGBS based on CuO (see Fig. 5) readily conducts the oxygen ions. The ionic conductivity reaches $\sim 1 \Omega^{-1} \text{ cm}^{-1}$ at 780°C . The magnitude of conductivity is characteristic of superionic conductors.^{88–92}

Judging by phase composition and structure, LGBS should be attributed to heterogeneous structures. The question about the passage of electric current through heterogeneous structures has been first raised by Maxwell.⁹³ In particular, he considered the conditions of the passage of current through a two-phase system, which is a continuous medium with randomly distributed spherical inclusions. Odelevskii⁹⁴ pointed out that heterogeneous structures can be organised in two ways. A feature of distributed matrix structures is that one of the two or several constituent phases always forms a bound matrix, however small volume the phase occupies. The phases constituting a statistically distributed structure do not form a bound matrix. Therefore, we shall treat LGBS as distributed matrix structures the matrix of which consists of liquid channels with a thickness from fractions of a micron to several microns localised at the grain boundaries.

In some cases, the ionic conductivity increases at a certain ratio of phases that form a distributed phase.^{95–100} For example, the ionic conductivity can increase due to boundary phenomena on hetero-junctions.^{98,99} This is caused by disordering of crystal lattices in boundary regions and an increase in the concentration of mobile carriers. This effect is only characteristic of ionic conductors whose conductivity originates from the Frenkel or Shottky defects. Analogous effects are also possible if segregation

of an admixture on phase boundaries produces surface transition phases of a different chemical composition with enhanced conductivity.¹⁰⁰

Unlike the distributed structures mentioned above, LGBS incorporates continuous liquid channels along the grain boundaries. These channels can serve as diffusion paths for ions, since the activation energy of diffusion in a liquid is much lower than that in a solid. Figure 11 shows the dependence of the effective diffusion coefficient (D_{ef}) in LGBS on the volume fraction of phases calculated according to Maxwell and Hart.^{93,101} The diffusion coefficient in the solid phase was assumed to be $\sim 10^{-9} \text{ cm}^2 \text{ s}^{-1}$. For example, D_{ef} is $\sim 10^{-6} \text{ cm}^2 \text{ s}^{-1}$ if the volume fraction of the liquid phase is 10%. Such a high diffusion permeability of LGBS is due to the presence of a highly conductive liquid matrix.

Thus, the high ionic conductivity of LGBS is caused by the formation of a distributed matrix structure rather than by structural disordering as is the case in superionic conductors.

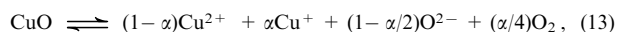
5. Mechanism of the fast stage in the catastrophic oxidation of metals

The LGBS model makes it possible to explain the high COM rates. Before discussing the mechanism of copper catastrophic oxidation, let us accept several key assumptions.

1. A liquid layer is formed on the surface of copper due to thermal dissociation (or melting) of Bi_2CuO_4 . Let us assume that reaction (2) involves at least two stages:



Each of these steps has its own equilibrium constant. Since ionic bonds predominate in all of the above oxides, it may be assumed that further dissociation into ions occurs in the melt. As an example, let us express reaction (12) in the ionic form



where α characterises the degree of CuO dissociation according to reaction (12). Reaction (13), which describes an equilibrium between ions in solution, was written assuming total dissociation of CuO. In reality, the degree of dissociation is much less than unity, therefore we shall consider the liquid layer as a dilute solution.

2. As a result of interaction of grain boundaries with the liquid phase, an LGBS is formed as a product of copper oxidation.

3. Copper is oxidised with oxygen dissolved in the liquid layer. The oxygen concentration is replenished continuously by the atmospheric oxygen.

4. The diffusion of oxygen ions through the liquid layer and liquid intergranular channels (Fig. 12) is the rate-determining step of the process.

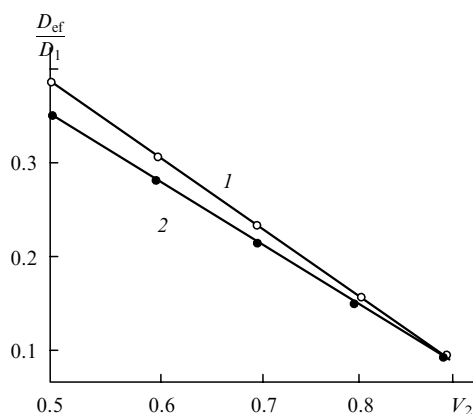


Figure 11. Effective diffusion coefficient of LGBS calculated according to Hart (1) and Maxwell (2); D_l is the diffusion coefficient in the liquid phase ($\sim 10^{-5} \text{ cm}^2 \text{ s}^{-1}$), V_2 is the volume fraction of the solid phase.

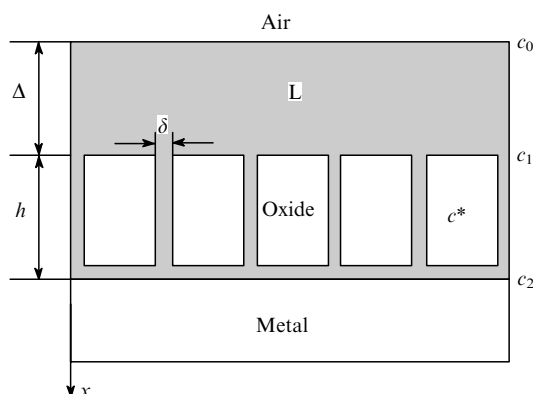


Figure 12. Topography of penetration of the liquid phase along the grain boundaries and interphase boundaries and a LGBS fragment in the catastrophic oxidation of copper.

5. The steady state is established locally all over the scale (where the scale is understood as the oxidation product + liquid layer).

6. The scale thickness is large in comparison with distances over which the effect of the bulk charge is felt (double electrical layer).

7. The solubility of oxygen in the metal can be neglected.

Let us consider the mechanism of diffusion growth of the oxide (see Fig. 12). Let us assume the thickness of copper oxide that formed to be h at time t and its growth to occur due to the oxygen supplied to the surface through liquid intergranular channels. If the concentration of oxygen in the growing oxide is designated as c^* , the mass balance equation is represented as follows

$$c^* \frac{dh}{dt} = J, \quad (14)$$

where J is the density of oxygen ion flux

$$J = -D \frac{dc}{dx}, \quad (15)$$

where D is the diffusion coefficient of oxygen ions and c is the concentration of the oxygen ions;

$$D = \frac{RT}{4F^2 \kappa}, \quad (16)$$

where κ is the partial specific electric conductivity of oxygen ions and F is the Faraday constant.

Let us consider two variants of the COM model. In the first one, the liquid layer is a film of thickness $\Delta = 10-100 \mu\text{m}$, $\Delta \leq \Delta_{\text{cr}}$, and $\Delta \leq h$ ($\Delta_{\text{cr}} \approx 100 \mu\text{m}$ corresponds to the experimentally obtained film thickness at which the maximum rate of copper oxidation is observed).^{28,29} It is assumed in this case that the material in the film is mixed and the concentration gradient of oxygen across the film thickness is absent. The oxygen concentration in the film is determined by dissociation equilibrium. However, a concentration gradient of oxygen exists in a liquid channel. The diffusion of oxygen occurs under permanent boundary conditions (stationary problem):

$$c(x=0, t) = c_0, c(x=\Delta, t) = c_1, c(x=\Delta+h, t) = c_2. \quad (17)$$

Assuming a linear distribution of oxygen concentration in the channel, one obtains

$$\nabla c = \frac{c_1 - c_2}{h}. \quad (18)$$

The oxygen concentration c_2 is very small, so one may consider $c_2 = 0$ and (taking into account the mixing in a liquid film) $c_1 = c_0$. Thus,

$$\nabla c = \frac{c_0}{h}. \quad (19)$$

Substitution of equation (19) into (15) gives

$$J = -D \frac{c_0}{h}. \quad (20)$$

The equation of mass balance (14) for thin films, taking account of (20), takes the form

$$c^* l \frac{dh}{dt} = \delta D \frac{c_0}{h}, \quad (21)$$

(l is the mean grain size of copper oxide and δ is the width of a liquid channel in LGBS) or

$$c^* \frac{dh}{dt} = D_{\text{ef}} \frac{c_0}{h}, \quad (22)$$

where

$$D_{\text{ef}} = D \frac{\delta}{l}. \quad (23)$$

Separation of the variables in equation (22) and integration gives a parabolic law of copper oxidation

$$h^2 = kt. \quad (24)$$

Here k is the rate constant for copper oxidation

$$k = 2D_{\text{ef}} \frac{c_0}{c^*}. \quad (25)$$

The diffusion of oxygen anions along the liquid channel to the growing oxide surface is accompanied by a less intense counter-diffusion of copper cations into the film, which increases their concentration in the film. According to equation (13), this shifts the equilibrium to the left. As a result, the concentration of oxygen anions c_0 , and hence k , decrease. If this phenomenon is named 'solution poisoning', it is obvious that the thinner the film the more pronounced this effect, and *vice versa*. Therefore, the dependence of k on the film thickness (for thin films, $\leq 100 \mu\text{m}$) can be explained by solution poisoning. This effect is insignificant and can be neglected for thick films.

Estimates show that if the degree of CuO dissociation according to reaction (12) equals unity and, accordingly, the degree of Bi_2CuO_4 dissociation according to reaction (11) is 0.25 (see Ref 59), and the degree of dissociation of Bi_2O_3 and Cu_2O into ions is about the same, the concentration of the oxygen anions in the liquid film is $c_0 \approx 0.03$ (in atomic fractions). The rate constant for copper oxidation under a thin layer of Bi_2CuO_4 is calculated according to the formula

$$k_{\text{theor}} = 2D_{\text{ef}} \frac{c_0}{c^*} \rho^2, \quad (26)$$

where ρ is the CuO density. At $c^* = 0.5$, $D_{\text{ef}} \approx 10^{-10} \text{ m}^2 \text{ s}^{-1}$, and $\rho_{\text{CuO}} = 6.45 \times 10^3 \text{ kg m}^{-3}$, we have $k_{\text{theor}} \leq 5.2 \times 10^{-4} \text{ kg}^2 \text{ m}^{-4} \text{ s}^{-1}$, which is comparable to the experimental value $k_{\text{exp}} \leq 2.1 \times 10^{-4} \text{ kg}^2 \text{ m}^{-4} \text{ s}^{-1}$ (see Fig. 3).

In the second case, the liquid layer thickness exceeds the critical value, $\Delta > \Delta_{\text{cr}}$ and $\Delta > h$. In this case, the gradient of oxygen concentration exists both in the channel and in the layer:

$$\nabla c = \frac{c_0 - c_1}{\Delta}, \quad (27)$$

where $\Delta = nh$, $n > 1$, i.e.

$$\nabla c = \frac{c_0 - c_1}{nh}; \quad (28)$$

in the channel

$$\nabla c = \frac{c_1}{h}. \quad (29)$$

The expressions for the flux of oxygen ions have the form:

$$J_{(\Delta)} = -D \frac{c_0 - c_1}{nh}, \quad (30)$$

in the channel

$$J_{(h)} = -D_{\text{ef}} \frac{c_1}{h}. \quad (31)$$

In the steady state

$$J_{(\Delta)} = J_{(h)}, \quad (32)$$

hence

$$D \frac{c_0 - c_1}{nh} = D_{\text{ef}} \frac{c_1}{h}. \quad (33)$$

Substituting (23) into (33), we obtain

$$\frac{c_0 - c_1}{n} = \frac{\delta}{l} c_1, \quad (34)$$

whence

$$c_1 = \frac{c_0}{1 + \delta n/l}. \quad (35)$$

The equation of mass balance (14) for thick layers is written in the form

$$c^* \frac{dh}{dt} = D_{\text{ef}} \frac{c_0}{h(1 + \delta n/l)}. \quad (36)$$

Integration of this expression gives a parabolic law of copper oxidation

$$h^2 = kt, \quad (37)$$

where

$$k = 2D_{\text{ef}} \frac{c_0}{c^*} \frac{1}{1 + \delta n/l}. \quad (38)$$

Thus, the number n increases and k decreases as the layer thickens, which is in accord with experimental results.^{28,29} The theory is also applicable if the rate of metal oxidation is controlled by the diffusion of cations. In this case, the picture changes symmetrically, and the liquid layer is adjacent to the metal (Fig. 12).

The suggested theory of COM is primarily valid in systems where oxidation results in the LGBS formation in the reaction products. As shown above, an LGBS is formed due to topochemical destruction or upon interaction of a liquid with grain boundaries of a solid. Therefore, the fast stage of the COM is most probable in metal–oxide systems in which formation of thermally unstable mixed or low-melting oxides is possible.

III. Super-fast stage of catastrophic oxidation of metals

1. Oxidation kinetics

In a study of the oxidation of copper under a bulk Bi_2O_3 layer thicker than 5 mm, it was found^{28,29} that at the instant when Bi_2O_3 melts (point A in Fig. 13) at $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} \geq 20$, copper plates (0.5–1 mm thick) undergo super-fast (in 5–10 s) oxidation in the medium of Bi_2O_3 , thus reducing the latter. If $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} < 20$, only the amount of copper equal to 1/20 of the Bi_2O_3 mass is oxidised super-fast, while the rest of copper is oxidised much more slowly. The $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$ ratio at which super-fast oxidation of

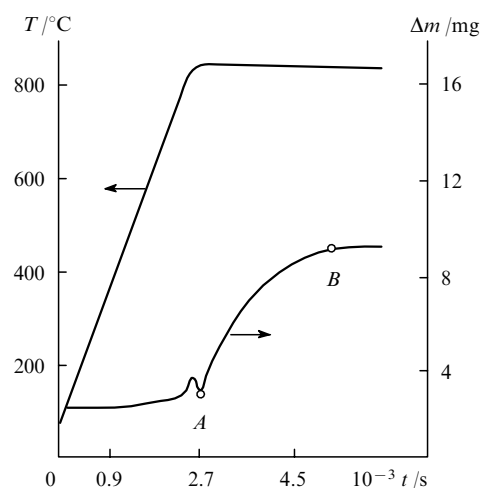


Figure 13. Kinetics of copper oxidation under a layer of Bi_2O_3 in air, $m_{\text{Bi}_2\text{O}_3} = 2.226$ g, $m_{\text{Cu}} = 0.036$ g.

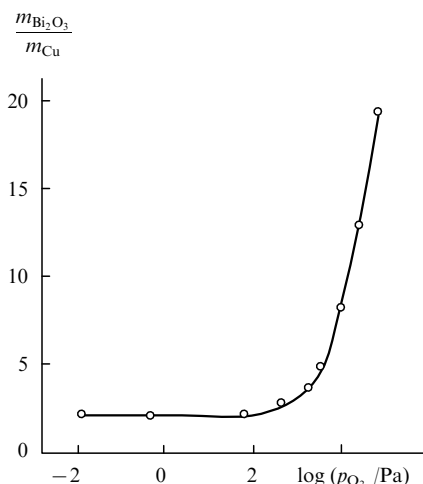


Figure 14. Dependence of the critical ratio ($m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$) on the oxygen partial pressure (p_{O_2}).

copper occurs depends on the partial oxygen pressure p_{O_2} : when p_{O_2} decreases, $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$ decreases as well. The minimum value $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} = 3.6$ is reached at $p_{\text{O}_2} \approx 10^2$ Pa (Fig. 14).

The literature contains controversial thermodynamic data for both the free energy of Bi_2O_3 formation and the dissociation pressure. According to some sources, copper reduces Bi_2O_3 , while it does not do so according to others.^{102–104}

2. Mechanism of the super-fast stage of catastrophic oxidation of metals

The high rate of copper oxidation under a layer of Bi_2O_3 melt at $p_{\text{O}_2} = 10^{-2} - 10^2$ Pa (see Fig. 14) can be explained as follows. The initial mass ratio $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} = 3.6$ corresponds to 60 mol.% of Cu_2O and 40 mol.% of Bi_2O_3 (taking into account that all of the copper is oxidised into Cu_2O and the initial amount of Bi_2O_3 decreases accordingly). According to the phase diagram of $\text{Bi}_2\text{O}_3 - \text{Cu}_2\text{O}$ (see Fig. 9), the composition of 60 mol.% of Cu_2O and 40 mol.% of Bi_2O_3 and the temperature 816 °C correspond to point C on the liquidus line. If $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} > 3.6$, the figurative point of the system is to the left of point C , while at $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} = 3.6$, these points coincide. Copper is oxidised (reducing Bi_2O_3) into Cu_2O , which in turn undergoes continuous dissolution. Hence, super-fast oxidation occurs at the metal surface (without a protective oxide layer) due to a redox reaction. Withdrawal of reaction products from the reaction zone probably occurs by convective diffusion.

At $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}} < 3.6$, a fraction of copper which is 1/3.6 of the Bi_2O_3 mass is oxidised super-fast. After that, the figurative point of the system shifts to the right of C . Copper oxide formed on the copper surface is in the solid state and does not dissolve. Subsequent dissolution of copper occurs by the diffusion mechanism.

Super-fast oxidation of the metal occurs also at higher partial oxygen pressures, so that the $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$ ratio increases (see Fig. 14). In this case, the mechanism of copper oxidation does not differ in principle from that described above and the increase in $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$ at which super-fast copper oxidation occurs is due to the fact that CuO is stable at $p_{\text{O}_2} \approx 6 \times 10^3$ Pa,¹⁰² therefore the formation of Bi_2CuO_4 is possible,^{39–42} which is in accord with experimental results.^{28,29} The decrease in the amount of copper oxidised super-fast in air in comparison with the critical mass of copper oxidised *in vacuo* is due to the formation of Bi_2CuO_4 and hence depletion in the starting Bi_2O_3 . Copper undergoes super-fast oxidation and reduces bismuth oxide to the metal, which is subsequently oxidised with atmospheric oxygen (section AB in Fig. 13). Simultaneously, Cu_2O is partially oxidised to CuO . The insignificant mass decrease in the kinetic curve of copper oxida-

tion in point *A* is due to partial dissociation of Bi_2CuO_4 according to reaction (2).

Thus, super-fast copper oxidation is caused by continuous dissolution of the protective oxide film of Cu_2O in a Bi_2O_3 melt. Oxidation occurs on a permanently bare metal surface due to a redox reaction. The critical ratio $m_{\text{Bi}_2\text{O}_3}/m_{\text{Cu}}$ at which super-fast copper oxidation occurs is determined by the position of the figurative point on the liquidus line on the Bi_2O_3 – Cu_2O binary phase diagram, or on the liquidus surface in a ternary diagram if mixed oxides are formed.

IV. Conclusion

It should be noted that COM can occur both according to the electrochemical mechanism (diffusion of ions along liquid intergranular channels) and according to the flux formation mechanism (dissolution of the protective oxide layer). The realisation of the particular mechanism depends on the mass ratio of the liquid phase (m_L) and the metal (m_M) and the Gibbs free energies of formation of the solid product (ΔG_1) and the liquid phase (ΔG_2).

1. If $|\Delta G_1| > |\Delta G_2|$ and $m_L/m_M \geq A$, where *A* is the number determined by the position of the figurative point of the system on the liquidus surface corresponding to a definite composition and temperature on the phase diagram. In this case, a redox reaction is possible, while the LGBS formation is impossible; the figurative point of the system is located above the liquidus surface or coincides with it. The metal oxidation occurs at a very high rate according to the flux formation mechanism. The metal is oxidised within seconds.

2. If $|\Delta G_1| > |\Delta G_2|$ and $m_L/m_M < A$, then both the redox reaction and the LGBS formation are possible. A fraction of the metal amounting to $1/A$ of the mass of the liquid phase is oxidised according to the flux formation mechanism. The figurative point of the system is then shifted below the liquidus surface. An LGBS is formed on the metal surface. Subsequent metal oxidation occurs more slowly according to the electrochemical mechanism.

3. If $|\Delta G_1| < |\Delta G_2|$ and $m_L/m_M \geq A$, then both the redox reaction and the LGBS formation are impossible. Both the flux formation and electrochemical mechanisms are operative, therefore, the rate of metal oxidation is much lower than that in case 1.

4. If $|\Delta G_1| < |\Delta G_2|$ and $m_L/m_M < A$, then the LGBS formation is possible but the redox reaction is impossible. The metal fraction which amounts to $1/A$ of the mass of the liquid phase is oxidised as in the preceding case. The figurative point of the system is then shifted below the liquidus surface. An LGBS is formed on the metal surface. Subsequent oxidation follows the electrochemical mechanism.

The general picture of COM can be represented as follows. The catastrophic oxidation of metals under a thin liquid layer no thicker than $\sim 100 \mu\text{m}$ occurs by the electrochemical mechanism and is caused by the LGBS formation in the corrosion product. In this case, the contribution of super-fast oxidation according to the flux formation mechanism is insignificant, as the metal fraction that undergoes super-fast oxidation is as small as 0.5%–3%. As the layer thickness increases, the contribution of super-fast oxidation becomes greater, which would change the character of oxidation and increase the rate of the process.

Thus, the following conclusions can be made on the basis of the data presented above.

1. The fast stage of COM is caused by the LGBS formation in the corrosion product. The oxidation rate depends on the diffusion of ions along the liquid intergranular channels.

2. The super-fast stage of COM is caused by the high rate of dissolution of the protective oxide film. The oxidation occurs by a redox reaction on a continuously bare metal surface.

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Cryotropic gelation of poly(vinyl alcohol) solutions

V I Lozinsky

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Abstract. The mechanisms of the cryotropic gelation of poly(vinyl alcohol) solutions as well as the influence of the characteristics of the polymer and the conditions of the cryogenic treatment on the structure and physicochemical properties of the cryogels obtained are examined. Data on the characteristics of the freezing of concentrated poly(vinyl alcohol) solutions are presented. The influence of soluble additives, possessing different lyotropic properties, on the course of gelation in frozen systems is discussed. The possibility of the cryocracking of poly(vinyl alcohol) chains is considered. The bibliography includes 349 references.

I. Introduction

The cryogels based on polymer systems are macroporous heterophase gels formed as a result of the freezing, storage in the frozen state, and subsequent thawing of the initial solutions or colloiddally disperse objects (colloid solutions, pastes, coagulates, *etc.*) in which preconditions for structure formation and transition into a gel are already present or are specially created (for example, by the introduction of a cross-linking agent). An obligatory condition for the formation of heterogeneous gels is then the crystallisation (freezing) of the main bulk of the low-molecular liquid (solvent). After its thawing out, anisotropic macroporous gel-like polymeric products, called cryogels, or cryostructurates are formed.^{1–4} As in the case of the usual gels, produced in a liquid solvent, the junctions of the three-dimensional network of the cryogels can be of different nature: they can be established covalently (chemically cross-linked preparations), maintained as a result of relatively undissociated salt or coordinate-ionic bonds (ionotropic systems), stabilised by noncovalent interaction forces [thermoreversible (physical) cryogels], or they may represent a combination of these types of intermolecular contacts.^{4–9}

Although individual examples of the formation of gel-like structurates after the freezing–thawing of solutions or dispersions of polymers have been known for a fairly long time (thus sponges produced by the freezing of starch paste were manufactured in Germany in the 1940s¹⁰), this type of gelation began to be studied systematically only during the last 15 years. These investigations

led to the creation of definite ideas about the principal mechanisms of the cryotropic gelation processes, specific effects characteristic of this process alone, its common features with gelation in unfrozen systems, and also the influence of various parameters of each stage of the cryogenic treatment on the properties of the materials obtained.^{2, 4–9, 11, 12}

The cryotropic gelation of solutions of poly(vinyl alcohol) (PVA) is examined in the present review. PVA-based cryogels are of great interest — both theoretical and applied. They have found extensive application in biotechnology, medicine, food industry, *etc.* In many respects, this interest is due to the excellent mechanical, diffusional, and thermophysical properties of the PVA cryogels (cryoPVAG), the availability of the polymer itself, its nontoxicity and biocompatibility, and also the relative ease of the method of formation of the gel (the PVA solution is simply frozen for a certain period and then thawed out). By varying the characteristics of the polymer employed (molecular mass, molecular mass distribution, the content of residual *O*-acyl groups, tacticity, PVA concentration in the system) the composition of the solvent, the nature of soluble additives (if these are introduced in the initial system), and also the regime in the cryogenic treatment (temperature and duration of freezing, rate of thawing, the number of refreezing cycles, *etc.*), it is possible to regulate within wide limits the physicochemical parameters of the final gels and their macro- and micro-structures. All these aspects will be discussed in the subsequent sections of the review.

The ability of PVA to give rise to gels after the freezing–thawing of its solutions (here and henceforth we are dealing mainly with a polymer having an insignificant content of acyl residues in the lateral chains) was apparently first observed by Inoue.^{13–17} He described the preparation of gel fishing baits from a mixture of a solution of PVA with fillers and aromatising agents. In order to obtain the gel, the initial suspension, poured into an appropriate mould, was initially frozen at a temperature below -5°C for several tens of hours and then thawed out. In the scientific literature, a direct indication of such gelation appeared in the paper of Kukharchik and Baramboim,¹⁸ who noted that in the case of PVA ($M = 80\,000$) solutions with a concentration $> 3\text{ g}/100\text{ ml}$ the cryolytic cycles (freezing for 2 min at -78°C and thawing at 25°C for 15 min) resulted not only in an increase in viscosity but also in gelation. However, none of the characteristic features of such gelation of PVA and the properties of the cryogels were reported in the above investigation.¹⁸

Mention should also be made of the work of Polish investigators,^{19, 20} who observed by the light scattering method the promoting effect of the cryogenic treatment on the association of

V I Lozinsky N A Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 85. Tel. (7-095) 135 64 92

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PVA macromolecules in aqueous media, and also of the somewhat later study by Peppas.²¹

Some time later, the PVA cryogels were, as it were, 'rediscovered'. This is probably associated with the observation of the possibility of increasing the mechanical strength of cryoPVAG as a result of the repeated freezing–thawing of the cryogel already obtained^{12, 22–31} or the partial dehydration of the frozen specimen *in vacuo* (partial lyophilisation).^{32–40}

According to *Chemical Abstracts*, about 500 communications have been published on the cryotropic gelation of PVA, only a small proportion of these publications having been considered in the reviews of Nambu¹¹ (1990) and Peppas and Stauffer¹² (1991), as well as in our earlier review⁴¹ (1992). The aim of the present review is to provide a more comprehensive pattern of the state of research into the given problem and also to note the problems which are still obscure.

II. Characteristic features of the freezing of poly(vinyl alcohol) solutions

It is well known that prolonged storage of concentrated aqueous PVA solutions at room temperature gives rise to gel formation (see, for example, Refs 42–46). A similar result can be achieved faster by cooling the system (without freezing)^{20, 47} or by impairing the thermodynamic quality of the solvent as a result of the introduction of nonsolvent additives.^{48–52} In all cases low-melting (melting point $T_m < 30–40\text{ }^{\circ}\text{C}$), mechanically weak, and as a rule almost transparent (opalescent) thermoreversible hydrogels are formed. On the other hand, if concentrated aqueous PVA solutions are initially frozen and are then thawed out after being maintained in the frozen state for a time, then turbid, elastic, high-melting ($T_m > 60–80\text{ }^{\circ}\text{C}$) heterogeneous gels (cryogels) are formed under certain conditions instead of the transparent hydrogels. Evidently the behaviour of the water–PVA system subjected to cryogenic action should affect the properties of the cryogels obtained and the kinetics of their formation.

Figure 1 presents a generalised picture of the variation of the temperature of the system at all the stages of cryostructuration, *i.e.* on freezing, storage in the frozen state, and thawing. Interval $A–B$ corresponds to the cooling of the specimen from the initial temperature to the temperature of the onset of crystallisation of the solvent (supercooling to a temperature T_u is frequently observed for PVA solutions). Owing to the evolution of the latent heat of crystallisation of ice, a 'crystallisation plateau' is usually recorded along section $C–B$, but at high rates of cooling ($v_c > 40\text{ K min}^{-1}$) this plateau may not in fact be observed on the real time scale.⁵³ A further decrease in temperature occurs

between the points D and E up to the experimentally specified value (T_s).

It has been shown^{4, 54, 55} that the depression of the crystallisation temperature of the system ($T_0 - T_f$) for 5%–10% aqueous solutions of PVA did not exceed $0.3–0.8\text{ }^{\circ}\text{C}$, while the extent of supercooling is a parameter poorly reproducible with respect to temperature in view of the statistical nature of the ice nucleation processes.⁵⁶ In the main, the trend is as follows: with increase in the PVA concentration in the initial solution, the supercooling temperature (T_u) falls and ice formation proper proceeds at a higher rate. The higher the rate of crystallisation, the finer are the polycrystals of the freezing low-molecular liquid produced.⁵⁷ Thus the size of the ice crystals in the 7% PVA solution frozen at $-10\text{ }^{\circ}\text{C}$ is several times smaller, and in the 14% solution — smaller by 1–2 orders of magnitude than in frozen pure water.⁵⁸

Such microstructure of the polymer-reinforced ice affects significantly the physicochemical characteristics of the frozen specimens⁵⁹ and an appreciable strengthening of such composite ice is observed even for a 1% PVA content in the initial solution and the ultimate uniaxial compression strength of the 10% preparation frozen at $-10\text{ }^{\circ}\text{C}$ is already an order of magnitude higher than for pure ice. After a time, this parameter slowly increases, which has been shown by studies involving the use of the NMR method,⁵⁸ to be accompanied by a gradual decrease in the amount of unfrozen water.

Important information about the properties of the water–PVA system at various negative temperatures has been provided by the study of the ESR spectra of a spin probe (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl) introduced into the initial polymer solution before freezing. It has been found^{60–63} that the correlation times of the rotational mobility of the stable nitroxyl radical, which depend directly on the viscosity of the micro-environment where reorientation movements of the probe take place, corresponds, for not unduly deeply frozen PVA solutions, to the rotations of the nitroxyl radical in a highly viscous but liquid medium. This shows that such polymer solutions, solidified by freezing (in particular aqueous PVA solutions), represent at least two-phase systems incorporating the crystalline phase of the frozen solvent and the phase comprising a heavily concentrated polymer solution — the so-called liquid microphase.^{64–66} Quantitative estimates of the volume of such liquid microphases of frozen PVA solutions have been made with the aid of a special method⁶⁰ for the analysis of ESR spectroscopic data. It has been shown that the amount of the liquid component varies from $0.86–0.88\text{ g}$ of H_2O per gramme of the polymer at $-9\text{ }^{\circ}\text{C}$ to 0.75 g of H_2O per gramme of the polymer at $-85\text{ }^{\circ}\text{C}$; the latter quantity was limiting and referred to unfrozen water. Approximately the same result ($\sim 0.8–0.9\text{ g}$ of H_2O per gramme of polymer) was obtained with the aid of NMR spectroscopy^{67, 68} and differential scanning calorimetry.⁶⁹ Taking into account the 10%–15% error of the determination by each of these methods, such agreement should be regarded as rather good.

In the region of 'high' negative temperatures (from -1 to $-7\text{ }^{\circ}\text{C}$), hysteresis phenomena are observed (Fig. 2), *i.e.* the amount of the liquid microphase and hence the concentration of the polymer dissolved in it depend greatly on the thermal pre-history of the system in the real (far from equilibrium) cooling or heating regimes. In particular, if fairly rapid heating of the frozen specimen is arrested at some intermediate temperature (in Fig. 2, this is $-4\text{ }^{\circ}\text{C}$), the system gradually relaxes to a phase state closer to equilibrium (transition 3, Fig. 2). Therefore, the slower the cooling of the frozen preparation or correspondingly the slower its heating during thawing, the greater is the extent to which the possible transformations of liquid water into ice are able to occur or, conversely, the closer to equilibrium is the amount of the liquid microphase.

Direct observations at negative temperatures of the mobility of the unfrozen part of water in the water–PVA system have been carried out^{67, 68} with the aid of ^2H NMR spectroscopy. For this purpose, the polymer was dissolved in D_2O . The NMR signals of

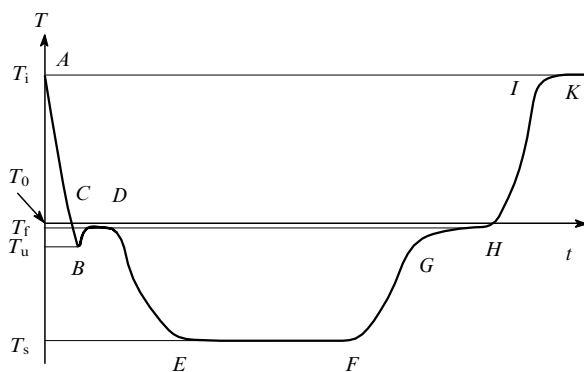


Figure 1. Generalised thermogram for cryotropic gel formation; T_i = initial temperature of the system, T_0 = temperature at which the pure solvent is frozen, T_f = temperature at which the system is frozen, T_u = lowest supercooling temperature, T_s = temperature at which the specimen is stored in the frozen state.

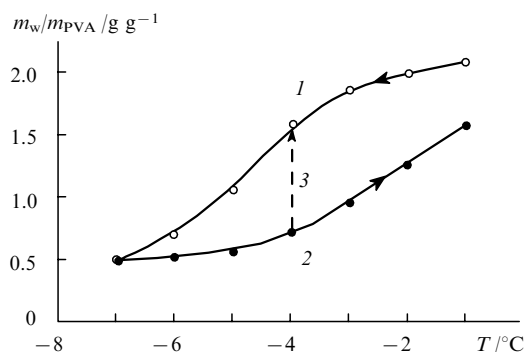


Figure 2. Dependence of the relative amount of unfrozen water on the temperature of the frozen 10% PVA solution (m_w = mass of water remaining liquid in the frozen specimen; m_{PVA} = mass of PVA dissolved in the liquid microphase);⁶⁰

(1) cooling of the specimen beyond the crystallisation plateau of pure water; (2) heating; (3) thermostatic regime at -4°C .

the heavy water deuterons in the solid and liquid states differ in width by two orders of magnitude and it is therefore possible to record the spectra referring to the D_2O molecules not incorporated in the ice structure. The ^2H NMR spectra of a 10% solution of PVA ($M=82\,000$), frozen to a temperature of -52.2°C , which is 56°C lower than the crystallisation point of the pure solvent ($T_0 = +3.8^\circ\text{C}$), contain one symmetrical signal without quadrupole splitting. The width of this signal depends on the temperature and in the temperature range indicated varies from several tens to ~ 5000 Hz. The nature of the spectra then indicates the virtually isotropic reorientation of the solvent molecule, which indicates the rapid (10^{-5} s on the NMR time scale) rotational and translational diffusion of water in the isotropic medium; *i.e.* in the unfrozen liquid microphase the water molecules are subjected to interactions which are virtually equivalent and equally probable in all directions. On the other hand, the proportion of the solvent located near the anisotropic interfaces is, firstly, small and, secondly, it apparently exchanges rapidly with the molecules from the bulk of the liquid inclusions. On further cooling of the specimen to temperatures $60\text{--}70^\circ\text{C}$ lower than its freezing point, the symmetrical Gaussian peak (with a width of ~ 5 kHz at the level of half its height) is transformed into a two-component signal, the upper component of which has been broadened by a factor of 4, while the lower component, the so-called 'pedestal', corresponds to a signal with a greatly increased spin-lattice relaxation time. It has been suggested⁶⁷ that this character of the spectrum at the temperatures indicated is caused by the slow exchange of the ^2H nuclei of the solvent and the polymer.

Thus it has been shown that moderately frozen PVA solutions are heterophase objects containing the unfrozen mobile solvent, the minimum amount of which corresponds to the ratio ~ 4 water molecules for 3 polar chain groups.

Yet another effect which can occur in principle during the freezing of polymer solutions, including aqueous PVA solutions, is cryocracking, *i.e.* the cryogenic mechanical degradation of the chains of high-molecular compounds under the influence of the dynamic stresses arising on crystallisation of the low-molecular solvent. Berlin and coworkers^{70–73} were the first to draw attention to the possibility of such mechanochemical transformations of polymers during the freezing–thawing of their solutions. Somewhat later Jellinek and Fok⁷⁴ calculated the critical rates of movement of the fronts of the crystallisation of the solvent (v_{cr}) and of the migration of the microstreams of the liquid ahead of the growing faces of the crystals, which are necessary to develop forces sufficient for the disruption of the covalent bonds of the main framework of the carbochain polymers. These calculations were performed for two types of physical action on the macromolecule: (a) impact across the chain fixed (frozen in) at both ends (which is generally speaking an extremely improbable event) and (b) the

frictional shear force of the liquid stream ahead of the crystallisation front exerted on the chain fixed at one end. Calculation yielded the following values of v_{cr} : $\sim 100\text{ m s}^{-1}$ in the first case and $\sim 0.5\text{ m s}^{-1}$ in the second. On the other hand, in practice the attainable rates for preparations with a volume of several millilitres do not exceed $0.002\text{--}0.003\text{ m s}^{-1}$.⁷⁵ For preparations with a volume of several microlitres, it is possible to achieve an increase in the rate by 1–2 orders of magnitude during their rapid freezing (for example, in liquid nitrogen), but even such increase in the rate makes it possible merely to approach the second case. Therefore one should apparently not expect a real manifestation of the mechanical degradation of PVA for shallow freezing of its solution under the conditions employed for the formation of cryoPVAG.

Thus in a study of the behaviour of PVA solutions during thawing and freezing with the aid of capillary viscometry, Kukharchik and Baramboim^{18,76} failed to observe any kind of cracking of PVA either during single or repeated freezing–thawing of dilute and semidilute solutions of the polymer ($M=80\,000$). Nevertheless, facts have been described which indicate, according to the authors,^{77–80} the occurrence of homolytic cleavage of PVA by the cryogenic influence; here it has also been suggested⁷⁷ that cracking is accompanied by the simultaneous covalent cross-linking of the polymer molecules as a result of reactions between the macroradicals formed and the neighbouring chains.

However, a thorough test of the results of the above studies^{77–80} failed to confirm the conclusions reached in them.^{81,82} In the first place, the cryoPVAG are thermoreversible gels which melt on heating (for example, on a boiling water bath). Here the viscosities of the initial solutions of PVA ($c_p = 6\%\text{--}10\%$) having different molecular masses ($69\,000\text{--}110\,000$) and solutions obtained from the corresponding cryogels after fusion of the latter hardly differ, which indicates the absence of intermolecular cross-linking. Capillary viscometry does not reveal reliably detectable changes in the intrinsic viscosities of the PVA preparations, provided that the initial polymer does not contain any impurities. Thus lines 4 and 5 in Fig. 3 illustrate the dependence of $[\eta]$ on the number of cycles in the cryogenic treatment of solutions of two different batches of the same brand of technical-grade PVA, for which both a decrease (line 5) and an increase (line 4) in $[\eta]$ were observed, whereas variation within wide limits of the freezing–thawing regimes for solutions of the same polymer purified by reprecipitation does not induce changes in the intrinsic viscosity (lines 1–3, Fig. 3). Thus the possible reactive impurities contained in industrial PVA, concentrated in the liquid microphase of the frozen preparations, may be the cause of the change in the properties of the polymer recorded after the cryogenic action.

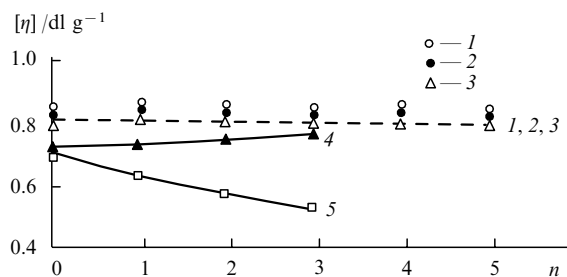


Figure 3. Dependence of the intrinsic viscosity $[\eta]$ of PVA on the number of freezing–thawing cycles (n) for a 10% PVA solution of brand 20/1.

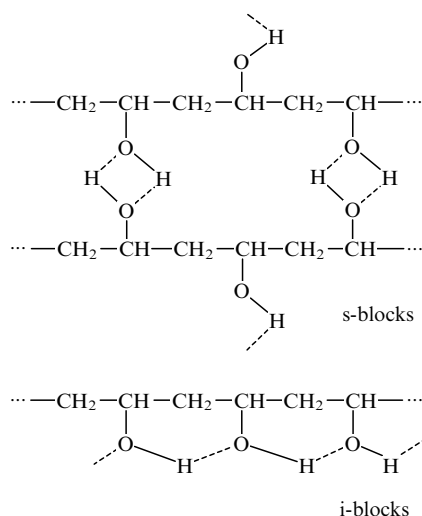
(1)–(3) PVA purified by reprecipitation ($M=81\,700$, $\text{DD}=98\%$); (4) and (5) unpurified PVA (two different batches of technical-grade polymer). Cryogenic treatment regimes: (1), (4), and (5) $v_c = 1.8\text{ K min}^{-1}$ (freezing at -15°C and storage at this temperature for 18 h), heating rate $v_{th} = 1.0\text{ K min}^{-1}$; (2) $v_c = 1.8\text{ K min}^{-1}$, $v_{th} = 0.3\text{ K min}^{-1}$; (3) $v_{th} = 180\text{ K min}^{-1}$ (freezing in liquid nitrogen for 30 min and storage at -15°C for 18 h), $v_{th} = 0.3\text{ K min}^{-1}$.

What precisely these impurities are is unknown, their compositions and amounts are not the same in different batches of the polymer of the same brand. On the other hand, in the case of specimens of pure PVA the changes in molecular mass and manifestations of mechanical degradation are not observed either viscometrically or with the aid of high performance GPC or any other physicochemical methods — IR, ESR, *etc.*^{81,82} One may therefore conclude, to within the sensitivity of the analytical procedures employed, that the cracking of the PVA chains on cryogenic treatment is negligible, if it does occur at all, which is in no way reflected in the cryotropic gelation of the given polymer.

III. Dependence of the properties of poly(vinyl alcohol) cryogels on the characteristics of the gel forming polymer

The structure and properties of PVA cryogels depend on many factors, including both the characteristics of the polymer itself and the conditions of the low-temperature gelation. One of the most important parameters determining the possibility, in principle, of the formation of cryoPVAG, is the presence in the polymer of residual *O*-acetyl groups.^{9,24,25,83} In the majority of cases described, the cryogels were prepared from poly(vinyl alcohols) obtained by hydrolysing poly(vinyl acetate). It was found that, for a degree of deacetylation (DD) below 90%, the cryoPVAG are not formed under any, even the most favourable, conditions. For a content of *O*Ac residues of 5%, very weak cryogels are obtained, and it is actually difficult to measure correctly their rheological characteristics. Only on the basis of concentrated aqueous solutions of PVA of highly deacetylated brands (DD > 97%) is it possible to form fairly strong cryogels. Bearing in mind that the bonds between the polymer chains in the gels formed are non-covalent, *i.e.* the intermolecular contacts in the regions of micro-crystallinity are ensured by a multiplicity of hydrogen bonds between the secondary alcohol groups of different chains,^{35,84} the steric hindrance generated by the bulky *O*Ac residues, interfering with the establishment of extended complementary contacts, should be included among the evident causes of the 'poor' gelation of the insufficiently deacetylated PVA preparations.

The macromolecules of atactic poly(vinyl alcohols) in water are known^{43,85,86} to tend to associate, whereupon the intermolecular hydrogen bonds arise mainly with participation of the OH groups of the syndiotactic (*s*) PVA blocks while the intramolecular hydrogen bonds are produced with participation of the OH groups of the isotactic (*i*) fragments.



Thus the higher the content of the *s*-diads in the polymer employed, the stronger is the manifestation of the tendency towards phase separation in its solutions^{87,88} with formation of a microgel fraction, a gel, or even a precipitate. The cryogels based

on PVA enriched in syndiotactic fragments have a higher degree of crystallinity⁸⁹ compared with specimens based on the atactic polymer of approximately the same molecular mass, which indicates the retention of the above tendency also on cryotropic gelation of this polymer. Unfortunately the cryoPVAG prepared from poly(vinyl alcohols) with an increased content of *s*-sections have been inadequately investigated, but there is no doubt of the interest in such studies, particularly since new ways of synthesising PVA with a controllable tacticity are being vigorously developed nowadays.

It is entirely evident that the molecular mass of the polymer used for the formation of cryogels must influence its properties. Thus fairly weak cryoPVAG are obtained from highly concentrated ($c_p = 20\%$) solutions of PVA with a low degree of polymerisation ($M < 30\,000\text{--}40\,000$),^{4,11,24,54,90} so that it is preferable to employ PVA brands with $M > 50\,000$ for the formation of strong cryogels.

Figure 4 presents the creep curves for equiconcentrated cryoPVAG prepared from PVA with different contents of the residual *O*Ac groups and different degrees of polymerisation. For the close molecular masses (curves 2 and 4), the additional presence in the polymer of even small amounts (1.3%) of unhydrolysed side groups affords a cryogel with a compliance greater by a factor of 3, whilst in specimens with an almost identical degree of deacetylation of PVA (curves 1, 2, and 3) less compliant (more elastic) cryoPVAG are obtained for the higher the molecular mass of the polymer.⁵⁴ These and similar results^{4,24,25,90–93} for the influence of the size of the PVA macromolecules on different characteristics of the corresponding cryogels are fully consistent with the well-known dependences of the properties of noncovalent thermoreversible gels (formed at positive temperatures) based on both PVA^{49,94–97} and other polymers.^{98–101} Since the hydrodynamic dimensions of the macromolecules increase with increase in the chain length, the degree of overlap of the coils in solution rises and the number of topological entanglements increases, *i.e.* there is an increase in the number of intermolecular contacts, as a result of which a denser physical network is produced in the gel formed. Such gels are harder and have higher melting points

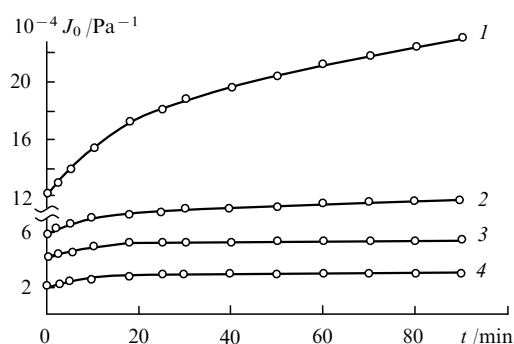


Figure 4. Creep curves for cryogels formed from 10% aqueous solutions of PVA with different molecular masses and degrees of deacetylation.^{54,91} (1) $M = 69\,000$, DD = 98%; (2) $M = 90\,000$, DD = 98%; (3) $M = 110\,000$, DD = 98%; (4) $M = 95\,000$, DD = 99.3%. Cryostructure regime: $T_s = -10\,^{\circ}\text{C}$, $t_s = 24\text{ h}$, $v_{th} = 1.0\text{ K min}^{-1}$.

The properties of cryoPVAG are influenced similarly also by the variation of the PVA concentration in the initial solution — the higher the concentration, the stronger and more thermostable (other conditions being equal) are the corresponding cryogels obtained.^{4,9,11,12,22–25,35–37,40,54,55,58,83,84,89,91,102–113} It is shown in Fig. 5 that the cryogel formed on cryotreatment of a 10% PVA solution is fairly compliant and is deformed appreciably during the application of a shear load, whereas the cryogels obtained from a 14% and especially a 16% PVA solution exhibit only a slight creep under the same shear stresses.

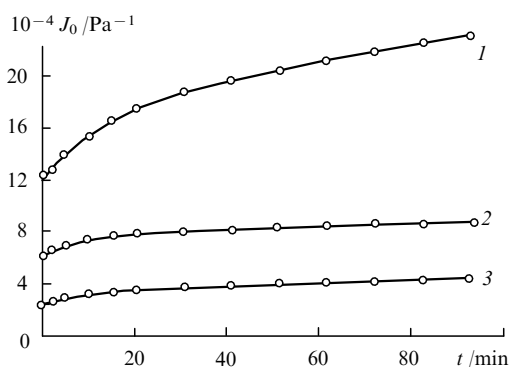


Figure 5. Creep curves for cryogels formed from aqueous solutions of PVA ($M = 69\,000$, $DD = 98\%$) with different polymer contents: (1) 10%; (2) 14%; (3) 16%.⁹¹ Cryostructuration regime: $T_s = -10\text{ }^{\circ}\text{C}$, $t_s = 24\text{ h}$, $v_{th} = 1.0\text{ K min}^{-1}$.

When a PVA solution freezes, the pure solvent crystallises initially (Fig. 1), while the solute is concentrated in the still liquid part of the specimen. Such cryoconcentration intensifies significantly the polymer–polymer interactions which ultimately leads to the formation of stable junction of the three-dimensional cryogel network. Since these processes occur in a heterophase system, a heterogeneous gel is obtained after it has thawed out. Pores of different size and geometry are formed in it under the influence of the crystals of the frozen solvent. Thus the solvent plays the role of a porogen. According to electron microscopy data, the structures of the cryoPVAG formed from solutions with unequal polymer contents differ, although their structural feature such as pronounced heterogeneity, *i.e.* the presence of micropores and macropores, is characteristic of any PVA cryogels. The morphology of 14% and 16% cryoPVAG is illustrated in the photomicrographs in Figs 6a and 6b. Their creep curves are presented in Fig. 5 (curves 2 and 3). The high porosity of the preparations is most striking. With increase in the PVA concen-

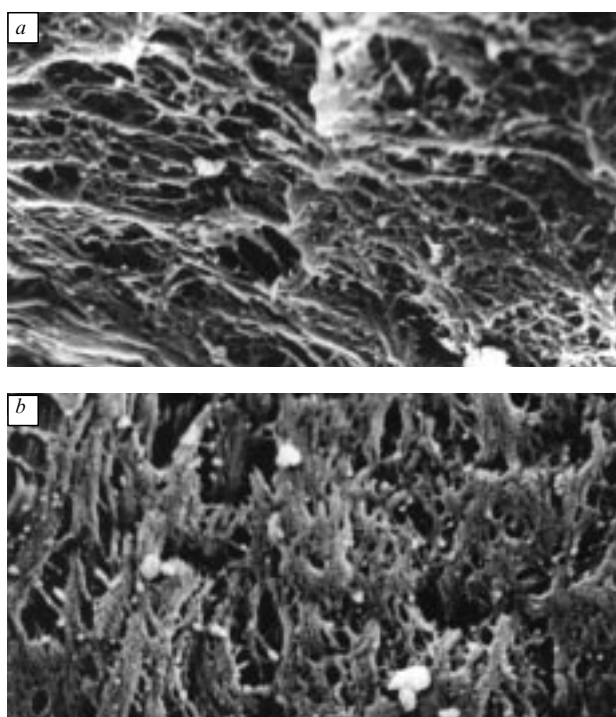


Figure 6. Structures of cryogels formed from 14% (a) and 16% (b) aqueous solutions of PVA ($M = 69\,000$, $DD = 98\%$).^{54, 91} Cryostructuration regime: $T_s = -10\text{ }^{\circ}\text{C}$, $t_s = 24\text{ h}$, $v_{th} = 1.0\text{ K min}^{-1}$.

tration, a decrease in the size of the macropores and a thickening of the elements of the polymer phase of the heterogeneous gel are observed, which agrees well with the smaller compliance of the more concentrated specimen.

Perhaps the only characteristic of PVA the influence of which on the properties of cryoPVAG has so far been virtually investigated is the molecular mass distribution (MMD) of the gel forming polymer. Nevertheless it is quite evident that the use of PVA with a narrower MMD should promote an increase in the strength parameters of the cryogels.

IV. The influence of the conditions in the cryogenic treatment on the properties of poly(vinyl alcohol) cryogels

It was already stated above that virtually all the parameters of the regimes in the cryogenic treatment influence, albeit not to the same extent, the characteristics of the cryoPVAG and the dynamics of their formation. These questions have been investigated in fair detail.

The process temperature and the effectiveness of the heat exchange determine the possibility of the supercooling and the rate of crystallisation of the specific specimen: usually the lower the T_f (Fig. 1), the lower the probability of the supercooling, and hence the more rapid the liquid–solid phase transition for the main bulk of the low-molecular solvent. By altering the thermal conductivity conditions (for example, by employing vessels made from different materials, or by increasing the thickness of the walls of the vessel, or by employing thermal insulation), it is possible to control the dynamic freezing and thawing parameters. As a result of such experiments, it has been found^{55, 102} that the degree of supercooling and the rate of crystallisation of ice do not vary in parallel with the variation of the rate of cooling, which indicates the complexity of the dependence of the freezing regimes for concentrated aqueous PVA solutions on different process factors. Thus, for a 14% polymer solution poured into a 5 mm duralumin mould, the change in v_c from 0.09 to 17.0 K min^{-1} (*i.e.* almost by a factor of 190) entails a change in v_{cr} in the range from 0.35 to 2.5 K min^{-1} (the difference is a factor of only 7.1), while the rheological parameters of the cryogels obtained altogether change very slightly and, other conditions being equal, depend little on v_c . Therefore, in comparing the properties of the cryoPVAG specimens formed at different T_f , the influence of the dynamics of the freezing itself may be virtually disregarded. In the main, the physical characteristics and the structure of the PVA cryogels are determined by the temperature and duration of the cryogenic action,^{24, 58, 91, 106, 114} provided that the preparations are thawed out under identical conditions.^{55, 115} Thus it has been observed that, after brief (up to 24 h) storage of the specimen in the frozen state, the lower the T_f , the less compliant the corresponding cryoPVAG. With increase in the duration of the cryogenic process, the trend changes (Fig. 7). The specimens kept at $-20\text{ }^{\circ}\text{C}$ and then for 24 h at $-10\text{ }^{\circ}\text{C}$ become harder than the preparations maintained at $-30\text{ }^{\circ}\text{C}$. A characteristic feature is that the duration of the storage in the frozen state ceases to influence their strength properties fairly early (after $\sim 24\text{ h}$), whereas in the specimens stored at -10 and $-20\text{ }^{\circ}\text{C}$ the values of J_0 after cryogenic treatment for 10 days still remain unstabilised,⁹¹ which indicates the continuation at these temperatures of the changes associated, as already mentioned, with the slow decrease in the amount of the uncrystallised solvent.⁵⁸

Like their strength, the thermophysical properties of the cryoPVAG also depend on the parameters examined above; the increase in the degree of deacylation or in the molecular mass of the polymer as well as in its concentration in the initial solution promotes an increase in the melting point of these thermoreversible gels.^{11, 23–25, 35–37, 40, 54, 55, 83, 105, 106} A decrease in T_f and an increase in the duration of the storage of the specimens in the frozen state exert the same influence.^{55, 106}

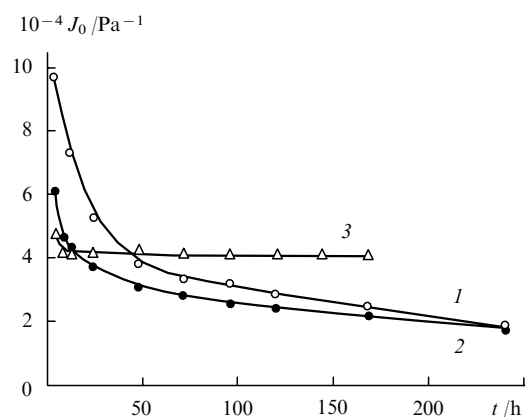


Figure 7. The influence of the temperature and duration of freezing of 14% solutions of PVA ($M = 69\,000$, $DD = 98\%$) on the rheological properties of the cryogels formed.⁹¹ T_s (°C): (1) -10 ; (2) -20 ; (3) -30 .

However, the most significant factors which radically affect the properties of the PVA cryogels are the regimes of the defrosting of the specimens.^{55, 106, 109, 115, 116} A detailed study of this stage of the cryostructure formation made it possible to establish the principal features of the mechanisms of this type of gel formation. It has been observed^{4, 54, 55} that, when the thawing out is carried out at a rate greater than 10 K min^{-1} , then, regardless of the conditions under which the initial polymer solution was frozen and then exposed to temperatures between -10 and -30 °C, one obtains after such 'rapid' thawing out not a gel but a viscous and turbid colloid solution. Conversely, on slow thawing out ($v_{th} \leq 0.05\text{--}0.01\text{ K min}^{-1}$) very elastic cryogels are formed.

Figure 8a illustrates the influence of the rate of thawing of the specimens on the apparent instantaneous compliances (J_0) of the PVA cryogels, whilst Fig. 8b demonstrates the dependence of the same rheological parameter on the polymer concentration in the initial solution for two series of experiments in which the thawing out was carried out at rates of 1.0 and 0.02 K min^{-1} .

Figure 8 shows that the compliance of the cryogels diminishes as the thawing out of the corresponding preparations slows down; for $v_{th} = 1.0, 0.1$, and 0.02 K min^{-1} , $J_0 = 8.1 \times 10^{-4}, 0.6 \times 10^{-4}$, and $0.45 \times 10^{-4}\text{ Pa}^{-1}$ respectively (Fig. 8a). If the PVA solution is maintained at -20 °C for 10 days and is then thawed out at a rate of 1.0 K min^{-1} , then a cryogel with $J_0 = 1.25 \times 10^{-4}\text{ Pa}^{-1}$ is obtained, while in the case where the rate of thawing is lower by an order of magnitude ($v_{th} = 0.1\text{ K min}^{-1}$), after freezing for 1 h at

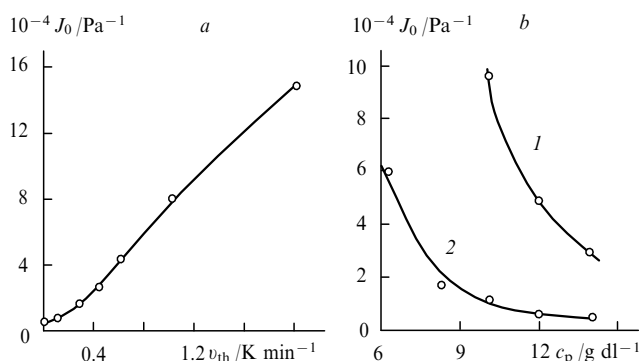


Figure 8. The influence of the rate of thawing of the specimen (a) and of the concentration of the polymer in the initial solution (b) on the rheological properties of cryogels formed from aqueous solutions of PVA ($M = 69\,000$, $DD = 98\%$).⁵⁵ (a) $c_p = 14\%$; (b) $T_s = -20$ °C, $t_s = 1\text{ h}$, $v_{th} = 1.0$ (1) and 0.02 K min^{-1} (2).

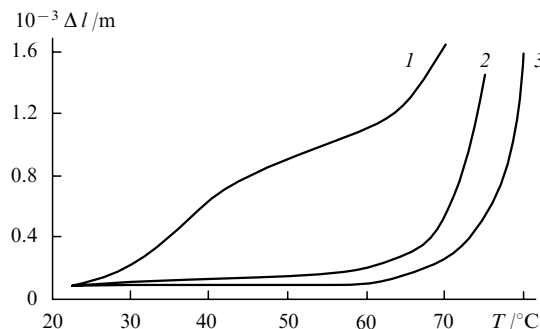


Figure 9. Thermomechanical properties of cryogels formed from 14% solutions of PVA ($M = 69\,000$, $DD = 98\%$) at $T_s = -20$ °C and $t_s = 1\text{ h}$ and thawed out at different rates v_{th} (K min^{-1}):¹⁰⁶ (1) 1.0 ; (2) 0.2 ; (3) 0.02 .

-20 °C a more rigid cryoPVAG is formed. Similarly a decrease in v_{th} makes it possible to lower the concentration of the gel forming agent without loss of the strength characteristics of the cryoPVAG (Fig. 8b).

Figure 9 presents the thermomechanical curves for specimens of cryogels thawed out at different rates. It is seen from the figure that the slowly thawed out preparations are, firstly, deformed to a smaller extent by an applied load as the temperature rises and, secondly, they melt at higher temperatures on heating, *i.e.* are more thermostable.¹⁰⁶ The presence of two inflection regions on the thermomechanical curve for the specimen which was thawed out fairly rapidly (curve 1, Fig. 9) indicates the presence in the structure of such a gel of at least two types of junctions differing in the thermal dissociation energies. Those of the first type melt at $35\text{--}45$ °C, while these of the second type melt at $60\text{--}65$ °C. Two endothermic peaks have been recorded in the same temperature ranges also with the aid of differential scanning calorimetry^{38, 116} and the first of these, corresponding to the decomposition of the low-melting nodes, is approximately at the temperatures ($20\text{--}40$ °C) at which melt the usual thermoreversible PVA hydrogels formed on ageing of concentrated polymer solutions without freezing.^{44, 117} On the other hand, the complete fusion of the cryoPVAG, caused by the thermal dissociation of the high-melting junctions (the microcrystallinity zones), occurs at a temperature higher by tens of degrees. The melting points T_m , like the other characteristics of the gel objects, are sensitive to the previous thermal history of the specimens (Table 1).⁵⁵

If the dependence of the melting point of the cryoPVAG on the polymer concentration in the system is represented in terms of the variables of the Eldridge–Ferry equation⁹⁸

$$\lg c_p = \frac{\Delta H}{2.3RT} + \text{const},$$

Table 1. The influence of the conditions in the cryotropic gel formation on the melting point of cryoPVAG.

Cryogenic treatment regimes			T_m / °C
T_f / °C	t_f / h	v_{th} / K min^{-1}	
-10	24	1.00	73.5 ± 0.3
		1.00	74.0 ± 0.2
		0.20	74.8 ± 0.2
		0.02	76.0 ± 0.2
-20	72	1.00	74.1 ± 0.2
		240	74.4 ± 0.1
		1.00	74.4 ± 0.1
		1.00	73.7 ± 0.2

Note. A 14% solution of PVA with $M = 69\,000$ and $DD = 99.0\%$ was used.

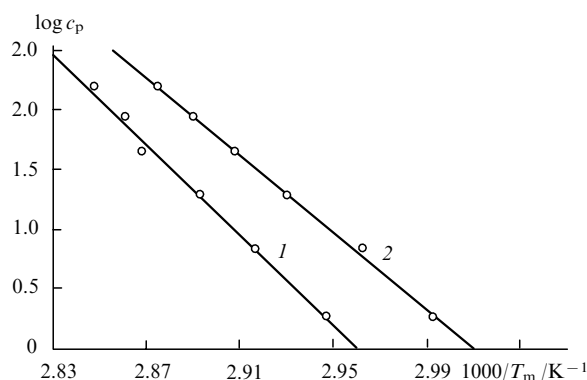


Figure 10. Relation between the melting points of cryogels and the concentration of PVA ($M = 69\,000$, $DD = 98\%$) in the initial solutions frozen at $-20\text{ }^{\circ}\text{C}$ during 24 h and thawed out at the rate of $0.02\text{ }^{\circ}\text{C min}^{-1}$ (1) and $1.0\text{ }^{\circ}\text{C min}^{-1}$ (2)⁵⁵ in terms of the variables of the Eldridge–Ferry equation.

it is possible to estimate the enthalpies of fusion of the cryogels obtained under different conditions (Fig. 10). The values of ΔH are $68 \pm 2\text{ kJ mol}^{-1}$ for preparations thawed out at a rate of $1.0\text{ }^{\circ}\text{C min}^{-1}$ and $87 \pm 2\text{ kJ mol}^{-1}$ for preparations thawed out at $v_{\text{th}} = 0.02\text{ }^{\circ}\text{C min}^{-1}$.⁵⁵ Comparison of these quantities with the available data⁴⁴ for the usual PVA hydrogels obtained on ageing of 10%–20% solutions of the polymer ($M = 60\,000$), the melting points of which are in the range $14\text{--}28\text{ }^{\circ}\text{C}$ and $\Delta H = 37\text{ kJ mol}^{-1}$, shows clearly that the energy of the thermal decomposition of the junctions of the cryogel network is at least twice as high as for the usual gel, *i.e.* the promoting effect of the freezing of the PVA solutions on the association of the macromolecules of the polymer and its crystallisation is clearly seen.

The microstructure of the PVA cryogels also depends on the dynamics of the thawing out process: the slower is the thawing out process, the lower the degree of heterogeneity of the preparations according to scanning electron microscopy data.^{4,54,55,118} According to transmission electron microscopy data,⁹¹ the primary elements of the supermolecular structure of the cryoPVAG are globular formations $0.01\text{--}0.02\text{ }\mu\text{m}$ in diameter, combined into larger globular aggregates $0.2\text{--}0.5\text{ }\mu\text{m}$ in diameter, which form in their turn bead-like strands of the three dimensional network of the macroporous cryogel. It is of interest that similar globular aggregates have been observed⁵¹ also in the structure of hydrogels obtained either on ageing of concentrated polymer solutions or after the introduction of a nonsolvent.

The following question is relevant: if the rate of freezing of the polymer solutions influences little the properties of the cryoPVAG, the temperature and the time of the cryogenic treatment exert a definite effect on the characteristics of the cryogels, and the dynamics of the thawing out process is of decisive importance for them, then what is the precise stage in the cryostructure formation process where gelation proper takes place — during freezing (where the polymer is concentrated in the liquid microphase as a result of the crystallisation of ice), during the storage of the frozen solutions at a negative temperature, or in the course of the thawing out process?

It has been shown⁵⁵ that, when the PVA solution is initially frozen at $-20\text{ }^{\circ}\text{C}$ for 1 h, is subsequently maintained at a temperature in the range from -0.5 to $-6.0\text{ }^{\circ}\text{C}$, and is then rapidly (in order to rule out the influence of the thawing out dynamics) thawed out, the dependence of the rheological characteristics of the cryogels formed by means of this scheme on the temperature at which they are stored has an extremum (Fig. 11). The least compliant (Fig. 11a), *i.e.* the most elastic, cryoPVAG is formed when the frozen system is maintained in the region of $-2.5\text{ }^{\circ}\text{C}$ (Fig. 11b): above and below this temperature, less strong cryogels are obtained. On the other hand, overall the region of the

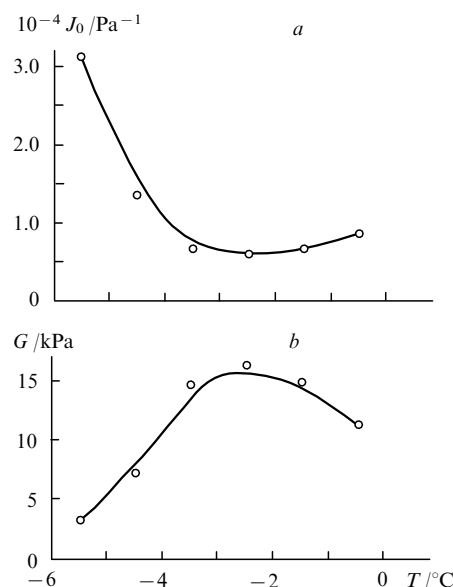


Figure 11. Dependence of the shear compliances (a) and the moduli of shear elasticity (b) of cryogels formed from 14% solution of PVA ($M = 69\,000$, $DD = 98\%$) on the temperature at which the frozen specimens were maintained in the subzero region.^{4,55}

maximum effectiveness of such cryotropic gel formation is in the subzero temperature range — only several degrees below the crystallisation point of the solvent.

Hence the influence of the thawing out kinetics on the properties of the PVA cryogels becomes understandable: the slower and closer to equilibrium conditions is the thawing out of the specimen, the longer it resides in the region of temperatures optimum for the formation of the gel network. For example, on rapid thawing ($v_{\text{th}} = 10\text{ }^{\circ}\text{C min}^{-1}$) the system ‘passes’ through the range $-5\text{--}0\text{ }^{\circ}\text{C}$ in only 30 s, in the moderate thawing out regime ($v_{\text{th}} = 0.1\text{ }^{\circ}\text{C min}^{-1}$) the passage takes 5 min, while in the slow regime ($v_{\text{th}} = 0.02\text{--}0.01\text{ }^{\circ}\text{C min}^{-1}$) the passage takes 4–8 h. Thus a slow increase in temperature during thawing out is in a certain sense equivalent to the storing of the frozen preparations for a long time at the temperatures corresponding to the formation of the strongest cryogels, when in the PVA–water system mainly the junctions of the three dimensional network of the cryoPVAG are formed. If the concentrated aqueous solutions of the polymer during their cooling to the temperatures of the most intense gelation ($\sim -2.5\text{ }^{\circ}\text{C}$) could be guaranteed to freeze, which is frequently prevented by supercooling effects, then in this case there would apparently be no need at all for the use of lower temperatures. In fact they are required to induce the crystallisation of ice.

It has been demonstrated with the aid of NMR spectroscopy^{67,68} that when the frozen preparations are heated after the attainment of a threshold temperature range, which is $4\text{--}6\text{ K}$ below the crystallisation point of the system, a sharp increase in the amount of the mobile solvent is observed. An additional amount of the liquid component appears precisely at these temperatures still in the solid frozen specimen in addition to the firmly bound unfreezable solvent (see also Fig. 2). By virtue of the partial ‘prefusion’ of the ice, a medium is produced in which the macromolecules (or their segments) acquire a certain mobility, which ultimately leads to effective polymer–polymer interactions with formation of microcrystallites performing the function of cryogel network junction knots.

It is shown in Fig. 12 that such mobility is reflected in the ^{13}C NMR spectra of the PVA–water system, while the signals of the $\text{CH}(\text{OH})$ and CH_2 groups of PVA are detected at 66 and 44 ppm respectively. Since the polymer is dissolved in D_2O in order to record the spectra, the temperature scale on the figure is

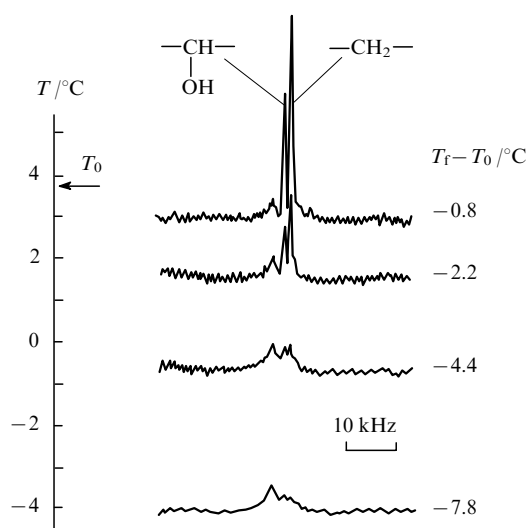


Figure 12. ^{13}C NMR spectra of a 10% solution of PVA ($M = 81\,700$, $\text{DD} = 98\%$) in D_2O frozen at -20°C and then maintained for 2 h at the temperature of the recording of the spectrum.⁶⁷

indicated both in absolute numbers and relative ($T_f - T_0$) to the melting point of the pure solvent.

At $T_f - T_0 = -7.8^\circ\text{C}$, the resonance peaks of the carbon atoms of PVA are hardly noticeable, while at a temperature three degrees higher, at $T_f - T_0 = -4.4^\circ\text{C}$, fully resolvable, although weak, signals are already observed. On further increase in temperature, but still $2-3^\circ\text{C}$ below the temperature of the thawing out of the specimen as a whole, the 'normal' spectrum of the polymer solution in D_2O is recorded. Hence it follows that, in the temperature range $5-6^\circ\text{C}$ below the freezing point of the system, there is a conventional boundary of the retardation of rapid (on the NMR frequency scale) movements of the carbochain framework of PVA. Estimation of the correlation times of the spin-lattice relaxation of the polymer carbon atoms, which serves as a criterion of the mobility of the kinetic segments of the chain, shows that the reorientation movements of the ^{13}C nuclei of the CH_2 groups of PVA in the system frozen at subzero temperatures occur more slowly by two orders of magnitude than in the initial liquid solution. It is precisely because of the low mobility of the polymer chains that a fairly prolonged time is needed for the occurrence of the cryotropic gel formation. The passage through an extremum of the dependence of the rheological properties of the cryoPVAG on the temperature of the cryotropic structuration process in its subzero region then becomes understandable (Fig. 11). On the one hand, at temperatures above the extremum there is a significant increase in the amount of the mobile solvent, *i.e.* the specific concentration of the gel forming agent is reduced in the liquid microphase. This entails a decrease in the probability of effective intermolecular contacts, which are also acted against by the intensification of the thermal movement in the system. On the other hand, at temperatures below the extremum there is a rapid decrease in the amount of the 'additional' mobile solvent (the polymer retains only very strongly bound water), *i.e.* the liquid medium in which movements leading to the mutual approach of the interacting sections of neighbouring chains may occur vanishes. Thus, having ensured a prolonged residence of the system in the temperature range -2 to -3°C after freezing, for example during slow thawing, it is possible to prepare even from solutions with a not very high PVA concentration a cryogel which is several times less compliant than the cryogel obtained from a significantly more concentrated polymer solution but under the conditions of a brief residence of the specimen at subzero temperatures [at $v_{\text{th}} = 0.02\text{ K min}^{-1}$ for an 8% PVA solution, $J_0 = 1.55 \times 10^{-4}\text{ Pa}^{-1}$ (Fig. 8b), whereas at $v_{\text{th}} = 1.0\text{ K min}^{-1}$ for a 16% PVA solution, $J_0 = 7.9 \times 10^{-4}\text{ Pa}$ (Fig. 5) for the same freezing time $t_f = 1\text{ h}$].

As regards the influence on the properties of the cryoPVAG of cryogenic treatment parameters such as the temperature and duration of freezing (Fig. 7), they are more likely to act on the process involving the formation of a microgel fraction, which then performs the function of building blocks for the formation (in the range of subzero temperatures) of a gel throughout the volume of the specimen. At any rate, the liquid colloidal systems formed were more viscous and turbid the longer the corresponding objects existed in the frozen state.⁵⁴ The structure of the supermolecular aggregates entering into the composition of such a microgel fraction has not so far been investigated, although data of this kind would be very useful for the understanding of the nature of the processes under discussion.

Yet another example of the cryogenic treatment which makes it possible to increase the strength characteristics of cryoPVAG is repeated freezing-thawing of the PVA-water system. A large number of communications (see Refs 11, 12, 23-25, 28, 30, 40, 69, 84, 104, 105, 108, 119-134) and patents^{22, 26, 27, 29, 135-151} have been devoted to the study of this phenomenon and its employment. Repeated cryogenic treatment ('temperature saw') promotes more far reaching gel formation in these systems. Thus the cryogel obtained as a result of four freezing-thawing cycles for a solution of PVA ($M = 75\,000$ and $\text{DD} = 99.5\%$, $c_p = 15\%$, $T_f = -20^\circ\text{C}$, $t_f = 24\text{ h}$, thawing at 15°C for 7 h) has a dynamic Young's modulus an order of magnitude greater³⁰ than that of the specimen obtained as a result of a single cycle. According to X-ray diffraction data,^{28, 84} such successive freezing-thawing increases the content of the crystallites and their dimensions in the cryoPVAG. The repeated 'passage' of the system through the region of temperatures corresponding to the most intense gelation both during thawing and freezing (starting from the second cycle for what are no longer solutions but cryogels) leads to the formation of new additional intermolecular contacts and to an increase in the extent of those existing beforehand. In particular, this is manifested by the appearance of numerous compacted regions in the structure of the cryoPVAG observed⁸⁴ even under the light microscope. Admittedly the authors⁶⁹ do not regard this as the main cause of the increase in the strength of the cryogels, attributing the main role to the intensification of the interactions (hydrogen bonding) between water molecules and the OH groups of the PVA chains with increase in the number of refreezing cycles. However, this conclusion appears controversial. It is more likely that the converse is true: as a result of the crystallisation of PVA, water is displaced from the microcrystallinity zones. It is apparently not permissible to disregard also the compaction of the supermolecular strands of the cryogel network by the purely mechanical mutual approach due to the action of the faces of the ice crystals growing in it. This results in an increase in the strength parameters of the cryoPVAG and an increase in their thermal stability (T_m increases).^{40, 105}

Yet another regime in the cryogenic treatment, influencing the characteristics of the PVA cryogels, is the partial sublimation of ice from the frozen specimens. As already mentioned in the Introduction, this method³¹⁻³⁹ makes it possible to increase the mechanical strength of the cryoPVAG, primarily as a result of the increase in the strength of the surface layers of the preparations,³⁷ because the sublimation of water vapour takes place initially from the peripheral open sections of the frozen block and the crystallised solvent sublimates from increasingly deeper regions only as evacuation proceeds. It has been shown³⁵⁻³⁷ that an increase in the duration of such lyophilisation leads to a lowering of the compliance of cryogels in relation to compression, to a decrease in the tangent of the mechanical losses angle following the application of a variable-sign load, and to an increase in the tensile strength of the specimens. According to patent data^{31-34, 38, 39, 152-162} the degree of hydration of the frozen PVA solutions subjected to such vacuum treatment can reach $> 90\%$, *i.e.* almost all the nonsolvate water may be removed. On subsequent immersion of the xerogel in an aqueous

medium, it swells slowly, after which the osmotic characteristics of the preparations remain unchanged for a long time.³⁷

Thus cryogenic action on the PVA–water system makes it possible to vary within wide limits the properties of the noncovalent cryogels of this polymer and to modify their macroporous structure. Here the dominant factor, determining the effectiveness of the cryotropic gelation of PVA, is the time during which the frozen preparation resides at ‘high’ negative temperatures.

V. Dependence of the properties of poly(vinyl alcohol) cryogels on the nature and composition of the initial solvent

The previous sections dealt with the influence of the characteristics of the PVA and the freezing–thawing regimes on the cryotropic gel formation and the parameters of the cryogels obtained. Only aqueous solutions of the polymer without appreciable amounts of other components were then considered as the initial objects. However, there is no doubt that the nature of the solvent employed and the presence of various additives should exert a definite effect on the freezing processes of the initial PVA solutions, the volume and composition of the liquid microphases, and the range of optimum temperatures of gel formation (if this occurs), on the one hand, and the properties and texture of the materials produced, on the other.

For example, 10%–16% solutions of PVA ($M = 69\,000$, DD = 99.0%) in DMSO ($T_0 = 18.4\text{ }^\circ\text{C}$) at room temperature remain liquid for a long time, whilst the freezing–thawing of such solutions leads, as for the aqueous solutions, to the formation of cryogels.⁹ However, the morphologies of the cryoPVAG obtained from aqueous and dimethyl sulfoxide solutions differ significantly.^{107, 163} In particular a layer of an aqueous cryoPVAG 0.6 mm thick ($M = 74\,800$ and DD = 99.5%, $c_p = 20\%$, $T_f = -20\text{ }^\circ\text{C}$, $t_f = 10\text{ h}$, thawing for 10 h at $5\text{ }^\circ\text{C}$) transmits about 40% of light at a wavelength of 570 nm, while the same layer of cryoPVAG formed from a solution in DMSO in which the organic solvent has been replaced by water transmits 76% of light, *i.e.* is more transparent.¹⁶³ Incidentally, the formation of PVA cryogels from solutions in DMSO itself disproves the hypothesis of Nagura *et al.*,⁶⁹ mentioned above, that water molecules are involved in the structure of the tight contacts between the polymer chains on formation of crystallites. The characteristic features of the cryotropic gel formation in the PVA–DMSO system are virtually the same as in the PVA–water system, although the dimensions of the molecules and the physicochemical properties of DMSO and H_2O differ significantly. In the cryogel formed from DMSO, it is possible to replace fully the DMSO by water on prolonged washing. This could hardly be done if DMSO molecules play the role of stable bridges (*via* hydrogen bonds) between the polymer chains.

The cryoprotecting properties of DMSO are well known.^{164, 165} The addition of 40%–80% of DMSO to aqueous systems very greatly reduces the freezing points of the latter. If PVA solutions are prepared in water–DMSO mixtures, they gelate on cooling long before the attainment of the freezing point,^{89, 95, 96, 166, 169} affording transparent thermoreversible gels, which after washing out the DMSO can be used for the preparation of soft contact lenses.¹⁶⁶ However, if the DMSO content in the initial system is either below 30 vol.% or above 90 vol.%, the corresponding PVA solutions freeze at $-40\text{ }^\circ\text{C}$ ¹⁰⁷ and after their thawing out macroporous cryogels are obtained (here it is important to employ rapid freezing to ensure that there is sufficient time for the crystallisation of the system before the onset of gelation).

The effects caused by the competition between the rates of freezing and formation of the ‘usual’ gels have been clearly demonstrated in studies of the cryotropic gelation processes in water–polyol–PVA systems.^{170–172} When polyols such as glycerol, ethylene glycol, and oligo(ethylene glycol) (OEG) are intro-

duced into aqueous PVA solutions, they lower the critical polymer gelation concentration and increase the temperature of the sol–gel transition as a consequence of the impairment of the thermodynamic quality of the solvent.^{48–52} However, the gelation process itself in the presence of a not unduly high content of such polyols is fairly slow and, in order to obtain the cryogels, it is therefore necessary to ‘accelerate it’ kinetically with the aid of rapid freezing. It has been found that the rate of freezing affects the compliance of the cryoPVAG prepared from aqueous solutions of the polymer to which oligomeric ethylene glycols have been added: the slower the freezing of the specimen, the weaker, other conditions being equal, the cryogel obtained.¹⁷² The main cause of the decrease in the strength of such specimens is that on slow cooling the gelation of the system begins before its freezing, as a consequence of which ice crystallises in the bulk of the gel formed, disturbing its structure. On the other hand, on rapid freezing the usual gel has insufficient time to arise and for this reason the mechanisms of the cryotropic gelation occurring in a medium significantly more concentrated in terms of the polymer than the initial solution ‘work’ subsequently in the frozen heterophase system.

The nature of the influence of the addition of ethylene glycol (EG) and its oligomers on the rheological and thermophysical properties of the corresponding cryoPVAG is illustrated in Fig. 13. An increase in the content of EG in the initial polymer solution leads to less hard and readily fusible cryogels (glycerol and propylene glycol act similarly), but, starting with triethylene glycol, an increase in the concentration of the cosolvent promotes the strengthening of the preparations and the growth of their thermal stability (incidentally, the addition of sucrose has the same effect on the properties of cryoPVAG¹⁷³). Diethylene glycol occupies an intermediate position: for a content of the additive up to $\sim 5\%$, weak cryogels are obtained, the cryogel being strengthened with increase in the concentration of diethylene glycol. It has been supposed that the strengthening effect of the OEG is caused by the liquid–liquid phase separation in the

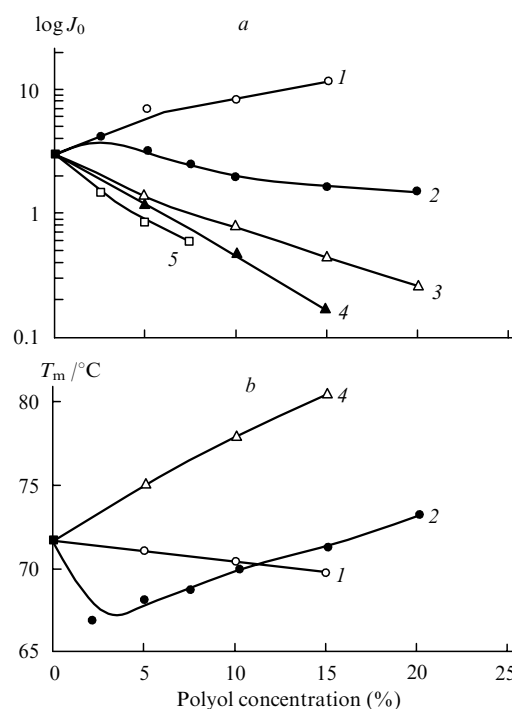


Figure 13. Rheological (a) and thermophysical (b) characteristics of cryogels formed at $-20\text{ }^\circ\text{C}$ ($t_s = 24\text{ h}$, $v_{th} = 0.2\text{ K min}^{-1}$) from 10% solutions of PVA ($M = 81\,700$, DD = 98%) in the presence of added polyols of the ethylene glycol series: (1) ethylene glycol; (2) diethylene glycol; (3) triethylene glycol; (4) PEG-400; (5) PEG-1000.¹⁷²

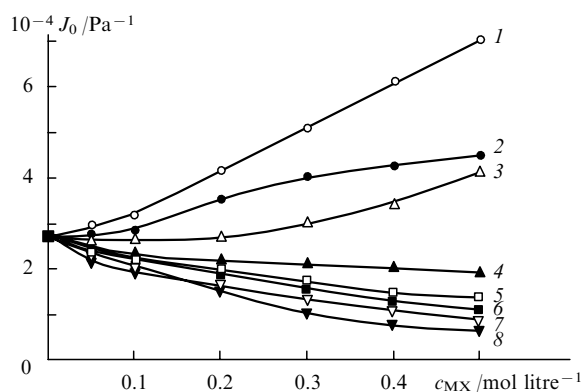


Figure 14. Rheological properties of cryogels formed at $-20\text{ }^{\circ}\text{C}$ ($t_s = 24\text{ h}$, $v_{th} = 0.2\text{ K min}^{-1}$) from 14% solutions of PVA ($M = 69\,000$, $DD = 98\%$) in the presence of low-molecular electrolytes MX at different concentrations¹⁷⁷ (1) NaSCN; (2) NaBr; (3) LiCl; (4) NaCl; (5) KCl; (6) NaOAc; (7) CsCl; (8) NaF.

unfrozen inclusions, whereas in the crystallisation of ice the system falls (on the phase diagram) into the region of thermodynamic incompatibility (liquid two-phase water–PVA–OEG systems are well known¹⁷⁴) owing to the increase in the concentration of PVA and of the low-molecular polyol. As a result of this the gel forming agent is additionally concentrated in its ‘own’ (*i.e.* PVA-enriched) liquid microphase. On the other hand, an increase in the concentration of the polymer usually leads to the strengthening of the cryogel and to an increase in its melting point, which has been observed experimentally.

The influence of electrolytes on the cryotropic gelation of the polymer has been investigated.^{54, 175–177} It was found that, in terms of the nature of their effect on the properties of the cryoPVAG formed from water–salt (MX)–PVA systems (Fig. 14), cations and anions can be arranged in a sequence corresponding to the positions of the corresponding ions in Hofmeister’s lyotropic series, *i.e.* chaotropic ions (Li^+ , Br^- , SCN^- , *etc.*), which destabilise hydrogen bonding, prevent to some extent the formation of strong cryoPVAG, whilst antichaotropic ions (Cs^+ , F^- , OAc^- , *etc.*) promote the strengthening of the cryogels. Neutral electrolytes of the type of NaCl, which have a weak influence on hydrogen bonds, exhibit a small strengthening effect with increase in concentration as a consequence of phenomena involving the salting-out of the polymer.

Thus the composition of the solvent, *i.e.* its cryoscopic properties, the affinity for PVA, the effect of the medium components on hydrogen bonding, and also the salting-out and salting-in effects influence the cryotropic gelation of the polymer and hence the parameters of the cryogels obtained.

VI. Conclusion

By virtue of their high porosity and at the same time effective mechanical strength as well as stability in any biological media, the materials based on cryoPVAG have found extensive applications in various branches of biotechnology. Poly(vinyl alcohol) cryogels proved to be excellent carriers for the immobilisation of biological macromolecules^{159, 178–187} and cells^{4, 41, 188–265} and not only of microorganisms, which can stand quite well the cryogenic treatment, but also of certain animal cells.^{266–268} Since the cryoPVAG are stable up to temperatures of $70\text{--}80\text{ }^{\circ}\text{C}$, the corresponding carriers have been used for the immobilisation of both mesophilic cells and thermophilic microorganisms,^{210, 232, 237, 242, 245, 251} which functioned for more than a year at $60\text{--}65\text{ }^{\circ}\text{C}$ without loss of activity.^{242, 251} This is a record-breaking feature for biocatalytic systems entrapped in thermoreversible gel matrices. It has also been proposed that polyol cryoprotectors can be introduced for the simultaneous protection

of cultures sensitive to freezing and in order to increase the strength characteristics of the gel carrier.^{170, 172, 252}

Solid nutritional media have been developed on the basis of PVA cryogels for the culturing of microbial²⁶⁹ and plant cells, in particular the ginseng biomass.²⁷⁰ The use of such media makes it possible to replace the valuable nutrient gel former agar-agar by a synthetic polymer produced on a large scale. CryoPVAG coatings have found applications in the food industry for frozen fish and meat.^{271–275} Chromatographic materials have been created from microgranulated cryoPVAG ($0.2\text{--}0.3\text{ mm}$),²⁷⁶ while artificial bait for sporting and amateur fishing has been made from larger ($2\text{--}3\text{ mm}$) coloured granules or gel in the form of small fish-like objects.^{13–17, 277} An interesting aspect of the employment of mixed cryogels (PVA + polyelectrolyte-type polymer) is the creation of mechanochemical actuators elements simulating the work of muscle (the studies in this field are being particularly vigorously prosecuted in Japan^{127, 132, 278–292}). There have been scientific publications and a multiplicity of patents describing a wide variety of versions of polymer systems, employed in medicine, based on cryoPVAG (Refs 28, 29, 31–34, 90, 92, 93, 110, 120, 129, 131, 135, 137–143, 146–149, 154–161, 266, 268, 293–310) containing both PVA and its mixtures with other high-molecular-mass compounds and constituting composites with disperse fillers—inorganic (of the type of titanium dioxide) or organic (for example collagen fibres,^{303, 310}) *etc.* These gels have been used successfully as substitutes for the cartilage tissue,¹¹ as prostheses for surgery within the mouth,^{11, 28, 29, 34, 148} as materials for ophthalmology¹³⁹ and dentistry,¹⁴⁷ as protective coatings for wounds and burns,^{31, 135, 154} as cooling dressing, and cold helmets which do not secrete water for the prevention of hair loss in cancer chemotherapy,^{31, 137, 138, 155–158, 293} and as special purpose catheters.¹⁴¹

The application of cryoPVAG as the gel medium for the tuning and calibration of NMR tomographs^{120, 140, 143} and as systems for the controlled release of medicinal substances has been described.^{12, 110, 129, 131, 142, 149, 161, 294, 297, 298, 302, 307, 309} Materials for cosmetics,^{311, 312} *etc.* are being developed. Macroporous PVA membranes formed by cryogenic structure formation procedures may apparently find application.^{123, 124, 153} The cryostructure formation process in PVA solutions has been proposed also for the preparation of artificial ice and snow^{59, 313} and for the fixation of soils which have thawed out.³¹⁴

There is no doubt that the successful application of the above materials in medicine and other branches of science and technology^{145, 315–333} must be based on the fundamental knowledge of the mechanisms of the cryotropic gelation of PVA and of the influence of the polymer characteristics and also of the freezing–thawing parameters on the properties and structures of the cryogels formed under these conditions. All these factors promote their further comprehensive investigation. Studies on cryoPVAG are concerned with the mechanisms of gel formation,^{334–336} the macroscopic properties of cryoPVAG and materials based on them,^{337–343} and the structures of gels formed under different conditions,^{344–347} on the one hand, and fine effects associated with the different states of the solvent molecules in such heterophase polymer systems,^{348, 349} on the other. This is in fact the reason why attention has been concentrated in the review on these problems. The interested reader may become acquainted in detail with the practical applications of cryoPVAG in the literature quoted.

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Heterogeneous hydrogenation catalysts

M D Navalikhina, O V Krylov

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Abstract. The main types of heterogeneous catalysts used for hydrogenation, the methods for their preparation, and the structure and chemistry of their surfaces are considered, as well as the catalytic activity and the mechanism of action in the hydrogenation of unsaturated and aromatic compounds, of CO, and of carbonyl compounds and in the hydrotreating of fuels. Chief attention is paid to supported Ni catalysts, to the methods for their preparation and physicochemical studies, and to the development of novel catalytic systems through modification. A novel type of catalyst for hydrogenation, *viz.* metal carbides, is described. Some aspects of the mechanochemical treatment of hydrogenation catalysts, including *in situ* methods, are discussed. Sulfide catalysts for hydrotreating are also discussed in detail. The bibliography includes 340 references.

I. Introduction

Catalytic hydrogenation includes a large group of addition reactions of hydrogen at unsaturated bonds $C=C$, $C=O$, $C\equiv N$, $C\equiv C$ *etc.*, as well as hydrogenolysis (cleavage and reduction) of $C-C$, $C-O$, $C-S$, and other bonds.

In addition to heterogeneous catalysts applied in large-scale processes, homogeneous metal-complex and hydride catalysts are also used (mostly, in fine organic synthesis). Enantioselective hydrogenation catalysts, basically metal-complex compounds of Ni, Co and other metals with optically active ligands, are also being increasingly used.

In 1991, of 1040 catalysts for oil processing produced by world industries the number of hydrogenation catalysts was 380.¹ However, modern technologies require more effective and less expensive hydrogenation catalysts. They can be designed only by development of novel scientific approaches to the preparation of

supported catalysts and by the use of new physicochemical techniques.

Supported nickel catalysts of hydrogenation are the most widely used ones; they are followed by catalysts based on noble metals. Binary Ni–Mo, Ni–W, Co–Mo and Co–W catalysts are extensively employed in the processes of hydrotreating and hydrodesulfurisation. Metal carbides appear to be new promising catalysts.

This paper reviews certain problems related to the preparation, composition, and mechanism of action of heterogeneous catalysts of hydrogenation of unsaturated compounds (including aromatics), hydrogenation of CO and carbonyl compounds, as well as to the processes of hydrotreating. Primary attention is given to supported Ni catalysts, which have found increasing use in recent years not only in large-scale processes but also in fine organic synthesis. Catalysts based on noble metals (Pt, Pd, Ru, Rh, Ir), supported sulfide catalysts of hydrotreating and some novel hydrogenation catalysts, such as metal carbides, which have been extensively studied in recent years, are also the subjects of discussion. Some examples are given of the use of mechanochemistry techniques for preparing catalysts allowing the synthesis of environmentally safe motor fuels.²

At present, the most widespread are the following hydrogenation catalysts:

Process	Catalyst
Hydrogenation of alkenes	supported Ni, Cu, Pt, Pd, Ru, and Rh
Hydrogenation of alkynes	supported Ni, Pd, Ni–Pd, Co–Pd, and Cu–Pd
Hydrogenation of aromatic hydrocarbons	supported Ni, Pd, Rh, Pt, and Co–Mo, Raney Ni
Hydrotreating of motor fuels	Ni, Ni–Mo, and Co–Mo on Al_2O_3 and kieselguhr
Hydrogenation of carbonyl compounds	skeletal and supported Ni and Co, supported Pd, Rh, and Pt, and Cu–Cr–O, Cu on kieselguhr
Hydrotreating (hydrodesulfurisation)	Ni–Mo, Ni–W, Co–Mo, Co–W, and Ru on Al_2O_3 and carbon, Mo and W carbides
Hydrogenation of nitriles	supported Ni, Pd, and Pt
Hydrogenation of CO and CO_2 (methanation)	supported Ni, Cu, Co, Fe, Pt, and Rh, Pt mesh, Mo and W carbides

M D Navalikhina Institute of High Temperatures, Russian Academy of Sciences, Izhor'skaya ul. 13/19, 127412 Moscow, Russian Federation. Fax (7-095) 485 99 22

O V Krylov N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117977 Moscow, Russian Federation. Fax (7-095) 938 21 56. Tel. (7-095) 939 71 68

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This review is confined to heterogeneous hydrogenation catalysts and leaves out consideration of numerous homogeneous systems, as well as Raney catalysts (Ni, Co, Cu, and others) and co-precipitated catalysts.

II. General characterisation of hydrogenation catalysts

1. Conventional hydrogenation processes and catalysts

The first industrial hydrogenation process used a nickel catalyst discovered by Sabatier in 1897.^{3,4} Other well known hydrogenation catalysts were proposed later: Group VI–VIII metals, including platinum group metals, both on supports and as components of complex oxide systems, as well as Raney metal catalysts.

The results of Ipat'ev's studies of catalytic hydrogenation reactions under pressure dating back to the beginning of this century have served as the basis for the development of processes that are widely used in modern industries. Many specific hydrorefining catalysts have been developed that were obtained by impregnation or co-precipitation (Al–Co–Mo, Ni–Mo, sulfide Ni–W–S catalysts, *etc.*) and proved to be resistant to catalytic poisons present in crude oil (S-, N-, and O-containing compounds).⁵

Production of catalysts for the synthesis of organic compounds is rather limited. Relatively large-scale industrial processes of this type are hydrogenation of fats, 2-ethylhexenal, acetylene (for its removal from ethylene), hydrogenation of benzene to cyclohexane required for the manufacture of caprolactam, and some others. Hydrogenation catalysts are increasingly used for the production of drugs and physiologically active compounds. Important properties of this category of catalysts are high selectivity, extended lifetime, and the fact that they meet environmental requirements. Such characteristics are basically displayed by supported metal (Ni, Pt, Pd, and Ru) catalysts, and co-precipitated Cu–Cr and Ni–Cr catalysts.

Hydrogenation of benzene to cyclohexane may be used as an example illustrating the trends for the use of particular catalysts depending on the strictness of requirements for the final product purity.^{4,6} Cyclohexane of high purity (99.88% and above) is used for the manufacture of caprolactam and fibres based on it, and for nylon-6. In the USA alone the cyclohexane output in 1992 was $1.363 \times 10^6 \text{ m}^3$ (Ref. 7).

Since the beginning of this century benzene has been traditionally hydrogenated on nickel (Raney Ni, impregnation catalysts) and on supported platinum group metals. In early industrial processes carried out under high pressure and at high temperature, the main reaction was accompanied by side reactions: cracking with production of n-hexane, isomerisation of cyclohexane to methylcyclopentane, isomerisation and cracking with the formation of lower hydrocarbons.⁴

A two-stage scheme gives the best results in the production of high-purity cyclohexane: in the first stage, a supported Ni catalyst is used (30%–45% Ni/Al₂O₃), while in the second stage, a supported Pt catalyst (0.2%–1.0% Pt/Al₂O₃) is used. Here, the purity of cyclohexane is 99.57%–99.88%.⁸

An important contribution to the development of hydrogenation catalysts has been made by D V Sokol'skii and his associates.^{9,10}

In our country, much attention was given to co-precipitated Ni–Cr catalysts enabling the production of high-purity cyclohexane in a few stages in tubular reactors provided the technological requirements are strictly observed. Such catalysts were prepared by precipitation of Ni and Cr nitrates with a sodium carbonate solution at room temperature. This was followed by filtration, washing of the precipitate to remove nitrate ions, drying, calcination, pelleting, and activation in a flow of hydrogen.¹¹ The contents of Ni and Cr₂O₃ were 48 mass %–63 mass % and 37 mass %–52 mass %, respectively. The disadvantages of

this and other techniques for preparing Ni–Cr catalysts are their multistage character, cumbersome filtration equipment, large volumes of waste water from the washing stage, *etc.*

In this connection, a sewage-free method was proposed for producing Ni–Cr catalysts¹¹ that included the stage of mixing Ni(NO₃)₂ and (NH₄)₂Cr₂O₇ solutions with subsequent drying and calcination of the resulting mixture by spraying it over a heated inert packing in the fluidised bed reactor system at 310–340 °C, pelleting, and reduction.

A multistage synthesis of Ni–Cr and co-precipitated Al–Co–Mo, Al–Ni–W and Ni–W catalysts used in oil refining^{5,12} is complicated, and the technology of catalyst preparation is also complex. Besides, these catalysts are insufficiently active and require large quantities of active additives. Even at a high Ni percentage in Ni–Cr catalysts the active surface does not exceed 25–30 m² g^{−1}, while their thermostability is preserved only up to 250–280 °C,^{9,11} which imposes definite restrictions on technological processes.

The method of impregnation of supports possessing specific structures and properties yields more active Al–Ni–Mo and Al–Co–Mo catalysts.

2. Modern trends in the development and application of new hydrogenation catalysts

In the 1980s, studies were undertaken aimed at developing supported Ni hydrogenation catalysts the activity of which and other parameters were not inferior to those of skeletal catalysts. Such properties are displayed, for example, by Euro-Ni-1 catalyst (25% Ni/SiO₂) developed by a large group of investigators headed by Coenen.^{13–15} This catalyst has been prepared by homogeneous precipitation in which part of the nickel forms hydrosilicate on the support. The specific surface of the active metal reaches 113–182 m² g^{−1} (Ref. 15). Homogeneous precipitation of Ni was carried out in the presence of urea on a water-suspended microspherical silica gel, which was prepared by direct flame pyrolysis of SiCl₄.¹⁴ In the presence of SiO₂, the pH of an aqueous solution of Ni(NO₃)₂·6H₂O does not exceed 5.3–5.5, whereas in its absence the pH reaches 5.8 during precipitation of nickel hydroxide and remains constant.

The existence of a strong interaction between Ni and SiO₂ in the preparation of the catalyst is evident from the difficulty of reduction of Ni species, especially in comparison with the non-supported Ni(OH)₂. Complete reduction of the Euro-Ni-1 catalyst requires temperatures above 400 °C, up to 600 °C.¹⁴

In the deposition of Ni on SiO₂, the development of the surface may take place due to the formation of intermediate nickel hydrosilicate.¹⁴ However, this depends on the conditions, Ni: SiO₂ ratio, and the reactivity of SiO₂. Along with Euro-Ni-1, in recent years novel technologies allowed preparation of Ni/SiO₂ catalysts with a lower metal content (10 mass %–15 mass %) for the hydrogenation of acetone.¹⁶ In these catalysts, the specific surface of Ni does not exceed 10–30 m² g^{−1}.

Other attempts aimed at increasing the specific surface of Ni on supports with a concomitant decrease in its content down to 4%–10% have also been undertaken.^{17,18} To this end, use was made of both the impregnation technique and organometallic complexes, modifying the surface of SiO₂ and Al₂O₃ supports, in organic solvents. According to the available data,^{18–20} the active surface of Ni may reach 124 and 197 m² g^{−1} at its content of 4.8% and 10%, respectively.

In the 1980s, great interest arose in Russia in the so-called 'sorptional' catalysts.^{19–21} The method of their preparation consisting of binding of organometallic complexes to the surface of the support, is rather complex and expensive. Nonetheless, this technique may be successfully used for the preparation of Pd catalysts with a unique mechanical strength, which is achieved by proper selection of supports, while the size and structure of metal particles may be controlled.^{21,22}

In recent years, public concern about environmental problems has become especially acute in many countries. For example, the

US 'Clean Air Act', of 1992 rigorously limits the content of carcinogenic aromatic compounds, sulfur and other noxious compounds in motor fuels (both hydrocarbon- and alcohol-based).^{23–32} New requirements stimulated the rapid development of refining of various fuels thus making the role of hydrogenation catalysts very important.

To meet all normative requirements under the conditions of a total ban on the use of tetraethyllead in gasoline, it is necessary to restructure the entire oil refinery sector; specifically, to replace reforming by other processes of high-octane gasoline production.^{2, 24, 25, 28} The size of the required investment amounts to hundreds of billion dollars.³⁰ There are doubts whether this task may be coped with at all.⁵

Nowadays, along with studies aimed at replacing reforming by alkylation, skeletal isomerisation, and synthesis of oxygenates allowing an increase in the octane number of gasoline, hydrogenation of aromatic and unsaturated hydrocarbons is extensively studied (to remove their excess from petroleum fractions), and the appropriate catalysts of hydrotreating of motor fuels are being developed and improved.

The content of aromatic hydrocarbons in gasoline and diesel fuel fractions can vary within broad limits. Fractions from direct petroleum refining contain from 20 vol.% to 40 vol.% of aromatic compounds, while diesel fractions after cracking range from 40 vol.% to 70 vol.%.

Hydrotreating of directly distilled gasoline involves mainly co-precipitated Al–Co–Mo catalysts capable of removing sulfur. These catalysts ensure only partial hydrogenation of aromatic compounds^{5, 12, 31} and are insufficiently active in general for the hydrogenation of aromatic and unsaturated compounds. In some cases, Ni–W–Al or Ni–Mo–Al catalysts are more suitable for this purpose.

In major modern catalytic upgrading technologies, the directly distilled gasoline is supplemented with products of secondary processing of heavier fractions, which are even more enriched in aromatic hydrocarbons and alkenes (gasoline of catalytic cracking, hydrocracking, reforming, pyrolytic gasoline). Therefore, catalytic hydrodearomatisation and hydrogenation of unsaturated hydrocarbons, which are also used for alkylation, have become highly important for the production of high-quality and ecologically clean reformulated gasoline, jet and diesel fuels. In the preparation of jet fuels by hydrodearomatisation of kerosene, the co-precipitated Ni–W sulfidised catalysts proved to be the best of the known Co–Mo, Ni–Mo, and Ni–W systems.^{5, 12} In such catalysts, the content of tungsten reaches 20 mass %–30 mass %; hence, they are rather expensive and their practical application is limited.

In recent time, much attention has been given to new types of supported Co–Mo, Ni–Mo, and Ni–W catalysts, as well as to the catalysts based on noble metals.^{5, 12, 31–40}

Sulfur-resistant catalysts are widely used in both single- and two-stage processes for hydrogenation of aromatics.^{31, 38–40} It was found³¹ that the Ni–W/Al₂O₃ catalyst is poisoned by sulfur more intensely than Ni–Mo/Al₂O₃. Therefore, two-stage hydrotreating involves the Ni–Mo catalyst in the first stage (mainly, hydrogenation of sulfur compounds), whereas in the second ('final' hydrogenation) stage low-percentage Ni–W catalyst *e.g.*, (6%Ni + 20%WO₃)/Al₂O₃ is used.³⁹

Since the late 1980s a number of companies dealing with hydrotreating of motor fuels have been developing new Ni–W catalysts on supports.^{31–35, 39} A common shortcoming of all proposed catalysts is the rather high content of WO₃; furthermore, effective hydrotreating on these catalysts requires high pressures (up to 10 MPa) and temperatures (up to 360 °C).^{35, 39}

Thus, at present the most attractive and inexpensive catalysts for the hydrogenation of unsaturated compounds (including aromatics) are supported Ni-containing catalysts modified with W or Mo oxides.

The nickel-based catalysts are also successfully used in other processes, *e.g.*, for the hydrogenation of CO into methane and

other hydrocarbons.^{41–43} Most catalysts of CO methanation are also prepared on supports (Al₂O₃, Cr₂O₃, kieselguhr, Mg-containing spinels). In addition to nickel, the role of active component may be played by Co, Pt, and Pd; however, the resulting systems are less active than the modified Ni-containing catalysts. Investigation of CO methanation has become topical due to attempts to adapt this process for the large-scale production of clean gaseous fuels through gasification of low-grade coals,⁴⁴ as well as for the realisation of chemical-energetic transfer and the use of heat from nuclear power stations and other industrial fields.⁴⁵ Effective methanation of CO has been found to require⁴⁶ thermally and mechanically stable Ni catalysts possessing the largest possible specific surface. These requirements can be met using appropriate supports supplemented with structure modifiers and promoters.

Until the 1980s, the long-term operation of a catalyst was believed to be associated with a sufficiently high content of an active metal (up to 35 mass %). For this reason, preference was given to co-precipitated rather than to impregnated catalysts.⁴⁶ However, the results of recent studies disprove this belief. At present, there is a trend for the use of modified low-percentage Ni catalysts (0.8 mass %–8.0 mass % Ni) on supports both for the hydrogenation of unsaturated and aromatic compounds^{34, 39} and for the methanation of CO.^{47–49}

3. Catalysts for the hydrotreating of motor fuels

According to the estimates of experts,⁵⁰ the oil reserves will substantially decrease and their quality will worsen by the year 2000. As pointed out above, further use for motor transport of fuels with excess levels of aromatic compounds and alkenes may result in air pollution hazardous to humans.^{23, 25}

Upgrading technologies for motor fuels (gasoline, diesel, and kerosene distillates) involve a number of catalytic processes that ensure the transformation of directly distilled crude oil or products of petroleum processing into high-quality fuels meeting rigorous norms for the levels of toxic admixtures, primarily reactive aromatics and alkenes. The actual content of aromatic hydrocarbons in the diesel fractions of petroleum is considerably higher than the mentioned norms and reaches 80%–95%. In the 1980s, they were mostly removed by extraction, while nowadays preference is given to catalytic methods of dearomatisation.^{5, 12, 31, 32, 35–37} This improves both the environmental and operational parameters of diesel fuels. Thus, the decrease in the content of aromatic compounds from 46.5% to 30% increases the cetane index of diesel fuel to the allowed level (from 31–34 to 40–46).⁵¹

Many reports^{31, 37, 40, 50} describe new catalytic processes for dearomatisation of different types of diesel fuel. The Arosat and Synsat processes developed by the Lummus Co. make it possible to reduce more than 50% of aromatic components of raw materials by the combined application of two catalysts designed by the Criterion Co. in a stationary layer under a relatively low pressure.³² The resulting diesel fuel meets the European standards (content of aromatics, 20%–25%; cetane index, 40–45).

The catalysts of the Criterion Co. offer four ways for the decrease in the content of aromatic compounds in diesel fuel.³²

1. Single-stage hydrogenation under high pressure (103 atm) and a moderate flow rate (1.0 h^{–1}). When supported catalysts (Ni, Ni–W, or Ni–Mo on Al₂O₃) are used, the level of aromatic compounds in raw materials can be > 50%.

2. Hydrocracking under high pressure (100–140 atm) at a moderate flow rate with the use of Ni-containing catalysts on different supports (Al₂O₃, aluminosilicates, zeolites). This one- or two-stage process is most popular.

3. Two-stage hydrogenation under pressure ranging from medium to high (83–105 atm.) with the use of supported noble metal catalysts in the second stage. The pressure is determined by the conditions of the first stage aimed at maximum removal of heteroatom-containing components by drastic hydrotreating on Al₂O₃-supported catalysts (Co–Mo, Ni–W, and other).

4. Single-stage hydrogenation under low pressure and small flow rate (the Synsat process). In this process, the above-mentioned combination of Ni-containing catalysts on supports is used. The catalysts are placed in the reactor in such a way that the products obtained in the first catalytic layer improve their characteristics upon passage through the second layer. Under a pressure of 43 atm and a flow rate of 0.5 h^{-1} the degree of saturation of aromatic hydrocarbons present in the diesel fraction reaches 40%–50%. When it is necessary to reduce the level of aromatics below 10% (for preparing a high-quality jet fuel), it is sufficient merely to increase the pressure. Realisation of the Synsat process requires relatively modest expense.

Modern catalytic processes for hydrotreating diesel fuels are more efficient, flexible and economical than the extraction used earlier for the increase in cetane index. The efficiency and simplicity of hydrodearomatisation are provided by the use of catalysts that in most cases refer to supported nickel contacts.

Nishijima *et al.*⁵² reported a two-stage process of hydrotreating of middle and heavy distillates with using new catalysts. Heteroatom-containing compounds are removed in both stages. In the first stage, hydrogenation takes place, whereas in the second stage the remaining aromatic component undergoes hydrocracking.

Fundamental physicochemical studies allowed the development of two types of industrial catalysts on supports for single- and two-stage hydrotreating. The composition of the catalysts obtained, predominantly Ni-containing ones, is presented in Table 1. Catalysts were modified in order to make them suitable for hydrogenation or hydrocracking. Changes in the character of hydrogenation were brought about by the use of specific supports. As regards their hydrogenation activity in the presence of sulfur-containing compounds, the Al_2O_3 -supported catalysts form the following series: Ni–W > Ni–Mo > Co–Mo.

Table 1. Catalysts for the two-stage hydrotreating of diesel fuels.⁵²

Active component	Support	Content of active components (mass %)				Process
		CoO	NiO	MoO ₃	WO ₃	
Co–Mo	$\gamma\text{-Al}_2\text{O}_3$	0–6	–	10–30	–	hydrogenation
	USY ^a – Al_2O_3	0–5	–	10–25	–	hydrocracking
Ni–Mo	$\gamma\text{-Al}_2\text{O}_3$	–	0–6	10–30	–	hydrogenation
	$\text{SiO}_2\text{--Al}_2\text{O}_3$	–	0–3	0–15	–	hydrocracking
	$\text{TiO}_2\text{--Al}_2\text{O}_3$	–	0–3	0–15	–	"
	USY ^a – Al_2O_3	–	0–5	10–25	–	"
	ZSM-5– Al_2O_3	–	0–3	0–15	–	"
	Mordenite– Al_2O_3	–	0–3	0–15	–	"
Ni–W	$\gamma\text{-Al}_2\text{O}_3$	–	0–6	–	16–48	hydrogenation
	USY ^a – Al_2O_3	–	0–5	–	16–40	hydrocracking

^a USY is an ultrastable zeolite of Y type.

Physicochemical studies pointed to a different behaviour of Ni–W and Ni–Mo catalysts on Al_2O_3 . They possess higher hydrogenation activity at a smaller and larger degree of sulfidation of tungsten and molybdenum, respectively. Consequently, the choice of a Ni-containing catalyst for a single-stage hydrotreating depends on the content of sulfur in the raw material.

Similar results were obtained earlier³¹ in the studies of Ni–W and Ni–Mo catalysts for hydrodearomatisation of diesel fuel fractions containing up to 70% of aromatic compounds. The ratios of the rate constants for hydrogenation on Ni–Mo and Ni–W catalysts were 100:90 (1.7% sulfur) and 100:225 (0.14% sulfur).

The trend for maximum decrease in the content of sulfur in motor fuels of all types (down to 0.01%–0.05%) will favour wider use in the near future of two-stage hydrotreating in which the first

stage provides for profound hydropurification of fuel from sulfur, while in the second stage aromatic compounds undergo hydrogenation on efficient Ni–W catalysts. At present, platinum catalysts (0.6%Pt/ Al_2O_3) are used in such processes at a residual sulfur concentration of 1.5 ppm.^{31,40} In the pressure range of 4.5–6.0 MPa, at temperatures 320–400 °C, and at flow rates of 0.75–1.0 h^{-1} , the degree of hydrogenation of the aromatic component is 60%–70%.

The Haldor Topsøe Co. has also developed single- and two-stage hydrotreating refinement processes⁴⁰ for producing high-quality diesel fuels (the so-called City Diesel) with the levels of aromatic compounds below 10 mass % and sulfur below 5 ppm. In the two-stage process, the first stage is based on the use of common sulfidised Co–Mo, Ni–Mo, and Ni–W catalysts, while the second stage relies on the Pt- and Pd-zeolite catalysts. The latter are more resistant to sulfur than the bimetallic catalysts Pt–Re/ Al_2O_3 , Pt–Sn/ Al_2O_3 , Pd/LaY, and others. The catalyst designed for the final hydrogenation preserves its activity at levels of sulfur up to 1000 ppm and nitrogen up to 50 ppm. After the first stage, the diesel oil contains 10 ppm of sulfur, less than 1 ppm of nitrogen and 18 vol.% of aromatic compounds, and the cetane index is 52. After the second stage, the nitrogen content remains at the same level, the sulfur content drops below 1 ppm, the level of aromatics decreases down to 4 vol.%, and the cetane index is 55.5. It is seen that the most significant removal of aromatic compounds is achieved in the second stage.

According to earlier estimates,^{36,50} by the year 2000 the predominant type of fuel produced will be low-sulfur fuel (sulfur content 0.05 mass % instead of 0.1 mass %–0.3 mass %) with a reduced content of aromatics. To achieve this, it was recommended:

(1) to restrict the content of high-boiling components in the diesel fuel since sulfur is most difficult to remove from fractions with b.p. > 315 °C;

(2) to conduct hydrotreating refinement at relatively low temperature, reduced flow rate, and high hydrogen pressure;

(3) to remove aromatic compounds on supported Ni–Mo or Ni–W catalysts.

These predictions are somewhat at variance with the critical need for additional resources of diesel and jet fuels.⁵³

The proportion of the diesel fuel and gasoline consumed is known to shift in favour of the former.⁵⁴ The need for the jet fuel also increases, while its production by direct distillation and hydrotreating refinement of crude oil fractions cannot meet the demand.^{55,56} For this reason, in some countries specialists propose to raise the limiting boiling point of diesel fuels to 360–370 °C⁵⁵ and to include in the diesel fuel some gasoline fractions, as well as secondary products of petroleum refining (gas oils from hydrocracking, fracturing, coking, *etc.*) that will unavoidably lead to a poorer quality of the final products. In gasoils from the secondary oil refining, the content of aromatic compounds reaches 46%–87%, while the cetane index does not exceed 25–39. Hydrogenation of such feed stocks improves their quality but makes them as expensive as synthetic liquid fuels. Hydrogenation of coal is equally expensive, while the products of its liquefaction contain up to 54% of aromatics.⁵⁴

The ways of expanding the production of high-quality diesel and jet fuels have been discussed.⁵³ It was pointed out that, in addition to the above methods, the processes of motor fuel production from alkenes (the MOGD[†] process of Mobil Co.) and from synthesis gas formed upon coal gasification (the Sasol process), are promising as well as the processes based on natural gas conversion (SMDS[‡] of Shell Co. and the Moss gas process) and gasification of any hydrocarbon raw material.^{57–66}

Selective oligomerisation of light alkenes to heavy isoalkenes over zeolite-based catalysts (ZSM-5, ZSM-12, H-offretites and

[†] Mobil Olefins to Gasoline and Distillates.

[‡] Shell middle distillate synthesis.

other) (the MOGD process) allows preparation of gasoline or middle distillates with upgraded characteristics after the hydrogenation stage in which noble metals on supports are commonly used as catalysts.^{57,58} After hydrogenation, the cetane index increases from 33 to 52, while the levels of aromatic compounds and sulfur become 2%–4% and 0.002%, respectively. These parameters are much better than those of diesel fuel from petroleum or coal (hydrogenation), while they remain inferior to the parameters of fuels from the synthesis-gas produced by the Fischer–Tropsch synthesis. For instance, low-temperature hydrogenation of CO on a Ru catalyst can yield diesel fuel that is predominantly composed of n-paraffins (72.4%) and is free of aromatics and sulfur. After the hydrostabilisation stage (removal of alkenes), the cetane index of the product is 90 and it may be used as a high-cetane component of the diesel fuel.⁶⁶

As regards its characteristics, the jet fuel produced by the MOGD process differs favourably from the existing commercial fuels of petroleum origin. It contains as little as 4% of aromatic compounds (instead of 25%), 1% of alkenes (instead of 5%), and less than 0.002% of sulfur (instead of 0.3%–0.4%), while the proportion of paraffins and isoparaffins is 96%. However, the aircraft engines are continuously upgraded with more and more rigorous requirements for the fuel.

Catalytic hydroprocessing of raw oil is a method widely used for producing high-quality aircraft fuels with low sulfur content, increased thermal and oxidation stabilities, and upgraded environmental characteristics.^{67,68} Earlier, hydrotreating of directly distilled fractions was mostly carried out¹² on Co–Mo–Al catalysts at 350–400 °C, 30–50 atm, and a raw material flow rate of 2–5 h^{–1}. The process of single-stage hydrorefinement of kerosene fractions reduced the level of sulfur, while the decrease in the level of aromatic compounds and alkenes was insignificant. The need for the hydrotreating of gasoils of secondary origin with a high content of aromatic compounds and alkenes, using the technology based on Co–Mo–Al catalysts that is popularly used in Russia, has necessitated an increase in the pressure in the system to 140 atm. To reduce the pressure down to 35–80 atm, the products of secondary refining were mixed with directly distilled fractions so that the percentage of aromatic compounds was 34%–36%.⁵⁶ However, even under a pressure of 83–85 atm, hydrotreating on the Co–Mo–Al catalyst was not sufficiently effective. The resulting product contained 18%–19% of aromatic compounds, which is considerably higher than the level admissible for jet fuels.

Two-stage processes in which hydrodesulfurisation (*e.g.*, on a Co–Mo–Al catalyst) and hydrodearomatisation (*e.g.*, on supported Ni–Mo or Ni–W catalysts) are conducted separately (see above) are efficient. In Western technologies, in the second stage the sulfur-free raw materials are hydropurified from aromatic hydrocarbons and alkenes on Pt- or Pd-containing catalysts since the exhaustive hydrogenation on Ni catalysts with oxide additives of the MoO₃ or WO₃ type requires elevated pressures.⁴⁰

Studies of benzene hydrogenation and thiophene hydrogenolysis on Ni–W–Al catalysts have shown⁶⁹ that both processes take place in the same active centres that are poisoned with hydrogen sulfide. The rate of benzene hydrogenation may be increased 30–70-fold under non-steady-state conditions and after pretreatment of the catalyst with hydrogen. The results obtained made it possible to develop a process of dearomatisation of petroleum fractions in a non-steady-state regime.

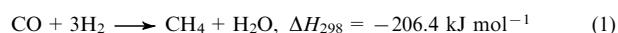
The production of environmentally clean gasoline is much more problematic. The products of catalytic reforming yielding a high-octane gasoline contain large quantities of aromatic hydrocarbons and alkenes. For this reason, reforming should be replaced by other processes. Even under the conditions of catalytic cracking, current technologies yield on average 29.7% of aromatic compounds (which is 20%–25% higher than the required level) and more than 5 mass % of alkenes (up to 30%).

In order to produce high-octane gasoline, attempts are made to use processes of skeletal isomerisation, alkylation, synthesis

and addition of oxygenates. Hydrodearomatisation and hydrogenation of alkenes as gasoline components attracted less attention, though these processes will in the near future be among the leading methods in the technologies of oil refining targeted at the production of environmentally clean motor fuels.^{23,24,29,70} In these processes a special role is played by supported Ni-containing catalysts. The possibility of their upgrading and the relatively low production cost (by an order of magnitude lower than that of Pt- or Pd-containing hydrogenation catalysts) make them rather attractive subjects for further studies.

4. CO Hydrogenation catalysts

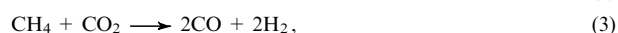
Like hydrorefining, catalytic hydrogenation of CO and CO₂ is highly interesting from the environmental viewpoint and may be used for large-scale production. Carbon mono- and di-oxides are contained in the exhaust gases from power stations and different chemical industries. The simplest reaction of CO hydrogenation (methanation)



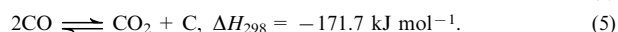
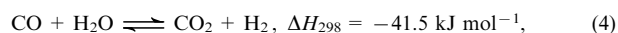
allows an energetically advantageous production of a valuable fuel, *viz.* methane, that is used further in gas turbines. In connection with the depletion of natural gas resources studies are being undertaken as to the possibility of the environmentally clean coal gasification with subsequent CO methanation.^{44,71–73} In the first decade of the 21st century, important facilities for coal gasification and methanation are expected to be put into operation.^{72–74} This requires the development of new technologies and active catalysts.

This review leaves out other reactions of CO hydrogenation that yield various products (paraffins, alkenes, alcohols,⁷⁵ aldehydes, *etc.*) depending on the catalysts applied and the conditions of the process.

Catalytic methanation finds applications in chemo-energetic cycles where atomic (nuclear reactors) or solar energy is used.^{74,76} The thermochemical cycle includes the exothermic reaction of methanation (1) and endothermic reactions of conversion of the methane produced



which are conducted in reactors with heat withdrawal or supply, respectively. These reactions require active and highly selective catalysts. Specifically, only the catalysts inhibiting side reactions in which CO can be consumed are suitable for methanation:



Common and widespread Ni catalysts for reactions (1)–(3) are rapidly deactivated, and it was proposed to replace them by noble metals on supports.⁷⁴ The major difficulties are associated with carbonisation in reactions (1)–(3), particularly, in the methanation at low H₂:CO ratios. On noble metals, the carbonisation is considerably less pronounced, especially in an excess of water vapour due to the reaction



Reaction (6) is best accelerated by Ru catalysts, while Rh is more suitable for methanation.⁷⁴

Thermodynamic calculations show that it is advantageous to obtain methane in reaction (1) at temperatures not exceeding 550–600 °C. The yield of CH₄ is increased at higher pressure and H₂:CO ratio. At low H₂:CO ratios and temperatures up to 600 °C, the common Ni and Ru catalysts may be replaced by an expensive rhodium catalyst (0.5% Rh/Al₂O₃).⁷⁴

The activity of metals on supports in the methanation reaction strongly depends on the mode of the catalyst preparation and

§ See also V N Parmon *Catal. Today* **35** 153 (1997).

conditions of its pretreatment and reduction. In this respect, Ni and Co catalysts have been studied in most detail. In the methanation reactions, supported catalysts containing Ni on metal oxides (MgO, Cr₂O₃, ThO₂, ZrO₂, MoO₃, SiO₂, Al₂O₃), promoted by Cu (0.1%–0.3%), promoted by alkali metals, and Ni sulfide on Al₂O₃ are the most efficient.⁷⁵

The specific activity of Group VIII metals on Al₂O₃ supports decreases in the following series: Ru > Ni > Co > Rh > Pd > Ir. It is noteworthy that the Ni catalyst with a well developed surface is highly active and rather selective in the methanation reaction. In some cases, depending on the mode of preparation, the nature of the support, and other factors, the Ru catalyst proves to be more efficient.⁷⁵

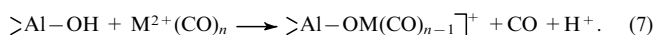
A Ni catalyst with a highly developed surface is applied for the selective CO methanation in the presence of CO₂.⁷⁷ On a number of catalysts, viz., 0.5%Ru/α-Al₂O₃, Raney nickel of ICI (30%Ni–18%Al–52%Al₂O₃), 58%Ni/kieselguhr (Harshaw), 47%Ni/Al₂O₃ (CCI), and 32%Ni/Al₂O₃ (Girdeer, G-65), selective hydrogenation of CO in a mixture 0.3%CO + 80%H₂ + 19.7%CO₂ can be carried out at atmospheric pressure and at 125–300 °C.⁷⁷ In all cases, the maximum conversion occurs in the temperature range 200–250 °C.

Some catalytic systems including Ni, Fe, Rh and Ru are more active and selective in the reaction of CO₂ methanation than in reaction (1).^{78,79} For example, the rate of CO₂ methanation on a Ni/MgO catalyst is higher than that of CO methanation, especially after the catalyst has been reduced at 600 °C.⁷⁷ Examples of higher activity and selectivity of different metal catalysts in the hydrogenation of CO₂ are reviewed.⁸⁰

Inui and Takeguchi⁸¹ described a Ru-containing supported Ni catalyst of methanation with a low content of components (3%Ni, 2.5% La₂O₃, and 0.7%Ru). The catalyst has a meso-macro-bimodal porous structure with finely dispersed components and displays a very high activity in the reaction of CO₂ methanation. The role of Ru in this catalyst is explained by its involvement in the hydrogen spillover to the active Ni centres.

Numerous studies and reviews are devoted to the problems of the catalyst formation and the mechanism of CO hydrogenation.^{75,82–86} Krylov *et al.*⁸⁵ consider in detail the results of studies into the formation mechanism of the active centres of Fe catalysts for the Fischer–Tropsch synthesis and of Ni catalysts of methanation and their effect on the catalytic activity and selectivity.

Much attention is given to the investigation of the formation of active centres in finely dispersed metal particles obtained by decomposition of carbonyl clusters on oxide supports. The carbonyl clusters interact with the hydroxyl groups of the support forming bridging bonds with the metal (M) atoms in a lower oxidation state:



Active and selective contacts can be obtained by deposition of carbonyl complexes [*e.g.*, Co₂(CO)₈] and a number of complexes with organic ligands on γ-Al₂O₃. In this case, the hydroxyl cover of the support is of critical importance.⁸⁵ Some complexes are oxidised to form Co²⁺ particles which aggregate into clusters on the surface. Heating under an inert gas atmosphere favours formation of a cluster containing 3 or 4 Co atoms. Further heating to 220 °C leads to dimerisation of the complex with subsequent formation of metal particles. To increase the activity of a catalyst in the CO hydrogenation, it is necessary to have large Co⁰ clusters. As to selectivity, it is increased when oxidised Co species that are produced on the hydroxylated Al₂O₃ surface upon deposition of low-nuclear complexes are present on the surface. Carbonaceous ligands present in the cluster inhibit the process of hydrogen spillover and impede the complete hydrogenation of CO to CH₄. The use of carbonyl clusters containing two different metals allows the preparation of catalysts with new properties. For example, hydrogenation catalysts prepared from Co–Fe carbonyl clusters manifest the activity of cobalt and the selectivity of iron.

High-resolution electron microscopy and X-ray phase analysis *in situ* were used to study the mechanism underlying the formation of Ni catalysts of methanation.^{85,87} In contrast to hydrogenation on Fe or Co, the hydrogenation of CO on Ni yields only methane. After the dissociation of CO on the Ni surface, the consecutive transformations C → CH → CH₂ → CH₃ take place. Active carbon exists on the surface in a rather narrow temperature range: it is not formed below 200 °C since there is no CO dissociation, while above 450 °C it is rapidly transformed into inactive graphite. The methanation rate at the Ni (100) face is higher the larger the carbon concentration on the surface, and the yield of higher hydrocarbons is larger the higher the CO concentration.⁸⁴

Two nickel specimens were shown to behave differently^{85,87} under the conditions of CO methanation. Nickel oxide obtained by a plasmochemical technique forms cubic crystals with the most developed face (100). Under the reaction conditions this face is the site of epitaxial growth of cubic Ni crystals, while the polycrystalline carbide Ni₃C is formed only in later stages. NiO prepared by decomposition of NiCO₃ is composed of lamellar crystals with the developed face (111) on which nickel carbide builds up epitaxially, whereas the phase of metallic nickel appears only after heating to 283 °C and decomposition of carbide. No direct correlation between the methanation rate and the carbide content was established. The reaction occurs most likely at the Ni/NiO interface (possibly, on NiO defects).

The nature of the support influences the catalytic properties of Co and Ni in hydrogenation of CO to methane and its homologues.⁸⁶ Thus, the activity and selectivity of supported metal catalysts depend on the nature and acid-base properties of the support. The specific catalytic activity of supported Co catalysts decreases in the following series of supports: SiO₂ > TiO₂ > ZrO₂ > BeO > Cr₂O₃ > Al₂O₃ > MgO > WO₃, while that of supported Ni catalysts decreases in the order: ZrO₂ > TiO₂ > BeO > MgO > Al₂O₃ > SiO₂ > Cr₂O₃ > WO₃.

The heat of adsorption of carbon monoxide (*q*_{CO}) and, consequently, catalytic activity and selectivity strongly depend on the mean size of metal particles. According to quantum-chemical calculations,⁸⁸ the M–CO bond is weakened on transition from small clusters to large crystallites. Co/SiO₂ (mean particle size *d* = 32 nm) and Ni/WO₃ catalysts (*d* = 97 nm) are the most active in the reaction of CO hydrogenation. Co/WO₃ and Ni/WO₃ catalysts (*d* = 60 and 120 nm, respectively) manifest noticeable activities only at *T* > 300 °C.⁸⁹ The only reaction product is methane. These data indicate that the optimum sizes of Co and Ni particles are different. Prokhorenko *et al.*⁸⁶ explain this by the difference in their *q*_{CO} values. The heat of CO adsorption on Co must be lower than that on Ni, and this was confirmed experimentally. In order to have similar *q*_{CO} values for both metals, the nickel particles should be larger than those of cobalt. At small *q*_{CO} values, the filling of the Co and Ni surfaces is insignificant and the selectivity is low. With the increase in *q*_{CO}, the extent of filling increases as well as the probability of non-linear stages of reactions of CO leading to the formation of higher hydrocarbons.

However, the heat of CO adsorption is not the only factor affecting the selectivity.⁸⁶ For example, Co/ZrO₂ and Co/SiO₂ have virtually the same degree of dispersion (*d* = 97 and 103 nm, respectively), though their selectivities differ by 34%. Transformations of an intermediate compound are supposed to involve the support and to occur at the metal/support interface. The increase in the acidic character of the support on transition from ZrO₂ to WO₃ results in an increase in the selectivity of methane formation to 100%.

5. Catalysts for hydrogenation of carbonyl compounds

Catalysts for the hydrogenation of carbonyl compounds (aldehydes, ketones, and carboxylic acids) present in alcohols as admixtures are of commercial interest. In particular, this reaction is used for hydrotreating of alcohol-based motor fuels. Hydro-

genation of aldehydes and ketones is also of an independent significance since it allows the preparation of alcohols free of by-products. For example, 2-ethylhexanol is produced from 2-ethylhexanal on an industrial scale.^{90,91}

The first industrial hydrogenation of aldehydes on copper catalysts dates back to the 1920s. However, after the appearance of Raney nickel (1925) most processes of hydrogenation of aldehydes were modified to use catalysts of this type. The industrial importance of techniques for the alcohol production from aldehydes increased after the discovery of oxosynthesis in 1938.⁹⁰

In parallel, a strong impetus was given by the production of plastics [specifically, poly(vinyl chloride)], where respective alcohols are used as plasticisers. Lower alcohols are used as solvents, while higher alcohols are used in the production of detergents. In 1992, the world production of alcohols was (millions of tons): n-butanol, 1.7; isobutanol, 0.4; 2-ethylhexanol, 2.4; higher alcohols, 0.2.⁹⁰

Despite the very high activity of Ni-containing catalysts, they prove sometimes to be unsuitable for the hydrogenation of aldehydes, especially when high selectivity of the process is required. Thus, the preparation of n-butanol from crotonaldehyde proceeds more selectively on copper catalysts. In addition, Ni unlike Cu, often catalyses splitting of CO from saturated aldehydes:



When a Ni catalyst is sufficiently active, subsequent hydrogenation of alkenes occurs with the predominant formation of alkanes.

Modified Ni catalysts on supports are free of these shortcomings. Their activity may be reduced using such supports as SiO₂ subjected to high-temperature treatment, or employing a special impregnation technique of Na⁺-containing SiO₂, and calcinating the specimens additionally at 600–700 °C.¹⁶ To this end, TiO₂ may also be used as a support.⁹⁰ The high activity of Ni and Ni–Cu catalysts allows their use in liquid-phase reactions, which facilitates the removal of heat released during the reaction.

In addition to Cu and Ni, supported Co and noble metals (Pt, Pd, Ru, and Rh) are also applied for the hydrogenation of carbonyl compounds. Of all noble metals only palladium is a component of catalysts for the selective hydrogenation of α,β -unsaturated aldehydes to saturated ones. Furthermore, along with nickel, palladium ensures complete hydrogenation of unsaturated aldehydes, *e.g.*, 2-ethylhexenal.⁹¹

III. Nickel hydrogenation catalysts

1. Methods for preparation

Industrial production of nickel catalysts relies basically on precipitation of components from aqueous solutions and suspensions and on impregnation of specially prepared supports with aqueous solutions of active metal compounds. The activity of hydrogenation catalysts prepared by the impregnation of supports is usually higher than that of catalysts produced by co-precipitation.^{9, 12, 22}

In the late 1980s, the relevant literature (especially the Russian) opposed the impregnation and ‘sorptional’ catalysts.^{17–20} In our opinion, the technology for the preparation of the latter does not differ substantially from impregnation. It consists of the deposition of an active component on a support from different solutions (including non-aqueous ones) using organometallic compounds. In this case, optimally distributed active centres are formed on the support surface, and their characteristics are best suited for hydrogenation.

Generally, the procedure for the preparation of Ni catalysts includes the stages of impregnation, drying, dehydration, activation (calcination), reduction, and passivation.

The preparation of precipitated and impregnated Ni catalysts involves the following processes.⁹²

1. Impregnation of supports (Al₂O₃, SiO₂, carbon, zeolite) with a salt solution, *e.g.*, nickel nitrate. Then the catalyst is dried and calcined at high temperature (400–500 °C) in air.

2. Mixing of precipitated active hydroxide Ni(OH)₂ with a hydrogel of the support. The mixing lasts for 20–30 h, followed by extrusion, drying, and calcination.

3. Deposition of one precipitate onto another. For instance, nickel hydroxide is precipitated with ammonia from a nickel nitrate solution in the presence of a suspension of hydrated alumina. The precipitate is filtered off, thoroughly washed, dried, and calcined at 500 °C for 2 h in air.

4. Co-precipitation. For example, a boiling solution of sodium silicate is slowly added to a nickel nitrate solution. The precipitate is filtered and washed. Also, ammonia may be added to a mixed solution of nickel and aluminium nitrates at 70 °C. Then the precipitate is filtered off, washed, dried, and calcined.

5. Hydrothermal treatment of mixed precipitates. A mixed paste of Ni(OH)₂ and SiO₂ is heated with water vapour in an autoclave for 25 h at 250 °C and 50 atm; the precipitate is filtered off, dried, and calcined.

6. Superhomogeneous co-precipitation. Three salt solutions, *e.g.*, Ni(NO₃)₂, NaNO₃, and Na₂Si₂O₅, are mixed to form a supersaturated solution. Under intense stirring, a homogeneous precipitate is formed which is separated, washed, dried, and calcined.

Prior to their use in reactions, the catalysts are reduced with hydrogen (sometimes with the reaction mixture) at 400–500 °C. The catalysts prepared by impregnation are the easiest to reduce, while those obtained by co-precipitation and hydrothermal treatment undergo reduction with more difficulty. In the supported catalysts the specific surface of the active nickel is usually 100–120 m² g^{−1}, whereas in the precipitated catalysts it varies from 20 to 70 m² g^{−1} (*cf.* Ref. 93). Depending on the treatment and reaction conditions, the metal particles on supports have sizes from 2 to 10 nm.^{94,95}

In recent years, efficient catalysts on supports have been prepared using the so-called CVD (chemical vapour deposition) technique. This consists of fixation of a metal in a layer of finely dispersed particles with the aid of vapour-phase adsorption of intermediate compounds, *e.g.*, metal acetylacetonates, which are subject to subsequent decomposition on the supports.⁹⁶ In this case, the surface is the first formation site for catalytic precursors, ensuring high metal dispersion upon their subsequent decomposition. The Amoco Co. proposed the use of CVD method for binding the silanol groups in zeolite matrices to prepare metal oxide catalysts of the Fe/Mo/support type. German scientists prepared catalysts for hydrogenation and a number of other processes in which Pt, Cr₂O₃, and V₂O₅ are fixed on SiO₂ or Al₂O₃.⁹⁶

Active film structures of the metal–oxide type on supports, the analogues of metal-ceramic films, in which metal particles are regularly distributed over the surface, were also designed.^{97,98} Fixation of metal on supports is ensured by co-precipitation of salts of an active metal (Pd, Pt, *etc.*) and salts of higher carboxylic acids (resinates, stearates, abietates, and others) from organic solvents. Similar structures can also be prepared using aqueous solutions of inorganic salts and compounds of noble metals in the presence of water-soluble polymers, colloidal oxide solutions, *etc.* The common feature of all these techniques is the formation of a film on the surface of a support.

The preparation by this method of highly selective catalysts for the hydrogenation of acetylene that are suitable for large-scale hydropurification of ethane–ethylene fractions from acetylene admixtures has been patented,⁹⁹ as well as of catalysts of oxidation, isomerisation, and dehydrogenation.^{100–104} The preparation of film catalysts is based on a specific combination of several conventional techniques.^{97–100} This leads not only to regular distribution of active components in the surface layer of the support and high dispersity of metal particles, but also to the thermal stability of the catalysts.

Nonetheless, impregnation from aqueous solutions still remains an industrially preferable way of preparing the hydrogenation catalysts on supports. This takes advantage of the recent developments in the field of formation of the catalyst active phase. For example, it was established that if conditions favouring retention of a metal in the ionic form in supports (Ni/Al₂O₃, Ni/SiO₂) are met, this favours the preparation of active and stable Ni hydrogenation catalysts.^{15, 104} In particular, two-stage deposition of nickel should be applied: the first stage consists of the incorporation of difficultly reducible Ni²⁺ ions into the support as a result of ion exchange, and the second stage includes physical sorption of a readily reducible salt. The Ni²⁺ ion appears to be the centre of crystallisation and stabilisation of Ni crystallites. Heating of a Ni/TiO₂ system often leads to a decrease in the active surface of nickel due to coating of the crystallites with metal oxide.^{101, 102} This may be regarded as a manifestation of a strong metal–support interaction (SMSI) effect. The SMSI effect is enhanced in the presence of hydrogen which affects the activity and selectivity of catalysts.

2. Influence of the preparation procedure on the structure, physicochemical properties, and activity of catalysts

Principal factors that affect the catalytic and physicochemical properties of impregnated low-percentage Ni/Al₂O₃ catalysts have been studied systematically.^{47, 49, 103–111} The conditions for the realisation of major stages in the preparation of these catalysts were shown to be related to their structure, activity, selectivity, and the degree of nickel reduction and dispersion. For example, the active surface of nickel and the proportion of the reduced metal are increased by the increase in the H₂ flow rate during reduction. Passivation of the reduced Ni/Al₂O₃ catalyst at room temperature in a flow of nitrogen containing 1% of air prevents ageing and bulk oxidation of nickel, which may result from its contact with the atmosphere.

The first stage in the preparation of impregnated nickel catalysts is highly important. When a support is impregnated with an aqueous solution of a salt (or salts) precursors appear on the support surface and in its bulk, and their formation is influenced by the electrolyte concentration, pH of the medium, and ionic strength of the solution.^{105, 112–114} The first stage is supposed to generate several forms of isomorphically substituted nickel in the support lattice. At low pH, aluminium oxide is solubilised, which favours isomorphic substitution in the final forms.

The effect of pH on the concentration of nickel precipitated from a Ni(NO₃)₂ solution onto Al₂O₃ is illustrated by the data presented in Table 2.

The concentration of electrolyte, ionic strength, and pH of impregnation solution influence not only the content of Ni in the catalyst, but also the amount of active nickel precursors and hence the physicochemical properties and the hydrogenation activity of the catalysts formed.^{103, 105}

Table 2. Dependence of the Ni content in a catalyst on pH of the impregnation solution of Ni(NO₃)₂.¹⁰³

[Ni] in the solution (mass %)	pH	[Ni] in the catalyst (mass %) ^a
0.7	1	0.2
	3	1.2
	5	2.1
2.9	1	3.5
	3	4.1
	5	3.0
5.2	1	6.6
	3	8.3
	5	7.3

^a With respect to the mass of the Al₂O₃ support.

Table 3. Content of nickel in supported catalysts, its specific surface (*S*_{Ni}), and dispersity (*D*_{Ni}).¹⁰³

[Ni] (mass %)	<i>S</i> _{Ni} /m ² g ^{−1}	<i>D</i> _{Ni} (%)
0.8	5.2	94
1.2	5.7	70
2.1	5.6	40
3.0	6.0	29
3.5	6.0	26
4.1	5.7	21
6.6	5.1	12
7.3	5.2	11
8.3	5.3	10

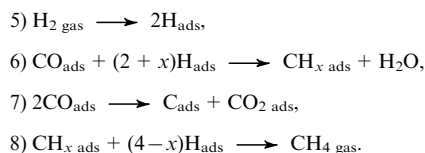
The procedure for the preparation of Ni/Al₂O₃ catalysts affects their structure, activity, and selectivity, *e.g.*, in the hydrogenation of CO.^{47, 49, 103–108} Temperature-programmed desorption (TPD) of H₂ and its interaction with CO allowed us to obtain data on the accessibility of surface Ni centres to H₂ and CO at various conditions of preparation of low-percentage catalysts. Surprisingly, the variation of Ni content from 0.8 mass % to 8.3 mass % proved to have little effect on the adsorption of H₂ and the active nickel surface calculated from the results obtained (Table 3). However, the metal dispersity varies noticeably depending on the concentration of nickel precipitated and precipitation conditions, *i.e.*, it decreases at higher concentrations.

At the same time, the analysis of temperature-programmed CO desorption spectra points to the existence of two types of adsorptional and reactive centres. The specimen with 0.8% of Ni is an exception, since its spectrum has a single peak at 260 °C. In all other cases, low-temperature (at 150–200 °C) and high-temperature peaks were observed. The increase in Ni content to 2.3% increases the portion of CO desorbed in the low-temperature range. In the case of specimens containing 2.3%–7.3% of Ni, the contribution of both peaks is nearly the same. According to Kester and Falconer,⁴⁸ the two CO peaks correspond to two types of active centres of different composition on the surface of the Ni catalyst. The low-temperature peak is supposed^{48, 105} to correspond to NiO, while the high-temperature peak corresponds to NiAl₂O₄. Stronger metal–support bonding is predominant in catalysts with low Ni content.¹⁰⁵ Low pH values facilitate isomorphic substitution of Ni in the octahedral lattice of Al₂O₃, which favours the predominant existence of this metal in the NiAl₂O₄ form. Only this structure was revealed in the 0.8% Ni/Al₂O₃ specimen.

The results reported by Huang and Schwarz¹⁰³ are at variance with those obtained by Tsai *et al.*¹¹² who have found that the increase in Ni content results in an increase in its specific surface calculated from the CO adsorption from 3.9 to 15.8 m² g^{−1}. The increase in Ni concentration from 0.8% to 2.1% is accompanied by a decrease in the degree of Ni dispersity, also calculated from the CO adsorption, from 70% to 31%, which then remained nearly constant (27%–35%).

The catalytic activity and selectivity of the Ni/Al₂O₃ specimens described above in the reaction of CO hydrogenation are closely related to their composition and conditions of preparation. This allows the prediction of their catalytic properties.¹⁰⁴ The limiting stage of the methanation is determined by the type of active centres prevalent on the surface. According to Huang and Schwarz,⁴⁷ the process of CO methanation includes the following stages:

- 1) CO_{ads} ⇌ CO_{gas},
- 2) CO_{ads} → C_{ads} + O_{ads},
- 3) C_{ads} + O_{ads} → CO_{gas},
- 4) CO_{ads} + O_{ads} → CO_{2 ads},



Investigation of the surface interaction of CO and H₂ on Ni/Al₂O₃ catalysts with variable Ni content by X-ray photoelectron spectroscopy (XPES), thermoprogrammed reaction (TPR)¹¹³ and other methods confirmed that in the case of prevalence of NiAl₂O₄ centres on the surface (catalysts with low Ni content) the methanation rate is determined by the rate of CO dissociation [stage (2)]. On catalysts with high Ni content, in which nickel is in the form of particles, the methanation rate is determined by that of hydrogenation of the CH_x fragments [stage (8)].⁴⁷ If the reaction of methanation is regarded as being structure-sensitive, then the changes in its mechanism are well explained by the lower degree of Ni dispersity and the increase in its content from 0.8 mass % to 8.0 mass %.

XPES and TPR¹¹³ studies have shown that NiAl₂O₄ centres predominate on an Ni/Al₂O₃ catalyst with 0.8% Ni, while Ni + NiAl₂O₄ centres predominate on a catalyst with 6.5% Ni.

Contrary to the CO methanation, the hydrogenation of aromatic hydrocarbons cannot occur on active centres of the NiAl₂O₃ type in which Ni is structurally bound. This requires that the active centres were formed by finely dispersed Ni particles on a support. Kester *et al.*¹¹⁵ consider the hydrogenation of aromatics as structure-insensitive reactions. There are fundamental difficulties that prevent the preparation of long-lived Ni catalysts on γ-Al₂O₃ with the Ni content below 5% for the hydrogenation of aromatic compounds. The point is that local overheating taking place during the exothermic reactions of hydrogenation induce the formation of inactive surface spinel and hence the absorption of the active component.^{48, 116–118} This explains why the industrial Ni catalysts of hydrogenation usually contain considerable quantities of metal (up to 65%) and include oxide promoter additives (Table 4) diminishing the SMSI effect.

Table 4. Industrial nickel catalysts for hydrogenation.

Composition of the catalyst			Specific surface /m ² g ⁻¹	Pore volume /cm ³ g ⁻¹
Ni (mass %)	additive	support		
Catalyst of Harshaw Co. (USA)				
60–65	–	clay	155–165	0.22
40	–	Al ₂ O ₃	160	0.69
68	–	special support	125	0.35
46	–	"		
14	WO ₃	Al ₂ O ₃	140	0.38
Catalyst of BASF Co. (Germany)				
4–10	WO ₃	active clay	–	–

Nickel catalysts on other types of supports (*e.g.*, SiO₂) modified by Ti, Zr, and Ce oxides also manifest low activity in the hydrogenation of benzene provided the SMSI effect is realised.^{116, 119} They are one order of magnitude less active than a catalyst analogous in composition [7%Ni/SiO₂–TiO₂(ZrO₂)], prepared by precipitation of Ni(OH)₂, which is free from the SMSI effect.

The technique of homogeneous precipitation was used to prepare a highly efficient Ni catalyst (Euro-Ni-1) containing 25 mass % of Ni.^{13–15} In this case, the major part of nickel is in the form of hydrosilicate. Therefore, it was necessary to activate the catalyst at elevated temperatures in a flow of hydrogen (Table 5).

The maximum degree of reduction of nickel (96%) is achieved at 630–650 °C, though in this case its specific surface is somewhat

Table 5. Effect of temperature on the extent of Euro-Ni-1 catalyst reduction and the specific surface of nickel.¹⁵

Temperature of reduction /°C	Extent of reduction (%)	S _{Ni} /m ² (g Ni) ⁻¹ (see ^a)	S _{Ni0} /m ² (g Ni ⁰) ⁻¹ (see ^b)
430–450	85	181	213
500	90	181	201
630–650	96	113	118

^a Total specific surface of nickel. ^b Specific surface of totally reduced nickel.

decreased, possibly because of sintering. Nonetheless, it exceeds nearly eightfold the surface of Ni in a precipitated Ni–Cr catalyst containing 50 mass %–60 mass % of Ni. The main part of the active component is bound by the support (SiO₂), which results in the formation of new surface phases. This means that this method cannot yield industrial low-percentage, highly active nickel hydrogenation catalysts on the SiO₂ support.

Romero *et al.*¹²⁰ showed that the specific surface of unmodified Ni/SiO₂ and Ni/Al₂O₃ catalysts and their capacity to absorb H₂ during thermal treatment or under hydrogenation conditions decrease very rapidly on heating to 650–750 °C. Thus, after treatment at 650–750 °C, the overall specific surface of an Ni/SiO₂ catalyst diminishes from 199 to 159 m² g⁻¹, and the absorption of H₂ becomes more than twice as low.

Transmission electron microscopy data showed that the size of Ni particles increases from 2.9 to 6.8 nm. After an analogous thermal treatment, the Ni particles in the Ni/Al₂O₃ catalyst are enlarged from 2.7 to 9.3 nm, though in this case the overall specific surface and H₂ absorption do not change as strongly as upon the thermal treatment of Ni/SiO₂. In both cases the degradation of porous structures takes place. Thermal treatment of Ni/SiO₂ and Ni/Al₂O₃ decreases the specific surface of Ni by 70% and 25%, respectively.

Thermal inactivation of supported Ni catalysts can be caused by the growth of Ni crystallites, degradation of a support, metal–support interaction, or by combinations of these factors.

3. Effect of the nature of supports on the catalytic properties and specific surface of catalysts

The chemical nature of supports and their structure influence the activity and selectivity of hydrogenation catalysts.^{116–119}

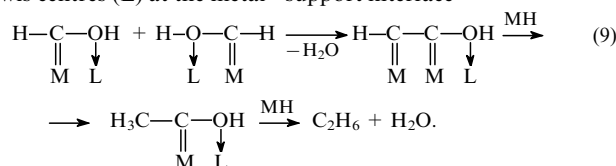
Pavlenko *et al.*¹¹⁷ investigated the adsorption and catalytic properties of Ni catalysts deposited on ZrO₂, MgO, TiO₂, and SiO₂ in the reaction of CO hydrogenation (Table 6).

Table 6. Kinetic and thermodynamic parameters of CO hydrogenation on supported nickel catalysts.¹¹⁷

Catalyst	Mean size of Ni particles /nm	T /K	Maximum pore radius /nm	E	
				q _{CO} /kJ mol ⁻¹	
Ni/ZrO ₂	97	495	137.0	43	45
	97	508	198.0	43	45
	97	533	292.0	43	45
Ni/TiO ₂	103	526	55.0	59	46
	103	545	92.0	59	46
	103	561	128.0	59	59
Ni/MgO	1	471	2.3	93	101
	1	495	7.2	93	101
	1	506	12.0	93	101
Ni/SiO ₂	6	498	1.5	52	76
	6	498	3.4	52	76
	6	498	8.1	52	76

The heat of adsorption q_{CO} increases as the dispersity of Ni increases. This is in agreement with the results of quantum-chemical calculations⁸⁸ according to which the metal–CO bond becomes weaker on transition from the primary clusters to large crystals reaching a constant strength at a mean size of Ni particles 10–20 nm. The specific catalytic activity of specimens at 220 °C decreases in the following order of supports: $\text{ZrO}_2 > \text{TiO}_2 > \text{MgO} > \text{SiO}_2$, *i.e.* there is no direct correlation with the size of crystallites. The selectivity of formation of higher hydrocarbons depends on the nature of the support and varies in the same order, while that of methane formation varies in the opposite direction.

Thus, the nature of the support affects mainly the size of the crystallites and the heat of CO adsorption q_{CO} , which in turn influence the reaction parameters. There are other factors, too. Thus, according to Huang and Schwarz,^{49, 107} with the same metal dispersity, the selectivity of CO hydrogenation depends on the acid-base properties of supports. This dependence can be determined, for example, by the intermediate interaction of the surface complexes CH_xOH bound through an oxygen atom to acidic Lewis centres (L) at the metal–support interface



According to this scheme, the selectivity of formation of higher hydrocarbons should depend on the strength of CO molecule bonding (q_{CO}) and the energy of acid–base interaction.

The influence of the nature and acidity of supports on the properties of Ni-containing catalysts and the metal state in them is clearly manifested in the formation of industrially important bifunctional catalysts containing from 0.5 mass % to 2.0 mass % of Ni.^{120–123} Depending on the differential acidity of supports, *i.e.*, on the ratio of the Brønsted (B) to Lewis (L) centres, catalysts are formed with different activity and selectivity in reactions of hydroisomerisation, aromatisation, and hydrogenolysis. The acidic properties of zeolite supports influence the dispersity of nickel, the extent of its reduction and the magnitude of the SMSI effect, which in turn affects the activity and selectivity of catalysts.

Hoang *et al.*¹²¹ investigated the state of nickel in the Ni-containing catalysts by IR spectroscopy of adsorbed CO and NH_3 , thermoprogrammed reduction, chemisorption of H_2 and O_2 , and thermoprogrammed desorption of NH_3 . When zeolite is impregnated with a nickel salt solution at pH 1.8, ion exchange of B-centres in the channels of zeolite occurs. The nickel fixed in these centres is difficult to reduce; it remains mainly in the NiO form and hence cannot be determined by IR spectroscopy of adsorbed CO. Impregnation of zeolite with a nickel salt solution at pH 4.8 results in the formation of metallic Ni localised mostly outside the channels. In these two cases, the Ni-zeolite catalysts manifest different activity and selectivity in reactions of aromatisation, dehydrocyclisation, and hydrogenolysis of n-hexane.

The acidity of the support and concentration of B- and L-centres also influence the state of Ni in a reduced catalyst (Table 7). In absence of L-centres on the surface (specimen I), NiO particles are formed that interact strongly with the support, the extent of their reduction being a minimum. The presence of even a small number of L-centres (specimen II) leads to the formation of reduced particles Ni^0 , which are less dispersed than those in specimen III with the maximum quantity of L-centres. The specimen III contains highly dispersed Ni particles. In all cases, part of the Ni interacts with the B-centres to form presumably $\text{Ni}(\text{OH})^+$ ions, which are not reduced to Ni^0 .¹²¹

Similar results were reported by Romero *et al.*¹²⁰ who used physicochemical methods to study the metal incorporation into zeolite. The use of a number of additives, *e.g.*, nickel acetylacetonate, and impregnation of zeolite with a Ni salt solution

Table 7. Effect of the acidity of the support on the state of nickel in a Ni/HZSM-5 catalyst after reduction.¹²¹

Specimen	[Ni] (mass %)	Concentration of acidic centres		Extent of reduction of Ni (%)	Ni dispersity (%)	S_{Ni} , /m ² · g ^{−1}
		B ^a	L ^b			
I	0.5	1.8	0	3	—	—
II	0.5	1.6	0.09	75	6.2	0.15
III	2.0	1.1	0.38	75	4.8	0.48

^a Determined from the absorption band of adsorbed NH_3 (1460 cm^{-1}) in the IR spectrum. ^b Determined from the absorption band of adsorbed NH_3 (1610 cm^{-1}) in the IR spectrum.

produces catalysts possessing different acidity, which influences the metal state, activity and selectivity of contacts in the process of hydrocracking of n-paraffins.

Analogous conclusions about the effect of the character of distribution of acidic centres over the support with regard to the strength of these centres on the metal state, activity, and selectivity were drawn from a number of studies dealing with the preparation of Pt, Pd, and Ni catalysts on zeolite supports.^{124–127} These catalysts are applied for dearomatisation in installations for hydrotreating of diesel fuels.⁴⁰ According to Hoang *et al.*,¹²¹ the acidic function of the support controls the formation of the active surface of nickel. Impregnation Ni catalysts are less active than those obtained by ion exchange, since the extent of Ni dispersity is lower in the former case.

The use of a set of physicochemical methods (IR spectroscopy of adsorbed CO, ferromagnetic resonance, chemisorption of O_2 and H_2 , thermoprogrammed desorption of NH_3) made it possible to reveal the effect of strong interaction of Ni with zeolite supports of the Y type characterised by the different extent of Na^+ exchange for NH_4^+ ions and hence by different total acidity.¹²⁷

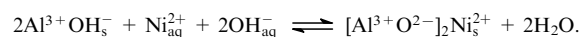
With the increase in the extent of ion exchange, the total acidity increases with simultaneous appearance of a trend for a larger size of Ni particles and a smaller number of d-electrons per nickel atom.

The results obtained allowed one to make a conclusion on the formation of nickel clusters on the surface of zeolite supports and a substantial role of electronic factors in this process. By controlling the formation of clusters, including SMSI regulation, one may prepare highly efficient Ni catalysts with different active centres enabling the occurrence of specific reactions involving H_2 .

Studies of the effect of the surface nature, porous structure and support crystallinity on the formation and properties of Ni catalysts are of considerable interest.⁴⁹

Table 8 presents the main characteristics of Al_2O_3 specimens of different origin (Degussa, Engelhardt, and Kaiser products) used to prepare impregnation catalysts of composition 6%Ni/ Al_2O_3 .

The preparation of catalysts involves several stages. In the first stage, the support is brought into contact with an electrolyte, which results in adsorption of precursors, most frequently by ionic adsorption. There are two ways of cation adsorption on the support surface. If the support is protonated, *i.e.*, it contains no heterometallic ions, the ion adsorption may be realised by treating the support with a solution containing metal ions at a sufficiently high pH. Then the surface H^+ ions are exchanged for metal ions, *e.g.*, Ni^{2+} , following the scheme



An increase in pH shifts the equilibrium to the right, and the concentration of metal ions may prove to be insufficient for precipitation of the metal in the form of hydroxide.

In the first stage, upon contact with a $\text{Ni}(\text{NO}_3)_2$ solution at pH 5 the support is partially dissolved and interacts with the electrolyte, whose pH is thus changed, and a portion of Al^{3+} ions

Table 8. Effect of the type of support on pH of the impregnation solution and Ni adsorption from solution.⁴⁹

Type of support	S_{sp} /m ² g ⁻¹	X-Ray crystallinity /rel. units	pH at zero charge	Pore volume (from N ₂) /cm ³ g ⁻¹	Al ³⁺ concentration /ppm ^a	Solubility /rel. units (see ^b)	Ni adsorption	
							g (g Al ₂ O ₃) ⁻¹	/rel. units
Degussa	97	1.8	5.2	0.003	0.26	1.00	3.25 · 10 ⁻⁴	1.0
Engelhardt	195	1.4	6.8	0.54	0.84	13.51	4.39 · 10 ⁻³	13.5
Kaiser	200	1.0	9.3	0.5	2.87	35.08	1.14 · 10 ⁻²	35.0

^a Concentration of Al³⁺ in the electrolyte formed upon Al₂O₃ solubilisation and ion exchange with Ni²⁺. ^b Solubility of Al₂O₃ in an Ni(NO₃)₂ solution at pH 5.0.

pass into solution. Here, ion exchange can take place with participation of both the OH groups and the surface cations. The hydroxy groups are donors of protons, while the hydrolysed cations are donors of hydroxyls. The departing Al³⁺ cations are substituted by hydrogen as a result of hydrolysis. Subsequently, the Al³⁺ ions are readsorbed. A mixed adsorption leads to the formation of nickel aluminate on the surface.

As is seen in Table 8, the crystallinity (ordering) of the structure of Al₂O₃ and its solubility in the electrolyte change in opposite directions: solubilisation of a support with a deformed lattice occurs more easily. Transition of Ni²⁺ ions from solution to support may be explained by ion exchange with a neutral or negatively charged surface of Al₂O₃ and incorporation of Ni²⁺ into the deformed lattice of Al₂O₃. The ion exchange requires a definite pH at which Al₂O₃ is dissolved in the electrolyte. The larger the number of Al³⁺ ions passing into solution, the more deformed the support lattice, which facilitates incorporation of Ni²⁺ into the support. The most soluble Al₂O₃ of Kaiser Co. adsorbs the largest quantity of Ni²⁺, whereas the Al₂O₃ of Degussa Co. has the lowest solubility and adsorbs the smallest quantity of Ni²⁺. The order of Ni²⁺ adsorbability on various supports is the reverse to the order of their crystallinity.

The efficiency of a catalyst is substantially dependent not only on the quantity of adsorbed Ni²⁺, but also on the size of its active surface and the structure of the latter. The catalysts of the Kaiser and Engelhardt companies have similar pore sizes. However, according to Ghen *et al.*,⁴⁹ the adsorption of Ni²⁺ from aqueous solutions and treatment with HNO₃ do not affect the structure of the support of Kaiser Co., but modify the structure of Al₂O₃ of Engelhardt Co.

Thermoprogrammed reduction (TPRd) of catalysts with hydrogen reveals differences between the porous (Engelhardt and Kaiser) and non-porous (Degussa) specimens. The TPRd spectrum of the Ni catalyst on the Degussa support has no high-temperature peak, whereas the catalysts on the porous supports are characterised by two peaks (at 141–149 and 223–230 °C), though their ratio for the two above-mentioned specimens is not the same. It may be suggested that the catalyst on the Degussa support possesses only the exchangeable surface Ni and centres of the NiO type. The presence of two peaks in the spectrum of TPRd on this catalyst is indicative of the presence on the surface of reduced nickel (Ni⁰) and nickel aluminate, *i.e.* a surface compound carrying incorporated Ni. Al₂O₃ of Kaiser Co. has very little surface Ni and much incorporated Ni in comparison with Al₂O₃ of Engelhardt Co. The quantity of surface (exchangeable) nickel decreases in the order Degussa > Engelhardt > Kaiser, which correlates with the data on crystallinity, solubility, and adsorption.

The porous structure of the support was shown¹²⁸ to influence the extent of metal reduction. On the Al₂O₃ support with a smaller pore size, the mean size of metal particles and the quantity of H₂ sorbed in the low-temperature range are larger.

The readily reducible nickel oxides are believed¹²⁹ to be localised in small pores, while the oxides that are difficult to reduce occupy large pores. The oxides of the first type are close in their structure to the bulk-distributed NiO and interact very weakly with the support. The reduction-resistant oxides may

occur as small crystallites and as surface compounds. The next section is concerned with the effect of the porous structure of supports on physicochemical and catalytic properties of modified nickel catalysts studied by one of the authors of this review.

There are two peaks in the TPR spectra of CO for all reduced samples. It is supposed that the low-temperature peak corresponds to the CO adsorbed on Ni,⁴⁹ whereas the high-temperature peak is associated with the CO spillover on Al₂O₃ or with its adsorption on a surface nickel compound. In the spectrum of the catalyst on the porous support of Kaiser Co. with an abnormally small specific surface of nickel ($S_{Ni} = 2.17$ m² g⁻¹), the low-temperature peak is smaller than that in the spectrum of the catalyst on the support of Engelhardt Co. (14.89 m² g⁻¹). The low-temperature peak is larger (14.22 m² g⁻¹) in the case of the sample on the non-porous support of Degussa Co.

Thus, by selecting the type and porosity of a support, one can control the formation of precursors of active Ni centres, the extent of metal reduction, and hence the activity and selectivity of a catalyst in specific hydrogenation reactions, and regulate thermostability and physicochemical and catalytic properties of impregnation catalysts.

4. Effect of modifiers and promoters on the properties of catalysts

The mode of support preparation and its nature substantially influence the activity, selectivity and physicochemical properties of supported catalysts; however, the strongest effect is achieved by the use of promoters and modifiers.

According to Roginskii,¹³⁰ modification, unlike promotion, is 'a more complicated phenomenon associated with more profound and complex changes in the catalytic properties and specific action of additives' the introduction of which induces 'not merely changes in the absolute magnitude of activity, but also a profound modification of the surface quality'. This can result in a change in the reaction route, *i.e.*, not only in the catalyst activity, but also in its selectivity. This concerns, for example, the modified Ni catalysts of hydrogenation, if the additives, as shown below, 'can react with the surface layer of the solid'.

The application of modern physicochemical methods allows a scientifically sound selection of modifiers and promoters for preparing efficient hydrogenation catalysts for any purpose.

At present, Ni-containing catalysts of hydrogenation are prepared mostly on supports, such as Al₂O₃, SiO₂, aluminosilicates, zeolites, *etc.*, which are modified by oxides.^{5, 12, 20, 116, 131} Modifiers, which are for the most part inorganic additives (SiO₂, zeolites, Mg, Zr, and Ti oxides, boric and phosphoric acids), are introduced into supports by precipitation or impregnation techniques. This results in the enhanced thermostability and mechanical strength of the support. The activity and selectivity of the catalyst change insignificantly when the additives introduced do not affect the extent of nickel dispersity, the degree of its reduction and the magnitude of SMSI.

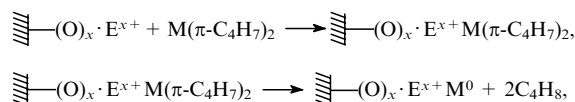
The fact that thermal treatment influences, as has been shown above, the dispersity and structure of supported Ni catalysts makes topical the enhancement of thermostability by modification. For example, addition of 3%–10% of BaO to γ -Al₂O₃ inhibits sintering and improves thermostability of the support.¹²

Addition of phosphoric acid to aluminium hydroxide favours an increase in the total porosity and the proportion of micropores. Other modifiers are also used.

Stabilisation of the existing Ni-containing centres, and creation of newer ones, often requires that considerable quantities of modifying oxide additives (up to 20 mass %–40 mass %) be incorporated into the catalyst.^{12, 132} Thus, the addition of 5% of B₂O₃ to the NiO–Al₂O₃ system leads solely to a lower concentration of Ni³⁺ ions that are not reduced to the metallic state. Addition of 10% of B₂O₃ precludes the formation of Ni³⁺ ions and stabilises Ni²⁺ ions (a sample with 3%Ni/Al₂O₃), though even in this case a large portion of nickel remains in the form of surface oxide associates, whose reduction to the metallic state is problematic.

An analogous situation is observed in the modification of γ -Al₂O₃ with oxides, such as WO₃ and Cr₂O₃, and zeolites. With hydrogenolysis of thiophene as an example Surin *et al.*¹³³ described the promoting effect of zeolite on the hydrotreating catalyst, Ni–Mo/Al₂O₃. Studies involving a set of techniques (DTA, TG, EPR, FMR) showed that zeolite forms thermostable compounds with molybdenum and interacts with γ -Al₂O₃. Introduction of zeolite in the Ni–Mo catalyst favours more uniform distribution of acidic centres, which exerts a substantial effect on the formation of an active hydrogenation phase: a more dispersed phase is formed upon reduction of nickel molybdates.

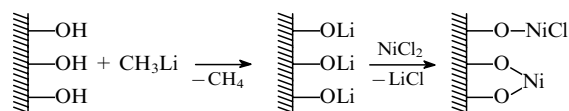
In recent years there has been a much greater use of nickel catalysts modified by surface hydrides formed in the process of catalyst preparation^{13–15, 134} and of the above-mentioned sorptional catalysts. The latter catalysts are highly dispersed, thermostable, and very active in hydrogenation processes, although the method of their preparation is not well-suited to industrial conditions because it includes decomposition on supports of organometallic compounds of elements belonging to Groups IV–VII (Mo, W, Re, and Sn) or Group VIII.^{18–22, 110, 116, 134} The most probable reason for the enhanced thermostability is the interaction of the active component with low-valent ions to form metal–metal bonds between cations of these modifiers and the metal of organometallic compound:¹³⁵



where $\text{M}(\pi\text{-C}_4\text{H}_7)_2$ is the organometallic compound; M^0 is the metal; E^{x+} is the modifying element of Group IV–VII.

Certain procedures developed for preparing sorptional catalysts, including nickel-containing ones, make it possible to reach a degree of dispersion close to the atomic state.^{18–22} Slinkin *et al.*¹¹⁶ described a process for preparing nickel catalysts based on ternary oxide systems Ni–SiO₂(MO₂) synthesised by the alkoxide technology. Catalysts prepared by precipitation from alcoholic or aqueous solutions and promoted with Ti, Zr, and Ce oxides were used for comparison. The extent of nickel dispersion in these catalysts and others obtained from the ternary systems using organometallic compounds proved to be much the same. However, due to the absence of a SMSI effect, the activity of the precipitated catalysts 7%Ni/SiO₂–10%TiO₂(ZrO₂) in the hydrogenation of benzene proved to be one order of magnitude higher than that of the systems synthesised by chemical mixing, where the SMSI effect takes place. In their capacity to stabilise high-dispersity crystals of nickel, the modifiers form the following series:¹¹⁶ CeO₂ > ZrO₂ > TiO₂.

A highly dispersed Ni catalyst for benzene hydrogenation was prepared by modifying the support surface with an organolithium compound from methanolic solution:¹⁸



In accordance with this scheme the so-called grafted Ni/SiO₂ catalysts with 0.8 mass%–4.6 mass% of metal were prepared. Physicochemical and catalytic studies of such catalysts showed that they possess a number of advantages compared to the impregnation systems of similar composition. The degree of reduction of the grafted catalysts at 250–400 °C does not reach 100%, and the size of Ni particles in them ranges from 4.8 to 8.5 nm, while it is 12.5 nm in the impregnation catalysts with 100% reduction. The maximum activity of grafted catalysts in the reaction of benzene hydrogenation is observed at 350–360 °C, which is 12–15 times larger than that of impregnation systems.¹⁸

The drawbacks of the method of support modification with organometallic compounds include a narrow set of compounds possessing satisfactory solubility even in organic solvents, complexity of their synthesis, high explosive tendency and fire hazard of the process, and the need for special pretreatment of supports.¹³

However, this method makes it possible to modify the support surface at the atomic level and to form active metal centres with a predetermined environment.

In our opinion, a method for preparing low-percentage Ni catalysts of hydrogenation by impregnation with mixed inorganic complex salts from aqueous solutions is more promising.^{136–145} In all cases, the role of modifier or active phase is played by heteropolycompounds (HPC) with anions of the general formula $[\text{H}_w\text{A}_x\text{B}_y\text{O}_z]^{n-}$, where A = Ni or Co; B = Mo, W, or V. Their decomposition yields supported Co–Mo, Ni–W, and Ni–Mo catalysts;¹⁴⁶ they may also be used as modifiers of Ni-containing catalysts.^{136–145}

Heteropolycompounds with anions $[\text{NiM}_6\text{O}_{24}\text{H}_6]^{4-}$ (M = Mo or W) were synthesised to prepare hydrogenation catalysts of this type aimed at modelling the known Co–Mo, Co–W and Ni–W catalysts of hydrotreating.¹⁴⁶ Their decomposition on the surface yielded the active phase. Previously, this type of salt and acid were mostly applied as catalysts of oxidation, hydration–dehydration and some other processes.^{147–151}

Supported Ni–Mo and Ni–W catalysts prepared by impregnation of their support with heteropolycompounds were tested in reactions of hydrodesulfurisation and hydrogenation.^{146, 152} They were found to be less active than the industrial Ni–Mo and Ni–W catalysts. This is rationalised by the lower content of Ni which cannot be increased because in this case HPC are used as an ordinary active phase.

In the 1980s, one of the authors of this review designed nickel catalysts of a fundamentally new type on different supports (activated carbon, Al₂O₃, and SiO₂) in which HPC of different composition (HPC₁, HPC₂, HPC₃, *etc.*) play the role of modifiers.^{136–143} They were tested in a broad spectrum of reactions (hydrogenation of alkenes, aromatic compounds, aldehydes, ketones, and CO; hydrogenation of coal; hydrodemethylation of toluene; hydrocracking of petrol fractions; dehydrogenation of cycloalkanes). It was shown that they possess high and controllable activity and selectivity. Common distinctive features of these catalysts are low metal content (2%–6% Ni), modifying salts on the surface of a support and a well-developed surface of metallic nickel with high dispersity. These catalysts exhibit high thermostability, and the procedures for their preparation match technological demands.

Table 9 presents values of the specific surface of nickel (S_{Ni}), its dispersity (d_{Ni}), and the degree of reduction (α) in modified catalysts of the new type on γ -Al₂O₃ with different HPC modifiers and, for comparison, in some industrial Ni catalysts of hydrogenation.

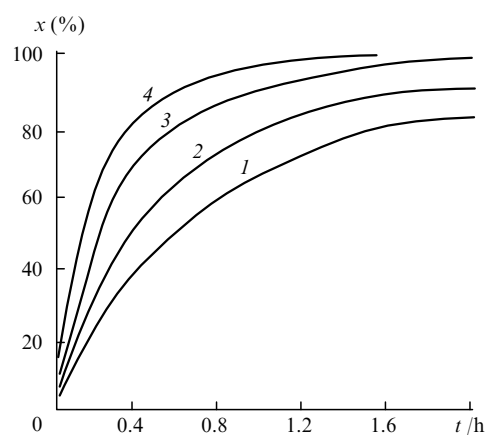
The extent of reduction of modified samples reaches high values, despite the fact that the reduction conditions are considerably milder (400 °C, 6 h) than, for example, those for the Euro-Ni-1 catalyst.¹⁵ In some cases, the α value for modified catalysts with low Ni content (*e.g.*, 2%Ni–HPC₁) reaches 100%. As noted above, this index is not reached for non-modified Ni/Al₂O₃ catalysts, since in these a fraction of the Ni is incorporated into the lattice forming a spinel.

Table 9. Specific surface of nickel, its dispersity, and the extent of reduction in HPC-modified and some industrial catalysts.

Catalyst	[Ni] (%)	S_{Ni} /m ² (g cat- alyst) ⁻¹	d_{Ni}^a /Å	α (%)
Ni–HPC ₁ /Al ₂ O ₃	4	220	26	70
Ni–HPC ₂ /Al ₂ O ₃	4	334	17	87
Ni–HPC ₃ /Al ₂ O ₃	4	56	100	87
Ni–Cr	48–63	25–27		
Euro-Ni-1 ^b	25–52	181	48–56	85–96
Ni/Al ₂ O ₃ (Exxon)	8–10	197	34	

^a Found from H₂ adsorption. ^b Reduction for 10–26 h at 630 °C.

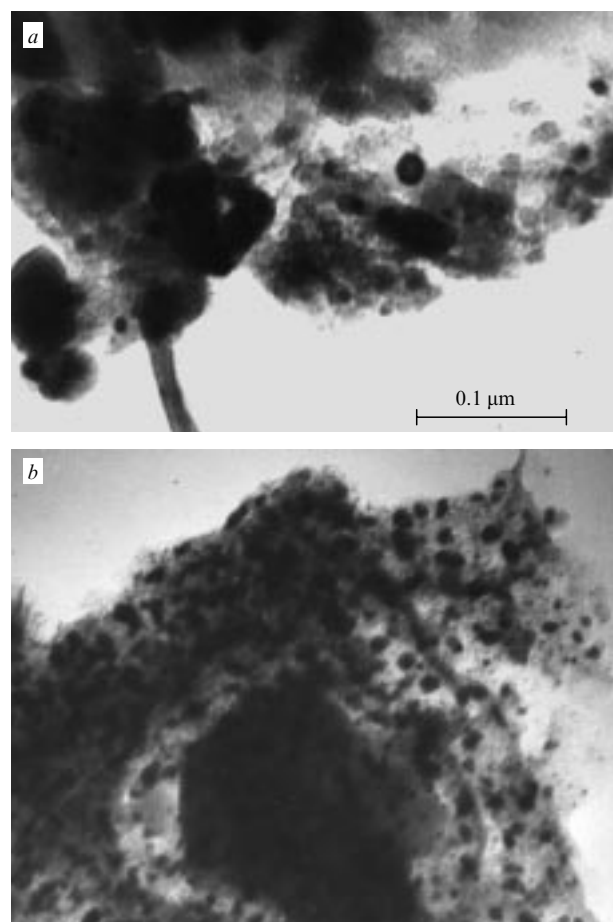
The HPC-modified catalysts with 2%–4% of nickel manifest enhanced activity in the hydrogenation of mono- and bi-cyclic aromatic hydrocarbons, and their selectivity reaches 100%. Hydrogenation of toluene on HPC-modified Ni catalysts with 2%–4% of Ni occurs considerably more easily than on industrial Ni–Cr catalysts with 50% of Ni (Fig. 1).¹³⁸

**Figure 1.** The extent of toluene hydrogenation vs. time on an industrial Ni–Cr catalyst (1) and modified Ni–HPC₂/Al₂O₃ catalysts with 2 mass %, 3 mass %, and 4 mass % of Ni [(2)–(4), respectively].

The catalyst Ni–HPC₁/Al₂O₃ with 2% of Ni is more active at 3 MPa and 220 °C than its analogue with 4% of Ni, and complete hydrogenation of benzene on this catalyst occurs within a contact time less than 0.1 h.¹⁴⁰

These results confirm direct participation of HPC in the formation of active centres of hydrogenation. This follows in particular from the data on the formation of HPC oxometallates, and the formation of W-containing hydrogen bronze upon reduction of highly dispersed particles in the Pt/WO₃ system.^{141, 150, 152}

Preparation of modified Ni–HPC catalysts on carbon supports is accompanied by the formation of an active phase in which Ni particles are distributed uniformly. Figure 2 presents microphotographs of modified and non-modified catalysts on a carbon support with a specific surface of 600 m² g⁻¹. In the absence of HPC the Ni particles are nonuniformly distributed, and their size exceeds that of particles in the modified catalyst.¹³⁸ In the catalyst 4%Ni–HPC/C reduced at 300–420 °C, the size of particles can be as small as 5–7 Å, and in the catalyst on γ -Al₂O₃ they can be even smaller. To achieve optimum dispersity of Ni (5–7 Å) and maximum reduction, it is necessary to have specific HPC concentration and a Ni : HPC ratio on each support. Complete reduction of Ni is possible at a low metal content (2%–4%). In this case, nickel virtually does not interact with γ -Al₂O₃ since it is distributed on the modifier surface. Catalysts Ni/ γ -Al₂O₃ containing less

**Figure 2.** Microphotographs of reduced (at 400 °C) catalysts containing 4% of Ni on carbon supports in the absence of modifier (a) and the presence of HPC₁ (b).

than 5% of metal are virtually inactive in hydrogenation of benzene because of the difficulty in reducing NiO that is in contact with Al₂O₃.

Modification of the Ni/Al₂O₃ catalyst containing 4% of Ni with heteropolycompounds shifts the range of CO hydrogenation towards higher temperatures (250–400 °C) and substantially diminishes the CO₂ concentration in the products on total CO conversion.¹³⁹ The transition of centres of type A (Ni/NiO) to centres of type B (Ni²⁺/NiO) ensures selective hydrogenation, which occurs at a lower temperature. In the absence of a modifier, the centres of the B type are possibly not formed at all.

The assumption of the different structure of Ni centres on modified and non-modified catalysts was confirmed by the analysis of electronic spectra of diffuse reflection. It was shown that Ni catalysts modified by HPC have two types of Ni²⁺ ions with different crystalline fields, while Ni³⁺ ions are absent. Spectral parameters do not correspond to the compound NiAl₂O₄, which shows that the modifier is involved in the distribution of nickel and that the direct interaction between Ni and Al₂O₃ is absent.

The B₂O₃ modifier added in quantities considerably larger (up to 10 mass %–20 mass %) than HPC influences the thermostability of catalysts since it destroys the Ni–O–Ni clusters, inhibits the formation of spinel with Al₂O₃, and stabilises the Ni²⁺ ions on the surface.¹³² Addition of B₂O₃ to the Ni/Al₂O₃ system strongly decreases the concentration of Ni³⁺ ions, which form the oxide associates Ni–O–Ni and alters the acid-base properties of a catalyst.

Heteropolycompounds serve not only as chemical modifiers, they also influence the microporous structure of catalysts.

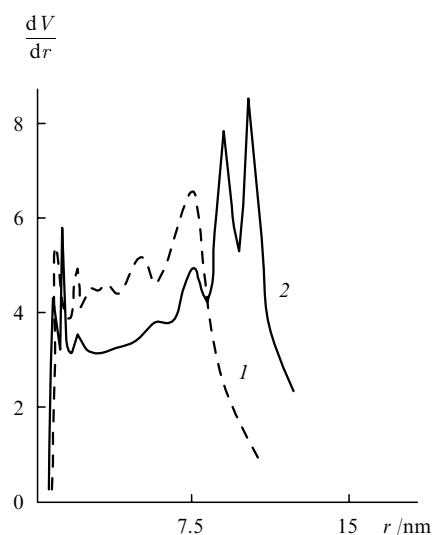


Figure 3. Changes in the porous support structure after formation of the active phase of Ni catalyst in the presence of HPC: (1) γ - Al_2O_3 support after thermal treatment; (2) Ni-HPC₁/ Al_2O_3 catalyst.

Figure 3 shows changes in the porous structure of γ - Al_2O_3 after introduction of HPC in the preparation of a Ni hydrogenation catalyst. The presence of micropores 20–30 Å in diameter influences rather favourably the activity of catalysts for the hydrogenation of aromatic hydrocarbons. The micropores are the sites where readily reducible nickel oxides are formed, after activation with hydrogen the oxides are transformed into highly dispersed metal particles, which ensure rapid hydrogenation of benzene. By modifying the porous support structure with HPC, one can prepare active and selective catalysts for the hydrogenation of aromatic and carbonyl compounds or CO methanation.

Table 10 presents some characteristics of HPC-modified catalysts with the same content of nickel and supports used for their preparation by impregnation. The supports were γ - Al_2O_3 with a predominant pore size of 9–12 nm (Al_2O_3 -1) or Al_2O_3 of the X type (X_1 , X_2 , X_3) with a pore size of 1–3 nm. Figure 4 shows the dependence of changes in the volume of pores (V) as a function of their radius (r) for the supports of the X type and Al_2O_3 -1.

The data presented in Table 10 show that the catalysts based on supports with similar total porosity (specimens 1, 4 and 8) and volume of micropores (specimens 1 and 4) exhibit different activities. The catalyst No. 9 prepared on the support with the largest volume of micropores is the most active in hydrogenation of benzene but is little active in the hydrogenation of acetone. On the contrary, specimens 2 and 3 prepared on Al_2O_3 -1 are not very active in the hydrogenation of benzene and highly active in the hydrogenation of acetone. The modified Ni catalysts with a well-

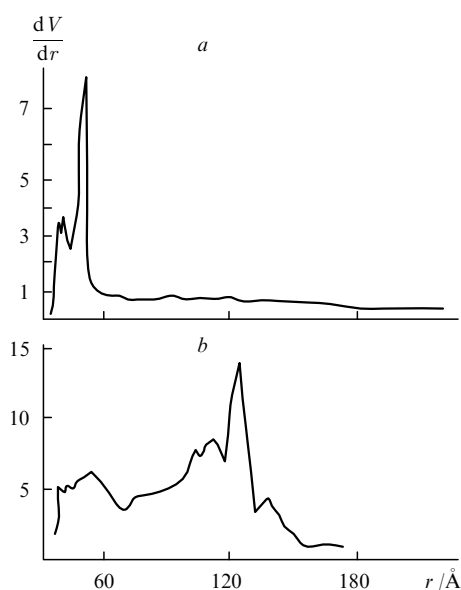


Figure 4. Distribution of the volume of pores in the supports γ - Al_2O_3 of the X type (a) and Al_2O_3 -1 (b).

developed microstructure (the predominant pore size 1–3 nm) were shown to have active centres of benzene hydrogenation and those with large pores (9–12 nm) — to contain active centres of acetone hydrogenation.

Dehydration of modified samples under conditions of thermoprogrammed heating in the temperature range 50–700 °C yields water as the sole product. Modification with HPC substantially alters the properties of the initial surface of Al_2O_3 . Specifically, hydrophilicity of the catalysts prepared was found to be higher than that of initial Al_2O_3 over all the measurement range. After deposition of Ni on modified Al_2O_3 , the liberation of adsorbed water in the thermolysis takes place in the temperature intervals 50–100 °C, 200–300 °C, ~400 °C, 500–600 °C, and even near 700 °C. The most actively modified Ni catalysts possess an increased capacity for H_2O (12% and more). They are characterised by the presence of water removable only in the high-temperature range.¹⁵³

IV. Catalysts based on noble metals

The Ni-containing catalysts are less expensive than those based on noble metals (Pt, Pd, Ru, Rh, Ir, and Os). However, for a number of industrial hydrogenation processes preference is given to the latter because of their high catalytic activity allowing operations at lower temperature and pressure. The lifetime of these catalysts often extends to several years. Pd, Pt, Ru, and Rh catalysts and

Table 10. Effect of the porous structure of supports on the activity of Ni catalysts in the hydrogenation of benzene and acetone.

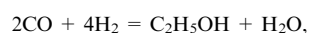
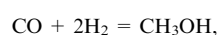
Entry	Catalyst or support	$S_{\text{sp}}/\text{m}^2 \text{ g}^{-1}$	Total porosity $/\text{cm}^3 \text{ g}^{-1}$	Microporosity $/\text{cm}^3 \text{ g}^{-1}$	Rate constant of benzene hydrogenation $/\text{h}^{-1} \text{ cm}^{-3}$	Degree of acetone conversion (%)
1	Al_2O_3 -1	170	0.59	0.10	—	—
2	Ni-HPC ₂ / Al_2O_3 -1	—	—	—	0.40	80
3	Ni-HPC ₅ / Al_2O_3 -1	—	—	—	0.12	60
4	X_1	193	0.42	0.11	—	—
5	Ni-HPC ₂ / X_1	—	—	—	0.86	—
6	X_2	214	0.45	0.14	—	—
7	Ni-HPC ₂ / X_2	—	—	—	1.16	20
8	X_3	201	0.51	0.20	—	—
9	Ni-HPC ₂ / X_3	—	—	—	1.44	12

bimetallic systems are of special interest. The use of special supports makes it possible to bring the content of noble metals down to 0.01%–0.005% and thus make catalysts less expensive, while preserving their qualities.^{154–157}

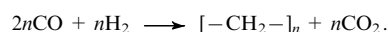
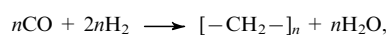
Modern physicochemical methods allow the investigation into the mechanism of action of these catalysts, optimisation of their composition, and development of methods for controlling the metal dispersity on the support surface. Some catalysts based on noble metals are resistant to poisoning with S- and N-containing compounds.^{158, 159}

1. Hydrogenation of CO

A number of studies (see, e.g., Refs 160–163) showed that supported Pt, Pd, Ir, Ru, and Rh catalysts allow one to bring about the methanation of CO under atmospheric pressure. Hydrogenation of CO under elevated pressure in the presence of Pt/Al₂O₃, Pd/Al₂O₃, and especially Ru/Al₂O₃ and Rh/Al₂O₃ (in contrast to Ni-containing catalysts) leads to the formation of alcohols and other oxygenated compounds^{164–166}



The Fischer–Tropsch synthesis may be also carried out on Ru/Al₂O₃ and Ru catalysts on specially selected supports to produce higher (C₅–C₂₀) hydrocarbons (with selectivity up to 81%) as well as methane, C₁–C₅ alcohols, and C₂₁–C₄₀ hydrocarbons.^{167–170}



Industrial processes (Sasol-II, SMDS, and Gulf Badger) on Ru-containing catalysts allow selective formation of a diesel fraction of synthetic liquid fuel or higher paraffins the cracking of which affords high-quality diesel and rocket fuels.^{167, 170}

During the period 1987–1990, the catalytic activity of platinum group metals on supports in the reaction of CO hydrogenation, its mechanism and kinetics were systematically studied.^{117, 118, 163} The dispersities (mean size of metal particles, d_{mean}) of the catalysts studied, their activities (k), and selectivities are presented in Table 11.

Table 11. Certain characteristics of different metal catalysts for the CO methanation ($p_{\text{CO}} = 20$ kPa, $p_{\text{H}_2} = 50$ kPa, $T = 275$ °C).

Catalyst	d_{mean} /nm	$10^7 k$ /mol m ⁻² s ⁻¹	Selectivity of methane formation (%)
Ru/Al ₂ O ₃	4.4	6.7	87
Rh/Al ₂ O ₃	2.5	5.5	94
Ni/Al ₂ O ₃	2.4	4.7	96
Pt/Al ₂ O ₃	3.9	0.4	99
Ir/Al ₂ O ₃	6.8	0.2	100
Pd/Al ₂ O ₃	5.0	0.1	100

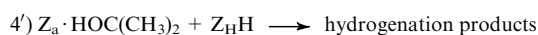
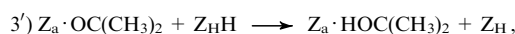
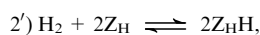
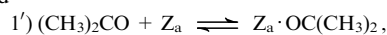
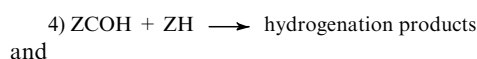
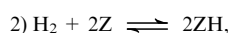
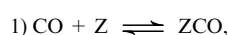
As seen in Table 11, the specific catalytic activity decreases and the selectivity increases in the series Ru → Rh → Ni → Pt → Ir → Pd. The catalytic activity decreases as q_{CO} increases.¹⁶³ The q_{CO} values determined from kinetic data increase in the following series: Ru < Rh < Ni < Pt < Ir < Pd.^{161, 171} On the whole, the specific catalytic activity of platinum group metals and nickel is lower the larger the size of the metal particles (*cf.* Table 11).

The effect of the phase structure of the support (Al₂O₃) was studied for Rh catalysts.¹⁷² Rhodium was deposited on δ-, θ-, and α-Al₂O₃ with specific surfaces from 5 to 90 m² g⁻¹. In these catalysts, rhodium was found to be present in three forms:

encapsulated, strongly interacting, and non-interacting with the support. The maximum extent of dispersity (11%) was reached on α-Al₂O₃ at low Rh content (< 1 μmol m⁻²). At higher Rh content (> 1 μmol m⁻²), the extent of dispersity was below 3%. The activity of a catalyst is enhanced if α-Al₂O₃ is used as a support, if Al₂O₃ is treated with water vapour prior to Rh deposition, and if the content of deposited rhodium is low.

2. Hydrogenation of carbonyl compounds

The similarity of the processes underlying hydrogenation of CO and carbonyl compounds on platinum group metals was reported in different studies.^{161, 167–171} The character of the dependence of specific catalytic activity on the heat of adsorption of the reactant proved to be nearly the same in both cases. The same holds for the influence of dispersity: the heat of adsorption of reactants increases with a decrease in the size of crystals leading to a lower catalytic activity. The mechanisms underlying the hydrogenation of CO and acetone were supposed to be similar (the Langmuir–Hinshelwood mechanism):



(Z, Z_a, and Z_H are the catalyst active centres).

The limiting stages are the addition of the first hydrogen atom to an adsorbed CO molecule or to the >CO group of acetone, respectively, with the formation of a ‘semi-hydrogenated’ reactant form.

However, certain differences also exist: in the CO hydrogenation, the most active catalyst is Ru, while the hydrogenation of carbonyl compounds is best catalysed by Pt. Some investigators believe^{167–171} that the reason for this difference consists in the stronger binding of C and O atoms ($q_{>\text{CO}}$) in a complex of the type



compared to the carbonyl compound binding (q_{CO}) in the complex



and thus $q_{>\text{CO}, \text{opt}} < q_{\text{CO}, \text{opt}}$. According to approximate estimates, $q_{>\text{CO}, \text{opt}} \simeq 20$ kJ mol⁻¹ and $q_{\text{CO}, \text{opt}} \simeq 100$ kJ mol⁻¹. These differences are reflected in the series of catalytic activity and selectivity. Table 12 presents data on the dispersity of metals of the platinum group and nickel deposited on Al₂O₃ and their specific activities in the acetone hydrogenation. The specific activities of catalysts with similar metal dispersion decreases in the order: Pt > Ir > Rh > Ni > Ru > Pd. The position of individual metals in this series depends on both their chemical nature and the dispersity. Hydrogenation of the carbonyl group of a ketone is a structure-sensitive reaction. This means that the probability of multipoint adsorption of complex molecules and the rate of their hydrogenation depend on the size, shape, and arrangement of microcrystals on the support. Possibly, the adjacent sites of the support surface take part in the substrate activation due to hydrogen spillover.¹⁶⁵

Table 12. Specific activity of some catalysts in the acetone hydrogenation reaction and the deposited metal dispersity.

Catalyst	d_{mean} /nm	$10^7 k$ /mol m ⁻² s ⁻¹	q_{CO} /kJ mol ⁻¹
Pt/Al ₂ O ₃	3.9	44	12
Ir/Al ₂ O ₃	6.8	11.7	20
Rh/Al ₂ O ₃	2.5	7.7	15
Ni/Al ₂ O ₃	2.4	7.5	85–25
Ru/Al ₂ O ₃	4.4	700	30
Pd/Al ₂ O ₃	5.0	0	–

3. Hydrogenation of unsaturated hydrocarbons

In some cases, noble metals rather than nickel are preferred as catalysts for the hydrotreating of motor fuels (dearomatisation, hydrogenation of alkenes).^{29, 40} Catalysts based on noble metals are more active and more resistant to poisoning by sulfur compounds. Platinum and palladium deposited on Al₂O₃ are easily deactivated at a sulfur concentration below 1 ppm;¹⁷³ however, their resistance to sulfur poisoning increases on acidic supports, such as zeolites.^{158, 159} For instance, 98% of the products of dodecane hydrocracking are alkanes on Pd/LaY under H₂S pressure of 63 kPa, *i.e.* when all palladium would be expected to pass to PdS; the catalyst activity and selectivity remain virtually unaltered.¹⁵⁹ Such an unusual behaviour of this noble metal is explained by the SMSI effect or changes in the electronic state of palladium upon its interaction with the acidic centres of zeolite.¹⁵⁸

Platinum catalysts are prepared by ion exchange or impregnation of the support with a solution of Pt(NH₃)₄Cl₂; its cation binds to an acidic centre of zeolite $\equiv \text{Al}-\text{O}^-$. The next important stage consists of the formation of centres $2(\equiv \text{Al}-\text{O}^-)\text{Pt}^{2+}$ upon calcination in air. On subsequent reduction with hydrogen, platinum becomes involved in clusters of the type $m(\equiv \text{Al}-\text{O}-\text{H}) \cdots \text{Pt}_n$. The clusters are in close contact with strong acidic centres, which makes possible the transfer of electrons from this noble metal and leads to the formation of electron-deficient metal particles (Pt^{δ+}), which are responsible for the specific properties of this catalyst.¹⁷⁴

In most cases, hydrogenation is conducted on supported palladium catalysts. Table 13 presents the data from studies of the hydrogenation reactions of CO, aldehydes, and unsaturated hydrocarbons on Pd/TiO₂ catalysts prepared by different methods and differing in the size of particles and the active surface of the metal.¹⁷⁶

The data in Table 13 indicate that the rates of CO hydrogenation and low-temperature hydrogenation of propionaldehyde to propanol increase with the Pd dispersity. However, in the hydrogenation of the C=C double bonds in ethylene, butadiene, and acrolein the reverse order of activity is observed, being particularly noticeable in the hydrogenation of the conjugated bonds of butadiene.

The relationship between the catalytic properties of supported palladium and its dispersity is widely discussed in the literature.^{174–184} In some reports, this phenomenon is explained by changes in the electronic state of Pd resulting from the SMSI

effect,^{175, 179} while in others, by the participation of both the catalyst and the support in the reaction.¹⁸⁰ Table 13 shows three Pd catalysts on the same support (TiO₂), which possess different activities and selectivities. Therefore, according to Barbier *et al.*,¹⁷³ the reason for the differences should be sought in the properties of the particles of palladium itself: in variations of their size, shape, electronic structure, and the nature of their interaction with the molecules subject to hydrogenation. For example, in the adsorption of CO an electron is transferred from Pd to CO, while in the adsorption of ethylene it is transferred in the opposite direction. This results in inverse dependences of the catalytic activity of Pd/TiO₂ on the degree of metal dispersity in different hydrogenation reactions.

Highly dispersed palladium is more active in the hydrogenation of electron-acceptor compounds, whereas the low dispersed palladium is more active in the hydrogenation of electron-donor compounds. As was shown above (see Table 11), Pd/Al₂O₃ is the least active catalyst of CO methanation. The metal in bulk is also weakly active in this reaction.¹⁸¹ Consequently, in Pd/TiO₂, palladium forms clusters or small particles which are endowed with special properties different from those of bulk Pd or Pd on Al₂O₃. Of all the catalysts listed in Table 13, the strongest Pd–support interaction may be expected for the first specimen, which is characterised by a well-developed active surface and small particle size. In this case, an effect of the SMSI type is possible.

4. Bimetallic and modified catalysts

Considerable interest arose in bimetallic catalysts on supports in connection with the development of sulfur-resistant hydrogenation catalysts based on noble metals. For example, combination of Pt and Pd deposited on zeolite is known^{183, 184} to enhance sulfur tolerance, the optimum Pt : Pd ratio being equal to 1. The support used was zeolite of the Y type with a high Si/Al ratio (Shell), and mordenites, borosilicates, and Y- and β-zeolites (Amoco).

The Haldor Topsøe company has developed two types of catalysts for the two-stage hydrotreating of petroleum fractions: Ni–Mo/Al₂O₃ for the first stage and TK908 containing a supported noble metal for the second stage.¹⁸⁵ The latter was in operation for 5600 h and the extent of its deactivation was less than 1% after 1000 h, despite the fact that the content of sulfur in raw materials reached 1000 ppm and that of nitrogen reached 50 ppm.

Ru–Pd catalysts prepared by impregnation of a support with salts of both metals are highly active. These catalysts were used to study the hydrogenation of benzene.¹⁸⁶

Bastiaux *et al.*¹⁸⁷ described in detail a new approach to the preparation of highly selective bimetallic catalysts for the hydrogenation of alkynes and dienes in the hydrotreating of pyrolysis gases and petroleum fractions. Industrial Pd catalysts were substantially upgraded by promoting them with a second metal. The choice of the second metal promoter was made on the basis of modern theories of homogeneous catalysis and of current concepts of changes in ligand mobility in organometallic compounds.¹⁸⁸ Alkanes, alkenes, and alkadienes localised on the surface of Pd catalysts may be regarded as ligands which form strong bonds with palladium in the absence of promoters, thus

Table 13. Mean activity (catalyst turnover) of different Pd/TiO₂ catalysts in the hydrogenation of CO, aldehydes, and alkenes.¹⁷⁶

Catalyst characteristics				Mean catalyst activity in hydrogenation					
[Pd] (%)	S_{sp} m ² g ⁻¹	d /nm	H : Pd	CO (methana- tion)	CO in CH ₃ OH (230 °C)	C=O bond in propion- aldehyde (80 °C)	C ₂ H ₄ (80 °C)	C=C bond in acrolein (80 °C)	C ₄ H ₆ (80 °C)
5.5	207	4.5–6.5	0.32–0.67	7.3×10^{-4}	4.3×10^{-4}	0.16	380	0.09	150
5.2	9	186	0.17	2.8×10^{-4}	4.0×10^{-5}	4.5×10^{-3}	500	–	680
4.4	9	295	0.067	5.5×10^{-4}	0	4.5×10^{-3}	580	0.4	1.05×10^3

decreasing the catalyst's activity. The strength of the alkyl–metal bond may be reduced by the addition of an electron-donor compound or a metal promoter which favours higher selectivity of acetylene hydrogenation.¹⁸⁷ New procedures for the preparation of highly selective bimetallic hydrogenation catalysts with controlled dispersities were developed using recent progress in the field of inorganic synthesis and synthesis of organometallic compounds.^{189,190} Higher yield of the target product and higher stability of catalysts are achieved by modification of the electronic properties of palladium by the second metal. This approach was employed to prepare the industrial catalyst LT-279 for the selective hydrogenation of acetylene in an ethane–ethylene fraction.¹⁸⁷

As noted above, the selectivity of acetylene hydrogenation may be considerably increased by preparing Pd catalysts on supports in the form of active film structures of the cermet type.⁹⁹ In this case, the electronic properties of palladium are modified in a different way, namely, due to the formation of a surface catalyst layer with incorporated modifying oxide additives (Al₂O₃). To this end, a simple technique may be used, such as impregnation, which is inapplicable for the production of bimetallic catalysts. The latter are synthesised by making recourse to a more complex technology using, *e.g.*, organometallic compounds or vapour condensation of two metals on a support.¹⁸⁷

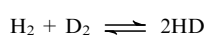
Film-type Pd catalysts modified with Al₂O₃ in their surface layer contain 0.1%–0.3% of Pd. They are thermostable and may be subjected to oxidative regeneration. Metal particles are formed in them on the surface of γ -Al₂O₃ supplemented with a thermostable alumina oxide in the ratio Pd : Al₂O₃ = 1 : 1. Alteration of Pd properties leads to higher catalytic activity in the reaction of acetylene hydrogenation, which allows one to conduct it at low temperature (30 °C), low H₂ : C₂H₂ ratio (2 : 1), and high flow rates (up to 10 000 h^{–1}), with a substantial increase in the selectivity of C₂H₂ hydrogenation, *i.e.*, the same effects as with bimetallic catalysts. Modification of film-type palladium catalysts is brought about by adding very small quantities of oxide (Pd : Al₂O₃ = 1 : 1), and the procedure for their preparation is much simpler than that of bimetallic catalysts.

As for the selectivity of acetylene hydrogenation, the Al₂O₃-modified Pd (0.1%Pd) is more than twice as effective as its industrial analogue MA-15 (0.5%Pd).⁹⁹ On a bimetallic LT-279 catalyst, transformation of acetylene increases by no more than 10%–20% compared to that on a common Pd hydrotreating catalyst.¹⁸⁷

Selective hydrogenation of unsaturated hydrocarbons can be performed on new highly dispersed Pt/MoO₃ and Pt/WO₃ catalysts in which the metal particles interact on the surface with the modified support.¹⁵² The ultradispersed MoO₃ and WO₃ particles obtained in a plasma reactor are reduced in a stream of hydrogen at 300 °C. Subsequent interaction with Pt or Pd leads to hydrogen bronzes, which serve as hydrogen reservoirs for hydrogenation.^{191,192} The hydrogen bronzes are formed upon deposition of 0.2% Pt on MoO₃ or 0.1% Pt on WO₃ owing to spillover of H₂ from the metal centres to the support under the hydrogenation conditions. This results in changes in the specific surface and the size of particles that form the centres active in the hydrogenation of alkenes. The molybdenum and tungsten bronzes themselves (without hydrogen) can also catalyse ethylene hydrogenation.¹⁹³

V. The mechanism of hydrogenation on metal catalysts

The mechanism of catalytic hydrogenation, in particular the sequential formation of different surface compounds, has been reviewed recently.¹⁹⁴ Hydrogenation is assumed to involve atomic hydrogen formed upon dissociation of H₂ on metals, such as Ni, Pt, Pd, and others. This assumption is confirmed by an intense isotope exchange



and formation of monodeuterioethane C₂H₃D upon deuteration of ethylene. On oxides, in particular on ZnO, deuterioethane C₂H₄D₂ is formed from ethylene, which indicates the participation of molecular hydrogen in this reaction. However, other data¹⁹⁵ point to the possibility of participation of both atomic and molecular hydrogen in the hydrogenation on metals.

Numerous forms of adsorbed alkenes were detected on the surface of metals that were found to compete for the active centres. Strongly bound forms of the type CH₃–CH=M, CH₃–C≡M, *etc.* are hydrogenated at high temperatures, whereas at low temperatures only weakly bound forms of the π -type and π -allyl complexes undergo hydrogenation.

The hydrogenation rate may be varied by regulating the strength of alkene adsorption. For example, modification with alkylsilanes increases the activity of ZnO 20- and 150-times in the hydrogenation of butadiene and pentadiene, respectively.¹⁹⁵ This is explained by a steric effect: bulky alkylsilanes prevent strong adsorption of dienes, but do not hinder hydrogen adsorption.

It is suggested that the centres of hydrogen activation involved in hydrogenation are localised on the metal surface. Therefore, the larger the surface of a metal the higher should be its catalytic activity. If the size of metal crystallites has no effect on the specific activity of a catalyst, the catalysed reaction is called structure-insensitive. The hydrogenation of the C=C bond in alkenes is an example of such reactions. On the contrary, the hydrogenation rates of an aromatic ring, the C=O and C≡C bonds, and conjugated compounds of the butadiene type depend on the metal dispersity and hence such hydrogenations are regarded as structure-sensitive reactions.

Investigation of hydrogenation of cinnamaldehyde on Ru/Al₂O₃ showed a decrease in the specific rate constant for the C=C bond hydrogenation with an increase in the metal dispersity.¹⁹⁶ This indicates that this reaction requires a planar adsorption of substrate, *e.g.*, in the form of a π -complex. At the same time, the rate constant for the C=O bond hydrogenation increased with increase in the metal dispersity. Evidently, this reaction requires point-type adsorption (Ru···O=C<). The adsorption coefficient of the C=O bond of cinnamaldehyde is independent of dispersion, while the adsorption coefficient of the C=C bond decreases with an increase in the metal dispersity.

Apparently, intermediate semi-hydrogenated forms can manifest properties of free radicals (C₂H₅· from C₂H₄, C₃H₇· from C₃H₆, *etc.*).¹⁹⁷

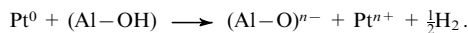
Small palladium particles with a size < 2.5 nm (Pd/MgO, Pd/Al₂O₃, Pd/SiO₂, Pd films and Pt black) are less active than larger particles,^{95,198–200} and they become totally inactive when their size is < 1 nm. This is explained by the fact that very small particles cannot dissolve hydrogen. Sintering of particles leads to enhancement of the catalyst's activity and selectivity in the hydrogenation of unsaturated compounds.

The hydrogen necessary for the hydrogenation can be accumulated not only on the surface but also in the bulk of the metal. The properties of the surface- and bulk-absorbed hydrogen differ considerably. For example, in the hydrogenation of CO and CO₂ on Pd/Al₂O₃, Pd black, and Pd foil the bulk hydrogen favours formation of oxygenated compounds, CH₃OH and CH₃CHO, while the surface hydrogen favours formation of CH₄ and other hydrocarbons.²⁰¹

Other phases of a complex catalyst can also absorb hydrogen and deliver it rapidly to the compound subject to hydrogenation. Hydrogenation reactions often require the activation of both hydrogen and the compound to be hydrogenated. The latter process can be brought about on another phase. The unsaturated compound can also be localised on the metal, although covering of the surface of the metal prevents adsorption of H₂ and hampers the delivery of hydrogen in quantities necessary for hydrogenation. Hydrogenation can occur as a result of alternating interactions of different components of a catalyst with hydrogen and the compound to be hydrogenated and hydrogen spillover from

one component to another. The latest data on hydrogen spillover have been reviewed recently.²⁰²

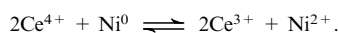
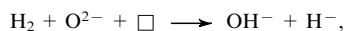
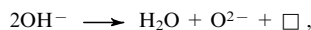
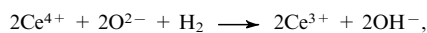
Hydrogen exchange between the metal phase and the support occurs with participation of acidic centres of the support. This was proved by experiments on the poisoning of Pt/Al₂O₃ catalysts with ammonia under the conditions of butadiene hydrogenation.²⁰³ The results are interpreted by the authors as a redox process



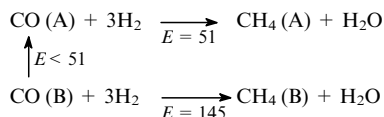
The increase in the catalyst crystalline lattice parameter in the course of hydrogenation may be regarded as an indirect evidence of hydrogen dissolution. The use of neutron diffraction revealed the intercalation of hydrogen into the ZnO phase in CO hydrogenation on a Cu–ZnO catalyst.²⁰⁴ Such an intercalation leads to the formation of a solid solution of Cu in ZnO in which half of the copper ions are replaced by protons. Carbon monoxide is adsorbed on copper, while hydrogen, though also being activated on copper, is involved in the hydrogenation from the subsurface ZnO layer.

Neutron diffraction also revealed the dissolution of hydrogen in the CuCrO₂ catalyst.²⁰⁵ The defects □_{Cu2+} stabilise the dissolved hydrogen. The catalyst has in its bulk two types of hydrogen: atomic hydrogen H in the lattice interpoint space and hydrogen in the form of the OH groups resulting from Cu²⁺ exchange for H⁺.

The intercalation of hydrogen into the lattice of CeM_xO catalyst (M = Cu and Ni; 0 < x < 5) was proved by X-ray, XPES, EPR, and DTG methods.²⁰⁵ The intercalation of H atoms and reduction of Ce⁴⁺ to Ce³⁺ results in the extension of the CeO₂ lattice:



In the above consideration of Ni supported catalysts, we repeatedly mentioned the existence of two types of active centres on the surface: metallic (Ni) and oxidised (Ni²⁺) centres. Different centres are already formed in the preparation of a catalyst, *e.g.*, upon incorporation of NiO into the lattice of γ-Al₂O₃. Non-modified catalysts with a Ni content of 3.2%–4.4% were studied by the method of TPR of carbon monoxide.²⁰⁶ The degree of Ni reduction at 500 °C did not exceed 25%. Two types of CO adsorption were observed, which followed from the two peaks of methane formed upon hydrogenation. The methanation proceeds according to the following scheme:



(values of *E* are given in kJ mol^{−1}).

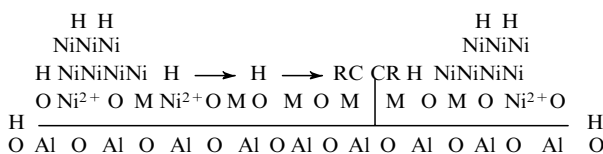
The conversion of CO (B) into CO (A) at temperatures below 250 °C proceeds very slowly, but upon completion of this transition, CO (A) is rapidly hydrogenated at 142–247 °C. Thus, the rate of methanation on low-percentage Ni/Al₂O₃ catalysts is determined by the rate of B → A conversion, *i.e.* of Ni atoms interacting with NiO, into the Ni centres on the metal surface. Hydrogenation of CO (B) requires a considerably higher activation energy than that of CO (A).

The presence of centres with Ni in different oxidation states is also characteristic of HPC-modified Ni catalysts on supports. We consider here a possible hydrogenation mechanism on such catalysts.

The hydroxylic cover formed on an HPC-modified surface differs substantially from that of the initial support and a binary

Ni catalyst. It is homogeneous and depends on the type and concentration of the modifier and metal concentration.

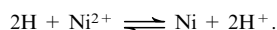
Heteropolycompounds (HPC) are directly involved in the formation of metal-containing active centres. Judging from electron microscopy (see Fig. 2), at the optimum HPC concentration the active phase is regularly distributed thus creating seeds of Ni microcrystal formation and stabilising the metal formed upon reduction. Nickel particles are distributed in the defect layer of the modifier where Ni²⁺ can also be present. They have no direct contact with the support and are exceptionally thermostable: the specific surface of the metal is not changed up to 600 °C. Hydrogen is adsorbed on the Ni surface and diffuses to the modifier (M) surface following the spillover mechanism with the possible participation of the hydroxy groups of the modifier, as shown below (the arrows indicate the direction of spillover):



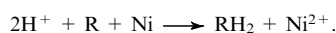
An unsaturated organic compound seems to be adsorbed on the modifier phase. Thus, the functions of the two catalyst's phases *viz.*, Ni and HPC, are different. Presumably, Ni²⁺ ions formed from the metal are incorporated into the HPC structure. The initial activation of hydrogen takes place on the Ni particles:



Then a reversible reaction occurs.



This results in the formation of very small Ni particles, which in some cases cannot be detected even by electron microscopy. HPC can interact with the organic compound with transfer of the accumulated hydrogen



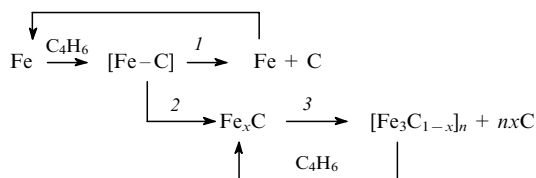
Probably, the active hydrogenation centres of unsaturated compounds and aromatics differ from those of CO and carbonyl compounds.

VI. Carbide catalysts

Boudart and Levy²⁰⁷ were among the first investigators to study the catalytic properties of carbides. They showed that Mo₂C possessed an unusually high catalytic activity close to that of platinum in reactions of hydrogenation and isomerisation. Nearly the same activity was found in tungsten carbide. These compounds are formed upon reactions of Mo or W salts or oxides with hydrocarbons. For example, a powder of tungsten carbide with a specific surface of 3.5 m² g^{−1} can be obtained in the reaction of WCl₅ vapour with butane at 1.3 kPa and 1340 °C.²⁰⁸ On the surface of tungsten carbide there is polymeric carbon, which decreases its hydrogenation activity. Adsorption of oxygen facilitates adsorption of H₂ by inducing the formation of islets of tungsten bronze, H_xWO₃, on the surface which is possibly a hydrogen reservoir. Under the conditions of catalysis the WO₃ oxide is not reduced. Thus, the catalytic activity is apparently manifested not by the carbide itself, but rather by a biphasic structure.

The interaction of MoO₃ with a CH₄ + H₂ mixture at 630 °C produces a powder of Mo₂C of hexagonal structure with a specific surface ranging from 50 to 100 m² g^{−1}.²⁰⁹ This also has a polymeric carbon on its surface which is removed under the hydrogenation conditions. A metastable carbide α-Mo₂C_{1-x} (x = 0–0.5) with a specific surface of 200 m² g^{−1} and particle size of 3 nm was prepared in the TPR mode by the reaction of MoO₃ with ammonia and methane.²¹⁰ First, the reaction Mo₃ + NH₃ yields nitride Mo₂N, which is then transformed into

The coke results from realisation of the so-called carbide cycle.^{212, 213} For example, the interaction of Fe with C_4H_6 involves the following transformations:

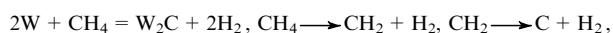


Electron microscopy studies^{87,216} showed that the general morphology of particles remained unaltered under the reaction conditions. The particles are overgrown with amorphous carbon; however, the latter does not seem to block the active centres. The size of the Fe_3O_4 and $\kappa\text{-Fe}_5\text{C}_2$ particles is ~ 60 nm and ~ 25 nm, respectively. The most interesting finding is evidence of intercalation of the carbide formed in the Fe_3O_4 lattice. In addition to electron microscopy, the electronographic analysis of selected

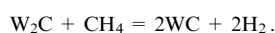
Thus, it is systems in which the oxide-carbide phases can be formed under the reaction conditions that are the active hydrogenation catalysts. Most recent studies have shown that the formation of oxycarbide structures favours the reactions with the participation of unsaturated compounds on tungsten and molybdenum carbides.

Many recent studies^{223–226} were devoted to the studies of hydrogenolysis of 2-methylpentane, n-hexane, and methylcyclopentene on tungsten carbide WC. This catalyst was synthesised by heating WO₃ in a mixture of 20% CH₄ + 80% H₂ in the TPR mode. In the process of reduction, intermediate species, *viz.*, W₂₀O₅₈, W₁₈O₄₉, and WO₂, were produced and a carbon layer was formed. After heating in this mixture at 800 °C for 10 h, the carbon layer disappeared to give way to WC with specific surface 12 m² g^{−1} possessing a biporous structure (the pores 2 nm and 6 nm in diameter predominate). On WC, which is similar in its catalytic properties to Ru, Ir and Ni, cracking and, to a much lesser extent, isomerisation take place in the presence of hydrogen.

According to Leclercq *et al.*,²²⁷ it is advantageous to prepare the tungsten carbide in two stages: first, carbidisation of metallic W or WO₃ with a mixture of 20% H₂ + 80% CH₄ at 650 °C produces W₂C and a small amount of free C



and then WC is formed at 800 °C in the reaction



In the presence of O₂ at 100–300 °C a complex mixture containing oxycarbide phases, WC, W₂C, WO₂, and metallic tungsten is formed.²²⁸ The properties of the catalyst are strongly changed, and it becomes similar to a bifunctional platinum catalyst and selectively accelerates skeletal isomerisation.

The development of procedures for preparing carbides with large specific surface (up to 200 m² g^{−1}) should be regarded as an important achievement.^{229–233} The hexagonal phase of Mo₂C is formed upon interaction of activated carbon with MoO₃ vapour. The unconsumed carbon is burned in the bulk of the carbide and can enhance the mechanical strength of the catalyst grains. According to the XPES data, the surface is covered by carbide alone, though the contact with oxygen leads to the formation of an oxide film. The oxide oxygen cannot be removed from the Mo₂C surface by heating in hydrogen at 850 °C without partial decarbidisation. To avoid this, the catalyst is treated with a mixture of H₂ plus a hydrocarbon. Alternatively Mo₂C or WC is impregnated with small quantities of Group VIII metal salts which accelerate decarbidisation.

However, oxygen is not always a poison for carbide catalysts. A discovery was made owing to the accidental aspiration of air into a catalytic installation:^{229–233} in the presence of hydrogen, the oxidised Mo₂C catalyses isomerisation of n-hexane into methylpentanes and dimethylbutanes without formation of aromatic compounds. This makes it possible to reform hydrocarbons into high-octane and non-carcinogenic fuel. The most efficient catalyst was obtained by treating the carbide with air for 14 h at 350 °C. This resulted in the formation of an oxycarbide layer on the catalyst surface. According to the results of XPES, the major part of the molybdenum exists in the Mo(VI) state on the surface of this catalyst (in contrast to Mo₂C). X-Ray studies showed that its structure corresponds to that of MoO₃, but the oxygen vacancies □_O on the surface are filled with carbon atoms that block the formation of MoO₂.¹⁹⁵

Such an oxycarbide possesses not only good selectivity, but also high activity and resistance to coking. It is 25 times as active as the Pt/Al₂O₃ catalyst but, unlike the latter, is little poisoned with the coke and retains its catalytic activity for a long time. The addition of methylcyclopentane to n-heptane results in slow deactivation of the catalyst due to blocking of active centres by the alkenes formed, which are readily hydrogenated. Moderate heating of the catalyst in an oxygen atmosphere is sufficient for its regeneration.²³³

High catalytic activity in the hydrogenation of isopropylbenzene is exhibited by molybdenum oxynitride. In this reaction its activity is increased due to carbidisation:²³⁴ MoN_{0.7}O_{0.7} is transformed into MoC_{0.27}N_{0.14}O_{0.76}.

VII. Mechanochemical treatment of hydrogenation catalysts

In most cases, mechanochemical treatment of solids leads to their fragmentation and the appearance of various defects. Many investigators have used mechanochemical techniques for the treatment of catalysts, since the catalytic activity usually (though not always) increases with the surface area and the number of defects. It is important that the changes obtained are preserved under catalysis conditions.

Moroz *et al.*²³⁵ studied the formation of defects in the mechanochemical treatment of a typical ZnO catalyst in a planetary centrifuge mill using stainless steel balls 0.5 cm in diameter. Electron microscopy and X-ray data showed that short mechanochemical impacts ($\tau < 180$ s) produce insignificant changes in the structure and size of the particles. At $180 \text{ s} < \tau < 600 \text{ s}$, one observes cracking of crystalline blocks, their mutual displacement, and rotation, relaxation of microdistortions in the direction (001) and their growth in other directions. At $600 \text{ s} < \tau < 1200 \text{ s}$ the crystals begin to undergo disintegration into primary crystalline blocks 5–10 nm in size with the formation of secondary aggregates of globular shape 1000 nm in size along with relaxation of microdistortions arising as a result of crystal breakdown. Thus, the general picture is not reduced to a mere increase in the catalyst surface and defectiveness of its lattice.

Streletskii *et al.*²³⁶ investigated the mechanism of changes induced by mechanical treatment of complex oxides with the perovskite structure. Powders of BaTiO₃ and SrTiO₃ were subjected to mechanical treatment in an eccentric mill with calorimetric measurement of the absorbed energy dose.²³⁷ The increase in the absorbed energy dose led to an increase in the specific surface from 7–8 to 25 m² g^{−1}, a decrease in the coherent scattering range (CSR) from 150 to 20 nm, and to the appearance of microdistortions and point defects (paramagnetic centres with a concentration up to 10¹⁸ g^{−1}). Each particle of the powder was shown to consist of several CSR blocks, the overall area of CSR being $\sim 60 \text{ m}^2 \text{ g}^{-1}$. Only a small fraction of the mechanochemical energy is spent in generating the defects preserved after the completion of mechanical treatment. The temperature of sintering of particles after mechanical treatment decreases by 300 °C. When such a treatment is performed in water, the CSR size corresponds to the particle size, while microdistortions are insignificant.

The mechanism underlying the mechanochemical transformations depends on the chemical and electronic properties of solids.²³⁸ In covalent dielectrics, *e.g.* in SiO₂, the defects after mechanical treatment are better preserved than in semiconducting metals. The application of mechanochemical techniques in the synthesis of catalysts can result not only in the formation of defects and an increased surface, but also in various chemical effects. In such a way one can prepare, for example, FeAl or FeW alloys, which cannot be formed in the usual processes because of the low mobility of the atoms, and even amorphous alloys. Recourse to mechanochemical treatment is often made in the synthesis of complex oxide systems from oxide mixtures, where the conventional thermal synthesis requires very high temperatures, which are difficult to achieve. Mechanochemical decomposition of salts and hydroxides may be used to prepare oxides with the preservation of the disordered state of their atomic structures.

There are some studies^{85,215} of the effect of mechanochemical treatment on the properties of catalysts in CO hydrogenation. We have already mentioned the formation of the two-phase oxide–carbide system in the catalyst based on α -Fe₂O₃ under the conditions of CO hydrogenation. A catalyst prepared from α -Fe₂O₃ after its treatment at high pressure with shearing on the Bridgman anvil was also studied. Such a mechanochemical treatment is known to form a great number of defects. The impact of the reaction medium on the ‘defective’ specimen is manifested

earlier than on the 'defect-free' one. In the first stage, the defective $\alpha\text{-Fe}_2\text{O}_3$ is rapidly transformed into magnetite, however its catalytic activity is lower than that of the defect-free specimen. Electron microscopy of the defective specimen reveals individual oxide and carbide particles and a small number of intercalated particles. The particle size in this specimen is smaller than that in the defect-free specimen, but the extension of the carbide-oxide interface, which determines the catalytic activity, is also smaller.

The CO hydrogenation reaction was also used for an investigation of the activity of amorphous, highly dispersed Fe-Ni-O alloys prepared by friction between two rapidly rotating discs made of iron and nickel. By modifying the friction conditions, it was possible to prepare an alloy of $\text{Fe}_{20}\text{Ni}_{20}\text{O}_{60}$ composition on the surface of which clusters are formed with a predominantly ionic type of Fe-O bonds, and an $\text{Fe}_{30}\text{Ni}_{40}\text{O}_{30}$ alloy in which, according to XPES and Auger spectroscopy, clusters with covalent-type of Fe-O bonds are prevalent. The former alloy is catalytically active in the CO hydrogenation to CH_4 and $\text{C}_2\text{-C}_4$ hydrocarbons, while the latter proved to be inactive. Under catalysis conditions a non-stoichiometric oxide $\text{Fe}_3\text{O}_{4-x}$, carbide FeC_y and metallic nickel are formed on the former alloy. The surface of the latter alloy is covered by a nonreactive oxide FeO_x , while in its bulk the spinel NiFe_2O_4 and a solid solution of iron in nickel are formed.

The formation of active centres of CO hydrogenation is crucially influenced by the type of chemical bonding. Iron carbide and oxide phases exist on the surface of active catalysts, while metallic iron does not take part in the active centre formation. In a binary alloy catalyst, iron is mostly in the oxidised state, while nickel is predominantly in the metallic state. The activation of H_2 seems to take place on Ni, whereas the CO activation occurs on Fe^{n+} .

The Fischer-Tropsch synthesis was brought about directly in a mechanochemical reactor by grinding the metal mixtures.²³⁹ Grinding allows formation of amorphous alloys $\text{Ni}_{40}\text{Zr}_{60}$, $\text{Ni}_{60}\text{Zr}_{40}$, $\text{Pd}_{30}\text{Zr}_{70}$, $\text{M}_{30}\text{Ti}_{70}$ ($\text{M} = \text{Fe}, \text{Co}, \text{Cu}$), $\text{M}_{30}\text{Ti}_{70}$ ($\text{M} = \text{Ni}, \text{Pd}$), which catalyse the CO hydrogenation. The alloy $\text{Ni}_{30}\text{Ti}_{70}$ manifests 100% selectivity. Detailed studies of structural changes in Ni-Zr alloys in the course of CO hydrogenation showed that prolonged grinding results in the formation of ZrO , ZrO_2 , Ni, and possibly ZrH_2 and ZrC phases. Zirconium oxides are formed due to CO dissociation on the segregated nickel. Hydrogenation of CO was also studied under the conditions of mechanochemical treatment of Ti, V and Zr hydrides. In contrast with the reaction on amorphous titanium and zirconium alloys, the formation of hydrocarbons on the above-mentioned hydrides proceeds without any induction period. The CO conversion reaches a stationary level and begins to decrease, when the hydrogen content in the metal becomes insufficient for the maintenance of the reaction stoichiometry.

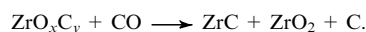
Analogous work was done by Morozova *et al.*^{240, 241} Powders of an amorphous alloy ZrNi_{1-x} were treated in a vibrational mechanochemical reactor consisting of a cylindrical steel chamber filled with steel balls 6–7 mm in diameter.²⁴² The amorphous alloy was prepared in the same reactor by mechanochemical fusion of Ni and Zr. Experiments were carried out in the static and flow modes; in the first case, the products were analysed by mass spectrometry, while in the second case, by gas chromatography.

Under conditions of mechanochemical treatment, sorption of hydrogen rapidly increased with the dose of absorbed energy and reached a maximum. The quantity of sorbed hydrogen was approximately proportional to the zirconium content in the alloy. X-Ray phase analysis indicated that the reaction of hydrogen with zirconium and ZrNi yields ZrH_2 and $\alpha\text{-ZrNiH}_2$, respectively. After the termination of mechanochemical treatment, sorption of H_2 continued at a decreasing rate until a stoichiometric hydride was formed.

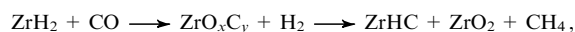
Under these conditions, chemisorption of CO increased proportionally to the absorbed energy and Zr content. It follows a dissociative mechanism and is accompanied by oxidation of Zr



In addition, reversible sorption of CO occurs, which corresponds to the nickel content. At large doses of absorbed energy, zirconium oxycarbides are decomposed

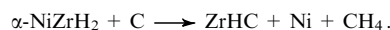


After saturation of the alloy with hydrogen, *i.e.*, after formation of ZrH_2 and ZrNiH_2 , methane, some ethane and hydrogen are formed under the conditions of mechanochemical treatment in a CO flow:



After termination of mechanochemical treatment, the formation of methane continues at a decreasing rate. Such treatment may be conducted in the flow of a CO + H_2 mixture. In this case, the rate of methane formation is 5–10 times lower than that in the stepwise process (in the hydrogenation of CO with dissolved hydrogen) under the same conditions.

In the mechanochemical treatment of a NiZr alloy, graphite also undergoes hydrogenation with formation of methane (and ethane at a high dose)



Thus, in the process of mechanochemical treatment the dissolved hydrogen acquires mobility indispensable for the realisation of reactions both on the surface and in the bulk of a powder. Interestingly, nickel, which is a typical hydrogenation catalyst, is a ballast in this case, while hydrogen is activated with participation of zirconium. In addition to the inertial process of CO hydrogenation, an inertia-free mechanochemical process leading to the formation of short-lived intermediate compounds takes place on the surface.

VIII. Sulfide catalysts for hydrotreating

1. Preparation of oxide precursors

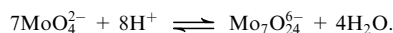
In the first sections of this review mention was made of the use of Ni-Mo, Ni-W, Co-Mo and Co-W oxide catalysts for the hydrogenation of unsaturated compounds, especially for hydrotreating. However, industrial processes rely most widely on the application of sulfide hydrotreating catalysts prepared from oxide precursors.

The major components of sulfide catalysts for hydrotreating (hydrodesulfurisation, hydrodenitration, hydrodemetalation, hydrogenation of oxygenated and aromatic compounds in petroleum) are as a rule Co (or Ni) and Mo (or W). Nickel is cheaper than cobalt and ensures a higher hydrogenation rate but it favours rehydrogenation, which results in an increased hydrogen uptake and a lower octane number of the products. Tungsten is similar to molybdenum in its catalytic properties, but it is more expensive.

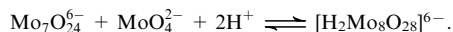
High activity is displayed by ruthenium, but this metal is very costly. The $\text{NiRu}/\text{Al}_2\text{O}_3$ catalyst is 30 times more active than $\text{RuS}/\text{Al}_2\text{O}_3$ in hydrogenation processes.²⁴³

A great number of studies (see, *e.g.*, reviews^{5, 244, 245}) are devoted to the preparation of hydrotreating catalysts, their formation under conditions of catalysis and the mechanisms underlying the relevant reactions. The common practice is to use catalysts deposited on $\gamma\text{-Al}_2\text{O}_3$ or carbon. Catalysts on $\eta\text{-Al}_2\text{O}_3$ are more active than those on $\gamma\text{-Al}_2\text{O}_3$, which is explained by the stronger bonding of MoO_3 with $\eta\text{-Al}_2\text{O}_3$ and easier subsequent sulfidisation.²⁴⁶

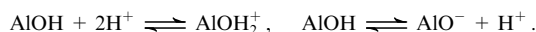
Ammonium molybdate $(\text{NH}_4)_2\text{MoO}_4$ is a precursor of MoO_3 . In acidic media, polymolybdates are formed



At high levels of ammonium molybdate, further condensation takes place



At $\text{pH} > 7$, polymolybdates dissociate to recover MoO_4^{2-} . These acid-base processes involve the surface of Al_2O_3 , which is amphoteric in its chemical nature



In order to form polymolybdates in the preparation of catalysts by the impregnation procedure, it is necessary that the pH be kept below the isoelectric point of a given support (3–6 for Al_2O_3 and below 2 for SiO_2). After impregnation, the catalyst is dried at 250–300 °C and calcined in air at 500–550 °C; the dispersity of MoO_3 changes insignificantly. The use of various physical methods (Raman and IR spectroscopy, EXAFS, and others) showed that at typical MoO_3 concentrations (10%–12%) the initial molybdates form Al–O–Mo bonds with Al_2O_3 and represent two-monolayer-thick islets containing seven molybdenum atoms.²⁴⁴

Supports may be impregnated with HPC solutions, *e.g.*, with nickel or cobalt heteropolymolybdates.²⁴⁷ In this case, however, because of the strong interaction of HPC with the OH groups of Al_2O_3 the precursor does not penetrate into the pores, and a ‘crusty’, rather than regular distribution, of the active component over the support takes place. Thioheteroanions are also used for the preparation of such catalysts.²⁴⁸

Another method for the preparation of the Mo–Al–O catalysts is the mechanical mixing of MoO_3 and Al_2O_3 at 400–500 °C in the presence of water. The system thus formed possesses virtually the same catalytic properties as an $\text{MoO}_3/\text{Al}_2\text{O}_3$ contact obtained by impregnation.²⁴⁴

A very large specific surface (174–184 m² g^{−1}) is characteristic of a catalyst prepared by precipitation of MoO_3 on SiO_2 in a solution of nitric acid with a mixture of urea and thioacetamide and with subsequent drying at 120 °C and sulfidisation at 400 °C.²⁴⁹

The second component (‘promoter’) is introduced by impregnating the support with cobalt or nickel nitrates; the sequence of impregnation steps may be different. It is assumed²⁴⁴ that impregnation of the support first with molybdenum and then with cobalt salts favours higher activity. There is an opposite viewpoint however, according to which it is more advantageous to impregnate the support first with cobalt salts or to bring about simultaneous impregnation with Co- and Mo-containing compounds. When Co^{2+} or Ni^{2+} are introduced by ion exchange, it is recommended to do it at low pH after deposition of molybdenum.

A two-stage method for the preparation of a catalyst includes impregnation of $\gamma\text{-Al}_2\text{O}_3$ in the fluidised bed with $(\text{NH}_4)_2\text{Mo}_7\text{O}_{24}$ solution at constant pH = 7, calcination in air at 500 °C, then impregnation with nickel or cobalt nitrates until the pores are filled, and further calcination at 500 °C.²⁵⁰

Active hydrogenation catalysts are prepared using thiosalts, *e.g.*, by impregnating a support with a mixture of $(\text{NH}_4)_2\text{MoS}_4$ and $\text{Ni}(\text{NO}_3)_2$ or $\text{Co}(\text{NO}_3)_2$ and subsequent heating in a mixture of H_2S and H_2 at 400 °C.²⁵¹

Unsupported Co–Mo–S catalysts are obtained by treating MoO_3 and Co_3O_4 powders with a hot solution of $(\text{NH}_4)_2\text{S}$ or by mixing solutions of $\text{Co}(\text{NO}_3)_2$ and $(\text{NH}_4)_2\text{Mo}_7\text{O}_{24}$ followed by addition of $(\text{NH}_4)_2\text{S}$, drying and calcination. In the latter case, the catalyst contains larger quantity of labile sulfur and is characterised by a higher dispersity of the Co_9S_8 phase and activity, though it is deactivated more rapidly.^{252, 253}

Lewis *et al.*²⁵⁴ assume that the catalyst activity depends on the acidity of the support. This is rationalised by the presence of surface OH groups capable of interaction with molybdenum and cobalt salts.

Catalysts are calcined at 400–600 °C, at which temperature the salts are completely decomposed but undesired solid-phase reactions have not yet occurred. According to results obtained by different physical methods,²⁴⁴ an amorphous MoO_3 phase and anions of the $(\text{Mo}_7\text{O}_{24})^{6-}$ type appear on the surface of Al_2O_3 after calcination of Mo–Al catalysts.

Calcination of mixed catalysts leads to the formation of polymolybdates, MoO_3 , CoMoO_4 or NiMoO_4 , Co_3O_4 , or NiO , $\text{Al}_2(\text{MoO}_4)_3$, $\text{Ni}(\text{Al}_x\text{MoO}_{4+1.5x})$ ($x = 0.1–1.0$) and Co or Ni aluminates.^{244, 255–258} At low calcination temperatures, the cobalt is mostly in the octahedral coordination. It is with the content of this Co form that the catalyst activity after its sulfidisation correlates. At higher temperatures, intercalation into the Al_2O_3 lattice results in the formation of tetrahedral cobalt, which undergoes sulfidisation with more difficulty. Therefore, calcination at temperatures above 600 °C is not reasonable.

Upon calcination, the nickel acquires octahedral coordination and interacts more strongly than cobalt with the Al_2O_3 lattice. Chukin *et al.*²⁵⁹ believe that the formation of nickel or cobalt molybdates or polymolybdates, which can be removed by extraction with water, is beneficial for the subsequent sulfidisation or formation of a mixed NiMo or CoMo phase. The introduction of NiMoO_4 prepared beforehand into the Ni–Mo–Al matrix makes it possible to enhance the catalyst activity.

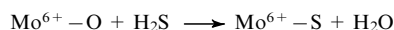
The content of the active component depends on the specific surface of the support. Usually, from 8 mass % to 15 mass % of molybdenum can be deposited on Al_2O_3 , which corresponds to a specific Al_2O_3 surface of $\sim 250 \text{ m}^2 \text{ g}^{-1}$. The Co : Mo ratio varies from 0.1 to 1.0. The ratio of molybdenum to cobalt or molybdenum to nickel depends on the sequence of impregnation steps and is equal to 2 in the best catalysts.

Active catalysts may be produced by decomposition of cobalt and molybdenum carbonyls on supports.^{260, 261}

The maximum effect of promotion of $\text{CoMo}/\gamma\text{-Al}_2\text{O}_3$ catalyst with WO_3 is attained at $\text{W} : (\text{W} + \text{Mo}) = 0.25$. Impregnation of the support first with a tungsten salt solution and then with a cobalt salt solution yields more active catalysts than those resulting from the reverse impregnation order. According to the results of EPR and XPS studies, tungsten favours the alteration of the molybdenum coordination from octahedral to tetrahedral and facilitates its reduction.²⁶²

2. Sulfidisation of oxides

Sulfidisation of $\text{Mo}/\text{Al}_2\text{O}_3$ catalysts at low temperatures leads to the substitution of the oxygen atoms by sulfur



and formation of the bridging bonds $\text{Al}-\text{O}-\text{Mo}-\text{SH}$ or $\text{Al}-\text{O}-\text{Mo} \begin{smallmatrix} \text{S} \\ \diagup \diagdown \end{smallmatrix}$ (Ref. 263).

Each of the species thus formed contains seven Mo atoms. Prolonged sulfidisation at 300 °C leads to the reduction of Mo^{6+} to Mo^{4+} and formation, as follows from electron microscopy data,^{244 264, 265} of planar hexagonal MoS_2 particles below 3 nm in size that are retained on the surface by the Mo–O–Al bonds and mostly situated normally to the Al_2O_3 surface. Sulfur-containing Co–Ni heteropolymolybdates are formed in the incomplete sulfidisation.²⁶⁶

At the optimum sulfidisation temperature (400 °C), the Mo–O–Al bonds are cleaved, and the distribution of the MoS_2 particles occurs parallel to the support surface; they are enlarged, the ratio of the basal to lateral planes of particles remaining constant. However, there is no oriented growth (epitaxy) of the MoS_2 particles on Al_2O_3 ; they are linked to each other by physical forces. The smaller the mean sizes of MoS_2 and WS_2 particles the more active the catalyst in the hydrodesulfurisation processes.²⁵⁷ Higher catalyst activity appears to be reached with the incomplete sulfidisation of MoO_3 .²⁶⁷ Complete transformation of the oxygen-containing surface phase into MoS_2 occurs only at 970 °C,

though at such a high temperature the MoS₂ phase is sintered.^{268, 269}

Apparently the nature of the support does not strongly affect the final form of molybdenum and tungsten oxides and sulfides. In most cases, Mo/C proves to be more active than Mo/Al₂O₃.²⁷⁰ Isolated molybdenum ions or highly dispersed MoO₃ particles were detected on a molybdenum catalyst deposited on activated carbon. These species are sulfidised more rapidly on carbon than on Al₂O₃: at 400 °C the sulfidisation is already completed. After the sulfidisation, MoS₂ forms plates on Al₂O₃ and three-dimensional particles on carbon. This is explained by a stronger interaction of its oxide precursor with the Al₂O₃ surface than with carbon. The catalytic activity of MoS₂ is higher on carbon than on alumina.^{271, 272}

Pratt *et al.*²⁷³ observed a somewhat different orientation of MoS₂ particles on supports: plates were found on Al₂O₃ and SiO₂ oriented normally to their surface, while on TiO₂ and ZrO₂, particles were coplanar. The latter displayed higher catalytic activity.

Treatment of a MoO₃–SiO₂ system with a H₂S + H₂ mixture at room temperature leads to the formation of MoO_xS_y. At 150 °C MoS₃ particles appear, while at 250–270 °C the MoS₂ phase is formed.²⁷⁴ Electron microscopy data showed that in a Co–Mo–S/Al₂O₃ system, MoS₂ particles are formed, and their size is increased from 1 to 1.5 nm at the sulfidisation temperature.²⁷⁵ These particles are linked to form chains. At high cobalt content, the Co₉S₈ phase is formed.²⁷⁶ In Ni–Mo–S and Ni–W–S catalysts, the phase NiS was also observed along with mixed phases.²⁷⁷

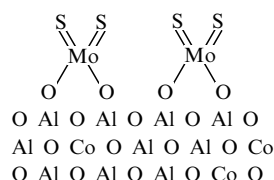
According to NMR and EXAFS data, the major active phase of a molybdenum sulfide catalyst consists of MoS₂ plates with Mo coordination number 4 or 5 and with the Co atoms at their edges.²⁴⁴ The formation of a continuous MoS₂ phase, *e.g.*, after long operation of the catalyst, leads to its deactivation. Analogous phases formed on SiO₂ or carbon are less strongly bound to these supports than to Al₂O₃.

To model sulfide hydrotreating catalysts, several layers of sulfur were applied onto the Mo(110) plane with subsequent spraying of Zn or Co.²⁷² Zinc and cobalt were found to accelerate the sulfidisation of molybdenum. The hydrodesulfurisation activity of catalysts was observed to correlate with the ease of molybdenum sulfidisation. The Mo atoms become coordinatively unsaturated in the presence of zinc or cobalt.

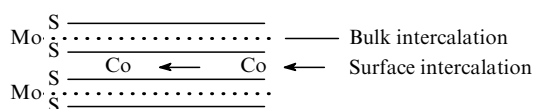
3. The role of different phases in sulfide catalysts

To elucidate the role of different phases in the active surface formation, the following models of sulfide catalysts may be considered.⁵

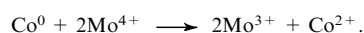
1. A structural model of a Co–Mo/Al₂O₃ catalyst implies the formation of a molybdenum monolayer on the surface of alumina.²⁷⁸ According to this model, molybdenum is bound to the Al₂O₃ surface through the OH groups, whereas Co²⁺ ions replace Al³⁺ ions in the surface layer. Due to its large size, the S^{2–} ion replaces two O^{2–} ions.



2. In the initial version of the intercalation model the cobalt (nickel) ions were supposed to intercalate between the layers of the MoS₂ (WS₂) structure.²⁷⁹ Later, it was found that intercalation inside the lattice is impossible, and the model has been modified. Now it is assumed that Co ions are intercalated near the sulfide surface:



The promoter atoms interact with MoS₂.²⁸⁰



3. According to the model of contact synergism,^{257, 281} hydrogen is activated on the Co₉S₈ or NiS phases, while the compound subject to hydrogenation is activated, on the MoS₂ phase. Hydrogen spillover takes place between these phases. A later modification of the model assumes hydrogen spillover between the CoS₂ and CoMoS phases.²⁸²

In recent times, the prevalent view is that the sulfide phases Co₉S₈ and NiS apparently play no special role in the hydrotreating processes.^{5, 283–296} The application of different physical methods (EXAFS, NMR, XPD, and others) revealed a kind of a ‘Co–Mo–S phase’ in which the Co atoms are localised on lateral facets or edges of MoS₂ microplates. According to EXAFS data, the coordination number of Co is 4 or 5. The catalyst MoS₂/Al₂O₃ undergoes no deactivation after its sulfidisation. It is the distribution of Co atoms at the edges of the MoS₂ particles that determines the optimum ratio between Co and Mo. At high Co contents all its atoms cannot be placed at the edges of the MoS₂ particles.

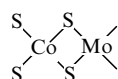
Mössbauer spectroscopy showed²⁴⁵ that the sulfidisation of CoMo/Al₂O₃ and CoMo/C leads to the formation of the same particles as in the Co/Al₂O₃ and Co/C systems, respectively. This casts doubts on the concept of the ‘Co–Mo–S phase’ and makes one suspect that the MoS₂ phase is merely a diluent. However, it is believed that the systems CoMoS/C and CoMoS/Al₂O₃ differ. The Co/C catalyst is only three times less active than CoMoS/C, whereas Co/Al₂O₃ and CoMoS/Al₂O₃ exhibit much larger differences.

According to Chianelli *et al.*,²⁴⁵ in the Co–Mo–S system the Co atoms are situated at the edges of the MoS₂ crystallites. The Co₉S₈ phase is also present; however, its function is reduced not to hydrogen spillover, but rather to the role of an additional support for the Co–Mo–S phase.

By analogy with the ‘Co–Mo–S phase’, the ‘Ni–Mo–S phase’ is also supposed to exist.^{255, 256} The nickel-modified sulfide (MoS₂) adsorbs three times as much hydrogen as the pure MoS₂.²⁹⁷ The excess phase Ni₃S₂ can be removed from the Ni–Mo catalyst by dissolution, and this does not affect its catalytic activity.²⁹⁸

Ekman *et al.*²⁹⁹ synthesised catalysts based on the so-called Chevrel phases (M₃Mo₆Z₈, where Z = S, Se or Te and M is a transition metal). In these phases, the transition metal cations may be localised not at the edges but inside the sulfide phase. Such systems differ from the usual mixed sulfide catalysts.

The results of ⁵⁹Co NMR suggested^{287, 300} that the high activity of a Co–Mo–S system is associated with the presence of Co atoms with perturbed tetrahedral environments. In this system, octahedral cobalt is also present but the catalytic activity correlates only with the concentration of the tetrahedral cobalt. The active centre is assumed to have the following structure:



Electron exchange stabilises the structure Co_{tetr}–S–Co_{oct}–S–Mo–S.

The appearance of the NiWO₄ phase in the Ni–W–Al catalysts upon calcination of an NiO + WO₃ mixture decreases the efficiency of subsequent reduction and sulfidisation. This results in the formation of an unordered WS₂ phase and of Ni²⁺ and Ni³⁺ ions rather than an NiS phase.^{301, 302} The higher activity of an Ni–W/C catalyst than that of Ni–W/Al₂O₃ is supposed³⁰³

to be due to the fact that the active nickel in the former is linked to six sulfur atoms. The major advantage of the use of carbon as the support apparently lies in the fact that, in contrast to Al_2O_3 , it has no acidic properties and does not undergo coking.³⁰⁴

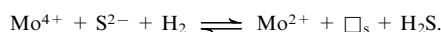
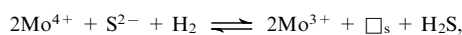
The role of cobalt (nickel) in a mixed catalyst may be dual. Presumably, cobalt (or nickel) favours the reduction of MoO_3 ³⁰⁵ or WO_3 .³⁰⁶ According to the opposite viewpoint,³⁰⁷ Ni^{3+} incorporated into the MoO_3 layer decreases its susceptibility to reduction. It is also believed^{268, 285, 299, 308, 309} that cobalt stabilises the dispersed MoS_2 microparticles preventing them from sintering. Some investigators^{283, 286, 300, 301} presume that Co does not increase the MoS_2 dispersity, but participates instead in the hydrogen activation. There are also reports^{310–312} that cobalt accelerates the sulfidation of MoO_3 and suppresses deactivation of catalysts after sulfidation.^{287, 313}

In the $\text{CoMoS}/\text{Al}_2\text{O}_3$ system, sulfur is hydrogenated at a lower temperature than in the $\text{CoS}/\text{Al}_2\text{O}_3$ or $\text{MoS}_2/\text{Al}_2\text{O}_3$ systems. The ease of sulfur hydrogenation correlates with the catalytic activity.³¹⁴ A higher rate of sulfur hydrogenation within MoS_2 was also observed when Co, Ni or Fe were deposited on a MoS_2 plate.³¹⁵

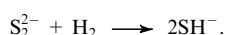
The presence of Ni in a Ni–Mo hydrodesulfurisation catalyst promotes the reduction of MoO_3 to MoO_2 and partly to Mo .³⁰⁸ Thus, nickel can act as a catalyst for MoO_3 reduction. Cobalt also accelerates the reduction of Mo(VI) to Mo(IV) and even to Mo(III) .^{316, 317} In this case, some vacancies appear in the sulfide layer.

4. The hydrodesulfurisation mechanism

The most popular hydrodesulfurisation mechanism includes the formation of anion vacancies in the sulfide layer and their subsequent filling with sulfur from a sulfur-containing compound, e.g., thiophene.^{244, 278, 318, 319} The thiophene molecules are adsorbed normal to the surface. The vacancies may either be initially present in the MoS_2 phase, most probably at the edges of the microplates, or be formed in the course of sulfide reduction with hydrogen



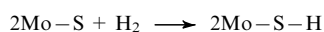
Low-valent forms of molybdenum were in fact revealed by IR spectroscopy and EPR. The use of these techniques also provided evidence of S–H group formation under catalysis conditions, while XPS revealed low-valent sulfur in the form of S^- or $(\text{S}-\text{S})^{2-}$.^{316, 320, 321} The disulfide groups, possibly localised at the MoS_2 edges, may take part in the hydrogen activation.



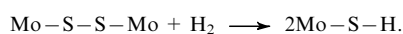
Hydrogen forms in sulfide catalysts were studied by IR spectroscopy and neutron diffraction.³²² No bands corresponding to vibrations of the Co–H and Mo–H bonds were found after the adsorption of H_2 in the systems $\text{CoMo}_{1.3}\text{S}_{1.6}$, MoS_2 and Co_9S_8 , but S–H vibrations bands were observed. This led to the conclusion that in the course of H_2 adsorption processes of the type



do not occur, giving way to the reaction

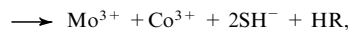
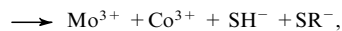


or



The Co (Ni) atoms may be directly involved in the formation of active centres or neighbours with the vacancy at the peripheral molybdenum atom. The number of cobalt atoms in the catalyst was observed to correlate with the number of peripheral molybdenum atoms. According to EXAFS,^{323, 324} the vacancies are formed near the cobalt atoms. This was confirmed in particular by experiments on the adsorption of selenophene (a thiophene

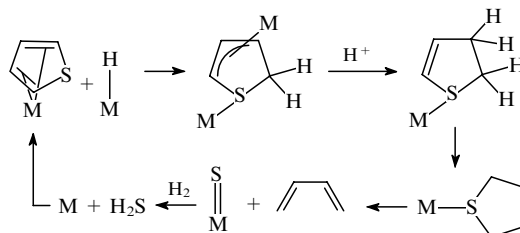
analogue).³²⁵ The vacancies available in the $\text{Co}_x\text{Mo}_{1-x}\text{S}_{2\pm\delta}$ phase are involved in the following reactions:



According to the results of TPR,³²⁶ sulfur is more weakly bound in the Co–Mo–S system than in Co_9S_8 or MoS_2 : the H_2S peak is observed at a lower temperature. However, an investigation of the isotope exchange of labelled hydrogen sulfide H_2^{35}S with the $\text{NiS}/\text{Al}_2\text{O}_3$, $\text{MoS}_2/\text{Al}_2\text{O}_3$, and $\text{NiMoS}/\text{Al}_2\text{O}_3$ catalysts unexpectedly showed that the exchange rate on $\text{NiMoS}/\text{Al}_2\text{O}_3$ was lower than on $\text{MoS}_2/\text{Al}_2\text{O}_3$, which in turn was lower than on $\text{NiS}/\text{Al}_2\text{O}_3$.³²⁷ This surprising finding was explained by the participation of sulfur atoms bound to both molybdenum and nickel in the reaction. The results reported by Topsøe *et al.*³²⁶ may also be explained by the associative mechanism of this reaction without participation of vacancies.

Experiments with ^{35}S showed that the loss of sulfur from the catalyst as a result of its interaction with hydrogen can be compensated for at the expense of thiophene sulfur.³¹⁸ The quantity of mobile sulfur and the catalytic activity increase in the presence of promoters (Co, Ni).

According to Markel *et al.*,^{328, 329} dihydrothiophene is formed as an intermediate in the reaction of thiophene hydrodesulfurisation



The idea of an associative mechanism underlying the hydrogenolysis of thiophene without participation of the sulfide layer vacancies was also put forward by Startsev,³²³ who assumed that thiophene is adsorbed on the Co(Ni)–Mo–S catalyst in the coordination sphere of cobalt, while dissociative adsorption of H_2 takes place at the terminal sulfur atoms flanking the electroneutral macromolecule MoS_2 . This viewpoint stands in need of more conclusive evidence.

Different opinions exist as to the nature of the active centres in the hydrogenation of various organic compounds. According to the most popular concepts, the role of the active centres in the hydrodesulfurisation is played by the molybdenum or cobalt atoms on the lateral facets of MoS_2 .⁵ The activity of hydrodesulfurisation catalysts was found to be proportional to the number of centres on the lateral facets of MoS_2 determined by the EXAFS method *in situ*.³²⁶ There is a relationship between the activity of catalysts and the concentration of Mo^{5+} in them (according to EPR data).³³⁰ The activity of WS_2 in the hydrogenation of benzene correlates with the concentration of $\square_{\text{s}}$ vacancies on the lateral sulfide facets measured by EPR.²⁷⁵

The mechanism of thiophene hydrodesulfurisation on the Co–Mo/ Al_2O_3 catalyst was investigated using the TPD and TPR techniques and D–H isotope exchange.^{331–335} The TPR and TPD spectra of thiophene, dihydrothiophene, and butane-thiol were found to be very similar on $\text{Mo}/\text{Al}_2\text{O}_3$ and Co–Mo/ Al_2O_3 , but somewhat shifted towards lower concentrations on the Co-containing catalyst. At the same time, the shape of the spectra on Co/ Al_2O_3 was completely different and most of the products formed in the first two systems under TPR conditions were not

produced in the latter case, whereas hydrogen was desorbed at a lower temperature. These results confirm the traditional viewpoint, according to which thiophene is adsorbed on the anionic vacancies of MoS₂, while hydrogen is activated on cobalt. We cannot say whether the Co and Mo centres are situated in different phases or in different crystallographic positions of the same phase, though they do not appear to be spatially separated. In any event, no results have been reported to disprove this viewpoint.

Desorption of thiophene at low temperatures characteristic of all catalysts is most likely to occur from the weakly bound π -adsorbed state. The high-temperature desorption of thiophene characteristic of Mo/Al₂O₃ and Co/Al₂O₃ catalysts seems to be related to the dehydrogenated forms. In such cases, strong retention of molecules by the surface is ensured by both the bonding of the sulfur atom and the σ -bonds (possibly several) of carbon atoms in the ring. When there is a surface hydrogen shortage the limiting stage of the thiophene desorption may be the interaction of such surface complexes with the hydrogen atoms.

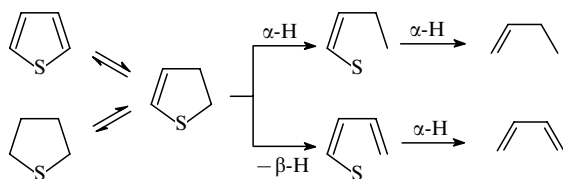
To bring about desulfurisation, it is necessary to activate the adsorbed molecule of the S-containing compound. This first requires the formation of sufficiently strong bonding of the sulfur atom with the surface and, second, surrounding of the reacting sulfur-containing molecule with hydrogen atoms situated in the immediate proximity. Under TPR conditions, such a complex may be formed with the participation of migrating hydrogen according to the mechanism of reverse spillover from the support.

The coincidence of kinetic parameters for the formation of C₄ hydrocarbons from thiophene and tetrahydrothiophene indicates that the hydrodesulfurisation of these compounds on Mo and Co–Mo catalysts proceeds *via* the same intermediates, probably dihydrothiophenes.

Markedly easier desulfurisation of thiols than of thiophene and tetrahydrothiophene may suggest that the cleavage of the second C–S bond in the surface intermediates is not the limiting stage of the entire hydrodesulfurisation process.

In contrast with the desulfurisation of tetrahydrothiophene and thiophene, butadiene is absent from the products of butanethiol desulfuration, which indicates that the surface butanethiolate cannot be an intermediate compound in the hydrodesulfurisation of thiophene and tetrahydrothiophene, at least under low hydrogen pressure in the gaseous phase.

Rozanov *et al.*³³⁴ proposed the following generalised scheme for the desulfurisation mechanism:



According to this scheme, thiophene and tetrahydrothiophene can be interconverted *via* dihydrothiophene as the intermediate compound. Depending on the hydrogen pressure and the reaction temperature, equilibrium may be shifted towards thiophene or tetrahydrothiophene. Butene may be formed from the intermediate dihydrothiophene as a result of two-stage hydrogenolysis of α -C with concomitant cleavage of the C–S bond, while butadiene may result from β -elimination in the first stage and α -hydrogenolysis in the second stage. Presumably, hydrogenation–dehydrogenation reactions occur on one type of centres, while hydrodesulfurisation occurs on another type of centre. The limiting stage of the whole process is the cleavage of the C–S bond.

This conclusion was drawn from studies on the hydrodesulfurisation of thiophene on Rh₂S₃, Co/C, and Mo/C catalysts.³³⁶ It can be mentioned that the limiting stage of the reaction on Co–Mo/C is hydrogenation, which determines the low selectivity of formation of hydrogenation products in this case.

Some investigators believe that hydrodesulfurisation and hydrogenation take place on the same active centres,³³⁷ while others think that these centres are different.³³⁸ Hydrogenation of propylene requires molybdenum(IV), and hydrogenolysis of propane occurs on the more reduced Mo forms, up to its metallic state. On different supports, one may observe different orientations of MoS₂ and Co–Mo–S particles.³³⁹ When these particles are deposited on Al₂O₃, their activity in the hydrogenation is higher and that in the hydrocracking is lower than in their deposition on Al₂O₃·SiO₂, MgO·SiO₂ or MgO. The molybdenum- and cobalt-containing phases have no synergistic effect in the hydrodesulfurisation of thiophene, but they do manifest this effect in the hydrogenation of butenes and butadiene.³¹⁸ In contrast to Co–Mo–S, the Ni–W–S system accelerates hydrogenation of biphenyl more strongly than hydrodesulfurisation of dibenzothiophene.³⁴⁰ According to Topsøe *et al.*,⁵ the stronger deactivating effect of H₂S on Co–Mo–S catalysts in the hydrogenation of aromatic compounds than in the hydrogenation of alkenes is indicative of the difference between the active centres in these reactions.

In conclusion, it is noteworthy that the reactions of hydrogenation and hydrodesulfurisation on Co(Ni)–Mo(W) catalysts are the best studied catalytic processes, judging from the number of publications devoted to them. Nonetheless, the mechanism of these reactions has not been totally elucidated and remains the subject of numerous discussions. This also holds for the preparation of hydrotreating catalysts. Studies in which the reaction mechanism was investigated by physical methods *in situ* are virtually absent. Without an adequate understanding of the mechanism of the process, it is impossible to develop scientific grounds for the preparation of catalysts. To this end it is necessary to elucidate what component of the catalysts activates hydrogen and what component activates an organic compound, and how to distribute these components most effectively on supports.

IX. Conclusion

The aim of this review was to consider hydrogenation catalysts, including modified supported Ni catalysts, carbides, sulfides, and others that have been most actively studied in recent years.

Investigation into the mechanism of action of hydrogenation catalysts by physicochemical methods made it possible to reveal some of their common features. It was found that hydrogen and compounds subject to hydrogenation are, as a rule, activated on different active centres: the former, on metallic (or reduced) centres, the latter, on oxidised centres which are often formed by ions of the basal metal intercalated into supports or modifiers. Hydrogen transport between centres may be brought about by the spillover mechanism. Therefore, the role of support or modifier is often played by systems capable of accumulating hydrogen. The secondary structure of the support and catalyst (specific surface, dispersity, porosity) has a significant effect on the supply of hydrogen to the compound under hydrogenation, as well as on the thermostability and selectivity of catalytic systems.

Co-precipitated metal–oxide catalysts, complex oxides, skeletal catalysts, and hydrides of intermetallides, which are also actively studied nowadays, remained almost totally outside the scope of this review.

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Synthesis of reactive nucleic acid analogues and their application for the study of structure and functions of biopolymers

I E Kanevskii, S A Kuznetsova

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Abstract. Data on the synthesis of reactive derivatives of nucleic acid analogues and their application for the study of structure and functions of biopolymers are generalised. The main types of such analogues including photoactivated reagents containing azido-aryl, halogeno, and thiol groups, psoralen and its derivatives, platinum-based reagents, and nucleic acid analogues containing substituted pyrophosphate or acyl phosphate internucleotide groups are presented. The mechanisms of interaction of these compounds with proteins and nucleic acids are considered. The prospects for the *in vivo* application of reactive nucleic acids in various systems are discussed. The bibliography includes 76 references.

I. Introduction

Synthetic fragments of nucleic acids containing modified units are widely employed in solving practical problems of molecular biology, biotechnology, and medicine. Derivatives of nucleic acids containing reactive groups are of special interest. These compounds can form covalent bonds with the reactive groups of biopolymers and are promising tools for the study of the topography of active centres of proteins, their functional features, and molecular mechanisms of DNA–protein recognition. The interest in these compounds has been considerably increased in recent years owing to the development of sense biotechnology. The main attention is concentrated on the search for new active groups and elaboration of methods for their directed introduction into nucleic acids.

This review describes the main types of reactive analogues of nucleic acids, *viz.*, photoactivated reagents, platinum-based reagents, and new promising analogues of nucleic acids containing substituted pyrophosphate or acyl phosphate internucleotide groups. The use of reactive nucleic acids in the analysis of proteins and nucleic acids and prospects for their further application in various systems *in vivo* are surveyed. A large class of alkylating reagents first proposed by Grineva and Knorre in the late 60's is

beyond the scope of this review because this material has been considered rather comprehensively in recent reviews (see, *e.g.*, Refs 1, 2). For the same reason, reagents with redox mechanisms of action^{1,2} have been omitted from consideration.

II. Photoactivated nucleic acid analogues

In recent years, reactive nucleic acids containing photoactivated groups have gained wide acceptance as helpful tools for directed modification of proteins and nucleic acids and for the investigation of the structure and functions of these biopolymers. Normally, groups that are activated upon irradiation with light of wavelength > 300 nm are employed. This excludes the possibility of other photochemical transformations of the biopolymers themselves.

Among photoactivated compounds, nucleic acid analogues carrying azidoaryl, halogeno, or mercapto groups and various psoralen derivatives are the most popular.

1. Nucleic acid derivatives containing the azido group

Reactive azido derivatives of oligonucleotides include synthetic oligonucleotides that are modified at the sugar-phosphate backbone or at heterocyclic bases by reagents containing the azido group. Irradiation converts them into reactive intermediates (nitrenes), which can further react with reactive groups of proteins and nucleic acids.

a. Introduction of azidoaryl groups into nucleic acids

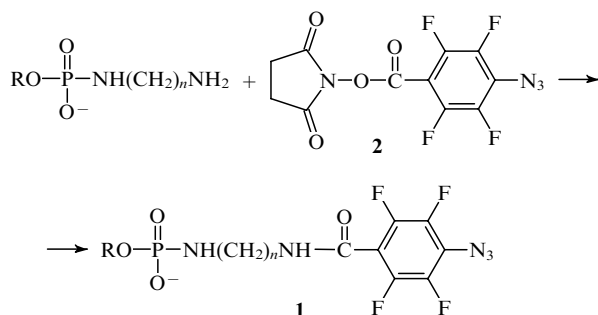
Azidoaryl groups are introduced into synthetic oligonucleotides either in the course of their synthesis with the use of modified nucleotide components³ or by postsynthetic modification of oligonucleotides by various aryl azide derivatives. The most popular reagents contain *p*-azidophenyl, 2-nitro-5-azidophenyl, and azidoperfluorophenyl groups,^{4,5} or azidoproflavin.⁶

Synthesis of azido derivatives of oligonucleotides makes use of the reactive groups inherent or incorporated into the oligonucleotides. The latter kind of groups involves aliphatic amino and thiol groups. Thus, an oligodeoxyribonucleotide azidoperfluorophenyl derivative **1** was obtained by acylation of the terminal amino group that had been introduced into the oligonucleotide using *p*-azidotetrafluorobenzoic acid *N*-hydroxysuccinimide ester **2**.⁵

I E Kanevskii, S A Kuznetsova Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119899 Moscow, Russian Federation. Fax (7-095) 939 31 81. Tel. (7-095) 939 31 53

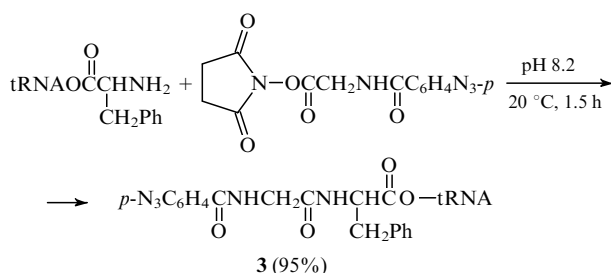
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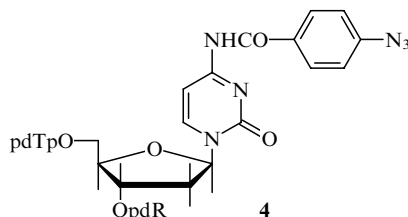


R is the oligodeoxyribonucleotide residue, $n = 2$ or 6 .

The azido derivative of *E. coli* tRNA^{Phe} **3** was obtained by acylation of the amino group of the phenylalanine residue that had been introduced into tRNA with *N*-(*p*-azidobenzoyl)glycine *N*-hydroxysuccinimide ester.⁷

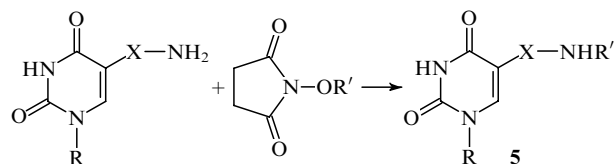


A similar approach was used to introduce the azido group at the exocyclic amino group of cytidine. *p*-Azidobenzoic acid *N*-hydroxysuccinimide ester was used as the acylating reagent. This reaction gave the pentanucleotide azido derivative **4**.⁸

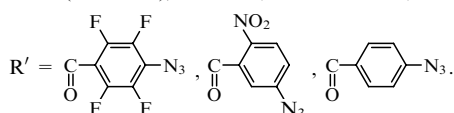


R — TAG

Various azido derivatives of the oligonucleotide d(UCCAATT) **5** were obtained by acylation of the amino group attached through a spacer to C(5) of the terminal deoxyuridine residue with *p*-azidotetrafluoro-, 5-azido-2-nitro-, or *p*-azidobenzoic acids *N*-hydroxysuccinimide esters.^{4,9}

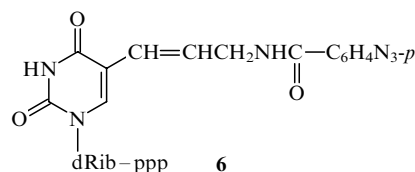


R = d(CCACTT); X = CH₂, CH₂OCH₂CH₂, CH₂NHCOCH₂CH₂;

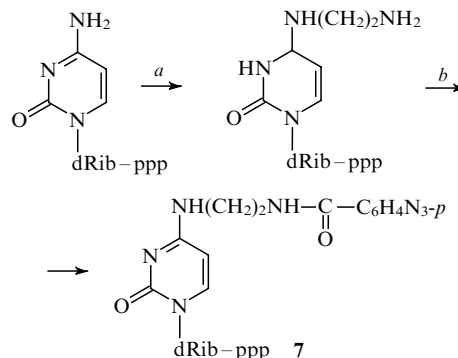


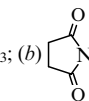
5-[3-(*p*-Azidobenzoyl)aminoprop-1-enyl]deoxyuridine 5'-triphosphate (**6**) was used to incorporate the azido group into the tRNA^{Tyr} SUP4 gene. This compound was obtained by the reaction of 5-(3-aminoprop-1-enyl)deoxyuridine 5'-triphosphate with *p*-azidobenzoic acid *N*-hydroxysuccinimide ester (DMF, pH 8.5, 20 °C, 3 h in the dark).¹⁰ This was followed by incorporation of compound **6** into DNA using DNA polymerase T4. The DNA thus modified was used for probing DNA–protein contacts

in a specific transcription complex comprising the modified DNA, RNA polymerase III, and several transcription factors.



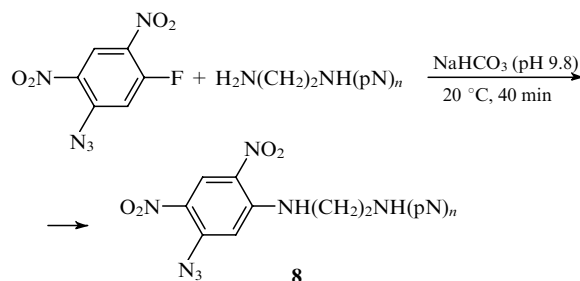
Recently, a novel azido-containing reagent 4-[2-(*p*-azidobenzoyl)aminoethyl]deoxycytidine 5'-triphosphate (**7**) has been proposed for this purpose.¹¹ This compound was also obtained using azidobenzoic acid *N*-hydroxysuccinimide ester.



(a) H₂N(CH₂)₂NH₂, NaHSO₃; (b) , pH 8.5, 3 h, 20 °C.

The first step of this synthesis included the hydrogen sulfite-catalysed transamination of the amino group of deoxycytidine 5'-triphosphate with ethylenediamine and isolation of the reaction product by column chromatography. The reaction of 4-(2-aminoethyl)deoxycytidine 5'-triphosphate with a 10-fold excess of *p*-azidobenzoic acid *N*-hydroxysuccinimide ester was conducted at reduced illumination. The target product **7** was also isolated by column chromatography and analysed by TLC. Compound **7** was introduced into a specific region of the tRNA^{Tyr} SUP4 gene. The modified DNA was used for the probing of DNA–protein contacts in the transcription complex.

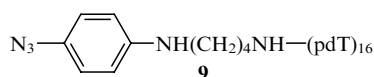
The reaction of 5-fluoro-2,4-dinitrophenylazide with the amino group of the ethylenediamine spacer attached at the terminal phosphate group of oligoribonucleotides gave photoactivated analogues of mRNA **8**, which represent oligoribonucleotide derivatives of various lengths having an arylazido group at the 5'-end of the oligoribonucleotide fragment.¹²



pN = pA, $n = 5$; pN = pU, $n = 4, 7$, and 8 .

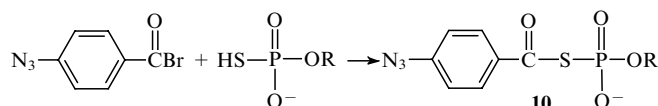
The reagents **8** were used for affinity modification of the 5'-region of the mRNA-binding centre of the *E. coli* ribosome.

To study the localisation of the protein environment of DNA in chromatin, Kobets *et al.*¹³ have used a photoactivated derivative of hexadecathymidylate **9**, in which the *p*-azidoaniline residue was linked to the 5'-terminal phosphate group through a 1,4-butanediamine spacer.



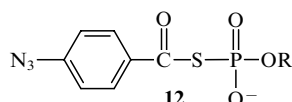
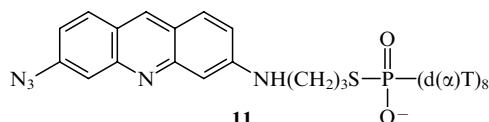
Compound **9** was obtained by phosphorylation of 4-(*p*-azidoanilino)butylamine with the oligonucleotide *N*-methylimidazolid. Earlier, Godovikova *et al.*¹⁴ have studied the ability of amino acid residues to undergo modification by oligonucleotide derivatives in which the *p*-azidoaniline fragment was linked to the terminal phosphate group of the oligonucleotide directly rather than through a spacer. It was found that these reagents yield *p*-benzoquinonimide derivatives on irradiation and subsequent reaction with amino acids results in splitting of the reagent from the oligonucleotide. On the contrary, modification of proteins with reagents of the type **9** occurs specifically to give covalently bound nucleic acid–protein complexes.¹³

In addition to arylation and aroylation of aliphatic amino groups, alkylation or acylation of a thiol group that had been introduced into oligonucleotides is also employed for the preparation of azido derivatives of oligonucleotides using the corresponding halide derivatives of aryl azides. Thus acylation of the 5'-terminal thiophosphate of oligothymidylate with *p*-azidobenzoyl bromide gives the *p*-azidobenzoyl derivative **10**.¹⁵



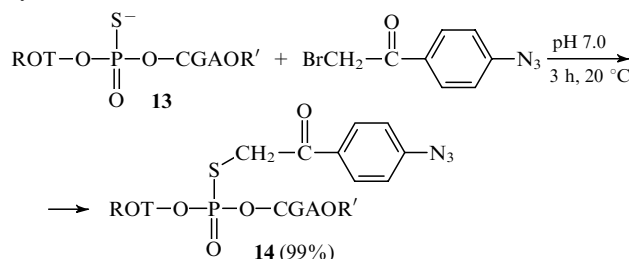
R is the oligothymidylate residue.

Analogously, the reaction of 3-azido-6-(3-bromopropylamino)acridine⁶ or *p*-azidobenzoyl bromide¹⁶ with the terminal thiophosphate group of oligothymidylate yielded azidoproflavin (**11**) or *p*-azidobenzoyl (**12**) derivatives of oligonucleotides, respectively.



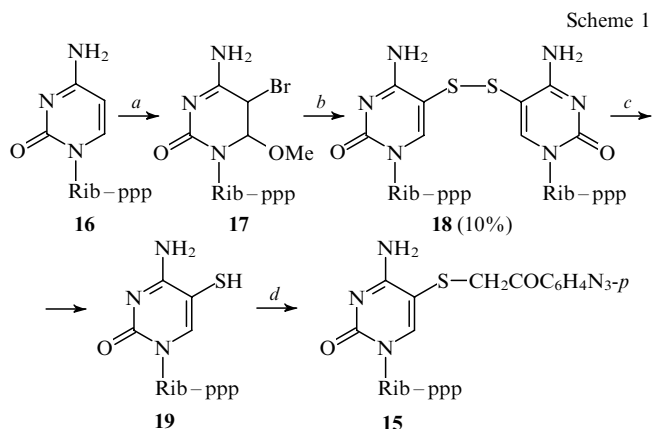
R is the oligodeoxyribonucleotide residue.

p-Azidophenacyl bromide¹⁷ was also used for modification of the oligonucleotide **13** containing an internucleotide thiophosphate group that had been introduced in the oligonucleotide synthesis.¹⁷



R and R' are fragments of the oligonucleotide sequence.

The azido group can be incorporated through a thiol group into a heterocyclic base as well. Thus 5-[(4-azidophenacyl)thio]cytidine 5'-triphosphate (**15**) has been synthesized according to Scheme 1.¹⁸ All the reactions were carried out in the dark or under reduced illumination.



(a) MeOBr, 4 °C, 12–24 h; (b) Na₂S₂, 4 °C, 5 h; 20 °C, 48 h; (c) NaBH₄, H₂O, 0 °C, 3 h; (d) BrCH₂COC₆H₄N₃-*p*, DMSO, 4 °C, 12 h.

Treatment of cytidine 5'-triphosphate **16** with methyl hypobromite gave a bromomethoxy derivative **17**. The reaction product of compound **17** with sodium disulfide was isolated by extraction and column chromatography. The yield of 5,5'-dithio-bis(cytidine 5'-triphosphate) **18** was 10%. Such a low yield was attributed to the negative charge of both reacting molecules.¹⁸ An alternative route to the disulfide from a nucleoside was also attempted.¹⁸ In this case, the yield of the reaction products was much higher. Then, the 2'- and 3'-OH groups of ribose were protected and the 5'-OH group of the disulfide derivative was phosphorylated. The final stage of this synthesis was more complicated and labourious due to a greater number of purification steps and more complex isolation procedure of intermediate compounds, which resulted in nearly the same yield of 5,5'-dithio-bis(cytidine 5'-triphosphate) **18**. 5-Mercaptocytidine 5'-triphosphate **19** was obtained from compound **18** by reduction with sodium borohydride. The reaction mixture was treated with *p*-azidophenacyl bromide in DMSO. The target product **15** was isolated by extraction and column chromatography (80% yield). The azido derivative of the nucleoside triphosphate **15** was introduced into various positions of RNA in the course of polymerase synthesis.

Thus, the methods available allow one to incorporate the azidoaryl groups both into heterocyclic bases of nucleic acids and the sugar-phosphate backbone. They involve acylation of aliphatic amino groups of nucleic acids with *N*-hydroxysuccinimide esters of azidobenzoic acid and its derivatives or alkylation (acylation) of a thiol group that had been introduced into nucleic acids using the corresponding azidoaryl halides. As a rule, these reactions occur with high efficiency (the product yield is 80%–99%). However, whereas the former route makes use of the exocyclic amino groups of heterocyclic bases of nucleic acids for the incorporation of the azido groups, in the case of azidoaryl halides an additional step is required, *viz.*, the incorporation of a thiol group into nucleic acids. This may complicate the procedure and reduce the yields of the target products.

b. Cross-coupling of nucleic acid derivatives containing the azido groups with biopolymers

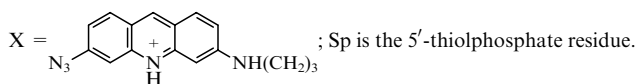
On irradiation with light (photolysis), compounds containing azidoaryl groups generate highly reactive short-lived radicals, *viz.*, nitrenes. In the singlet state, the lifetime of nitrenes depends on the nature of substituents in the aromatic nucleus and varies from nano- to microseconds.¹⁹ This state of nitrene radicals is very unstable: they either undergo intramolecular rearrangements to yield various reactive intermediates or react with neighbouring reactive groups. In the latter case, intermolecular covalent bonds may be formed. Using azidophenyl derivatives as examples, it has been shown that introduction of fluorine atoms or nitro groups into the benzene ring decreases the probability of intramolecular

rearrangements and simultaneously increases the probability of nitrene involvement in intermolecular reactions.²⁰

For the first time, azido derivatives of oligonucleotides have been used for the study of the formation of cross-coupled DNA duplexes **20** from a 27-membered matrix oligonucleotide and a complementary octa(α -thymidylate) carrying an azidoproflavin residue linked with the 5'-thiolphosphate group of the α -anomer through a spacer arm.⁶

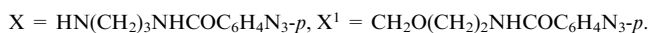
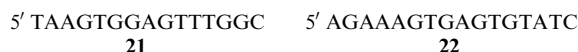


20



UV irradiation of oligonucleotides constituting the system **20** ($\lambda > 300$ nm) in 0.1 M NaCl resulted in cross-linking. The photoaddition product was treated with an alkali, which resulted in selective cleavage at modification sites. The residues T⁹ and T¹⁸ (1 : 3) of the DNA template were found to be the main sites of this cleavage. This ratio was rationalised by postulating parallel and antiparallel orientations of the oligonucleotide probe during the formation of a complementary complex or the existence of a triplex structure. Further experiments showed that the second hypothesis was more probable, since octa(α -thymidylate) in 0.1 M NaCl can form ternary complexes with the template.

Photomodification of the pentadecanucleotide **21** and the hexadecanucleotide **22** with the oligonucleotide derivatives **23–28** carrying the azido group at various positions of the nucleotide probe has been carried out by Levina *et al.*²¹



The oligonucleotide derivatives employed contained the azido group attached through a spacer to the 3' (5')-terminal phosphates (reagents **23**, **25**, and **26**) or to the C(5) atom of a terminal deoxyuridine (reagent **24**) or deoxyuridine inside the chain (reagents **27** and **28**).²¹ The reagents complementary to the adjacent sites of the target were also used in pairs: tandems of reagents **23** + **25** and **23** + **26**. UV irradiation at $\lambda = 303\text{--}365$ nm yielded products of covalent addition of one or two (in the case of tandems) reagents to the target. The efficiency of photoaddition of reagents **23** and **26** containing the azido group (at the 5'- or 3'-ends, respectively) to the pentadecanucleotide was approximately the same, and the yields of the photoaddition products were 70%. However, the use of a tandem of these reagents increases the efficiency of photomodification up to 80%. The modification predominantly affects the G⁹ residue of the oligonucleotide **21**, which is not involved in the formation of the complementary complex. The adduct yield decreases to 55% and 51%, respectively, when reagents **27** and **28** containing the uridine azido derivative inside the chain are used. The decrease in the photoreaction efficiency is apparently due to the involvement of the modified base in a complementary reaction. This is confirmed by the fact that the efficiency of photoaddition in the

case of reagent **24** having an azidonucleotide at its 5'-end reaches 69% and modification affects predominantly the G⁷ residue of the oligonucleotide **22**, whereas the G⁸ residue is modified in a lesser degree.

Highly reactive nitrenes generated from the azido derivatives of oligonucleotides upon photolysis can instantaneously react with the neighbouring reactive groups as well as with amino acid residues of a DNA–protein complex.

Investigation of the structure of the transcription factor TFIIC of RNA polymerase III was carried out using a genomic DNA sequence of yeast tRNA^{Tyr} SUP4 containing one or several azido derivatives of deoxyuridine **6**.¹⁰ A complex of modified DNA with the protein was irradiated with UV light ($\lambda = 254$ nm) for 5 min. Analysis of photoaddition products allowed one to identify four subunits of TFIIC and to establish their position relative to SUP4 in the DNA–protein complex. This study was extended by using a genomic DNA sequence SUP4 containing azido derivatives of cytidine **7**.¹¹ In contrast with the previous example, a non-purified protein fraction was used for modification. Analysis of photoaddition products revealed a protein with molecular mass of 40 kDa, which could not be detected when purified TFIIC has been used. It was assumed that this protein is a component of the transcription complex.

Affinity modification of the 5'-region of the mRNA-binding centre of the *E. coli* ribosome was studied using *N*-[2-(2,4-dinitro-5-azidophenyl)aminoethyl]-5'-phosphoramidites of oligouridylates **8**.¹² It was found that compounds **8** ($N = \text{U}$, $n = 4, 7$, and **8**) stimulate binding of code-specific aminoacyl-tRNA with the ribosome. Upon UV irradiation of the ribosome–reagent **8**–tRNA ternary complex ($\lambda > 350$ nm), covalent binding of the reagent **8** with the ribosome occurred. Up to 10% of the reagent **8** in the ternary complex was cross-linked with the ribosomal proteins of the 30S and 50S subunits. It was found that in the 30S subunit modification affected proteins S3, S4, S9, S11, S12, S14, S17, S19, and S20. In the 50S subunit, it was proteins L2, L13, L16, L27, L32, and L33 that were modified. The array of the modified proteins strongly depended on the length of the oligonucleotide fragment of the reagent and on the binding of the tRNA molecule to the site A of the ribosome.

By virtue of their ability to form stable covalent bonds with the reactive groups of proteins, azido derivatives of oligonucleotides are successfully employed for identifying amino acid residues in the active centres of DNA-recognising proteins. Thus identification of the amino acid residues of the restriction endonuclease *TaqI* that reacts with the recognition site was made using the photoreagent **13** containing the azido group just at the *TaqI* cleavage site.¹⁷ The complementary complex 'oligonucleotide probe **13**–template DNA' was UV-irradiated ($\lambda = 306$ nm, 5 min) following 5-min incubation with *TaqI*. The efficiency of formation of the covalently bound DNA–protein complex was 15%–20%. An analysis of photoaddition products allowed one to identify the amino acid residue involved in the formation of a covalent bond with the oligonucleotide probe as Tyr161.

Modified fragments of RNA containing 5-(4-azidophenyl)thiocytidine residues at the 3'-end or in the middle of the chain were used for photoaffinity modification of T7 and *E. coli* RNA polymerases.¹⁸ The complexes of modified RNA with T7 and *E. coli* RNA polymerases were UV-irradiated ($\lambda = 302$ nm) for 2–4 min at 20 °C. An analysis of photoaddition products revealed RNA-binding domains in the corresponding RNA polymerases.

In recent years, azido derivatives of oligonucleotides have been employed for modification of the proteins of chromatin. Thus reagent **9** was used to study structural rearrangements in chromatin during the cell cycle.¹³ To this end, the spectra of proteins modified in the nuclei isolated from *HeLa* cells in two different phases of the cell cycle, *viz.*, the S-phase and in the region

of transition from the G₁ to the S-phase (G₁/S), were compared. Modification of proteins in the nuclei isolated in the S-phase of the cell cycle gave five nuclear proteins with molecular masses 160, 87, 72, 59, and 46 kDa and was specific. The spectrum of the modified proteins changed on going from the S-phase to the G₁/S interface. In particular, the 160 kDa protein was not modified. The results obtained by other authors¹³ confirm the idea that photoactivated oligonucleotides are promising for studies of the structure and functions of chromatin.

Wide application of azido derivatives of nucleic acids in the studies of nucleic acid–nucleic acid and nucleic acid–protein interactions is indicated by the existence of reproducible protocols for the synthesis and their high reactivity. However, in some cases the high reactivity of nitrenes photogenerated from the azido derivatives may decrease the specificity of the reactions and thus imposes certain limitations on the application of azidoaryl derivatives of nucleic acids in structure–function studies of biopolymers.

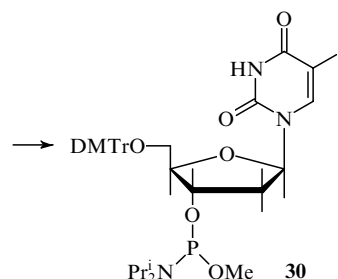
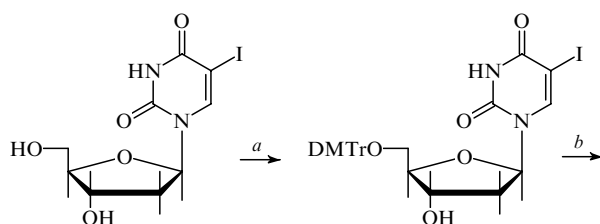
2. Derivatives of nucleic acids containing halogen or mercapto groups

In recent years, photoactivated oligonucleotide derivatives with bromo, iodo, or mercapto groups have been widely employed for the study of nucleic acid–protein or nucleic acid–nucleic acid interactions. The interest in these compounds is due to their ability to generate free-radical intermediates that can form covalent bonds with electron-donor groups of proteins and nucleic acids on irradiation with long-wave UV light. Reactions according to radical mechanisms are also possible, but only in the case where the reacting groups are at a distance of several angström.²² This circumstance makes possible the use of oligonucleotide halogeno and thiol derivatives for identifying direct nucleic acid–nucleic acid or nucleic acid–protein contacts.

a. Synthesis of halogeno and mercapto derivatives of oligonucleotides

Oligonucleotide derivatives carrying halogeno or mercapto groups are usually obtained by chemical or enzymic syntheses using modified nucleotide components, such as 4-mercapto or 5-bromo(iodo) uridine or cytidine. DNA derivatives containing halogeno or mercapto groups are obtained by solid-phase phosphoramidite synthesis with bromo-, iodo-, or mercapto-deoxyribonucleoside phosphoramidites as monomeric units. Thus, 5-bromo-2'-deoxyuridine (5-BrdU) derivatives of DNA that included a recognition site for the transcription factor NF-κB were obtained by Liu *et al.*²³ The modified uridine was introduced into various positions of DNA by solid-phase synthesis with 5-BrdU phosphoramidites.

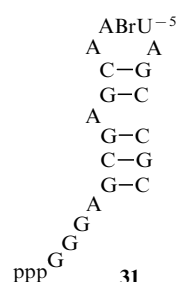
The 5-iodo-2'-deoxyuridine derivative of the deoxyribonucleotide GCTCACCAGAA–IdU–GC **29** was synthesised in a similar way²⁴ from compound **30** obtained in quantitative yield according to the following scheme:



(a) DMTTrCl = (*p*-MeOC₆H₄)₂C(Ph)Cl, Py; (b) (Pr₂N)₂P(OMe), Pr₂N⁺Et, CH₂Cl₂, 20 °C, 10 min.

It should be noted that the high sensitivity of aromatic iodides to nucleophilic substitution prevents deprotection of internucleotide phosphates and heterocyclic bases by conventional treatment with NH₄OH at 55 °C. Removal of protective groups leading to the oligomer **29** could be carried out by treatment with NH₄OH for 48 h at room temperature. Under these conditions, no nucleophilic substitution of iodine in the aromatic nucleus occurred, while phosphate groups and heterocyclic bases were completely deprotected.

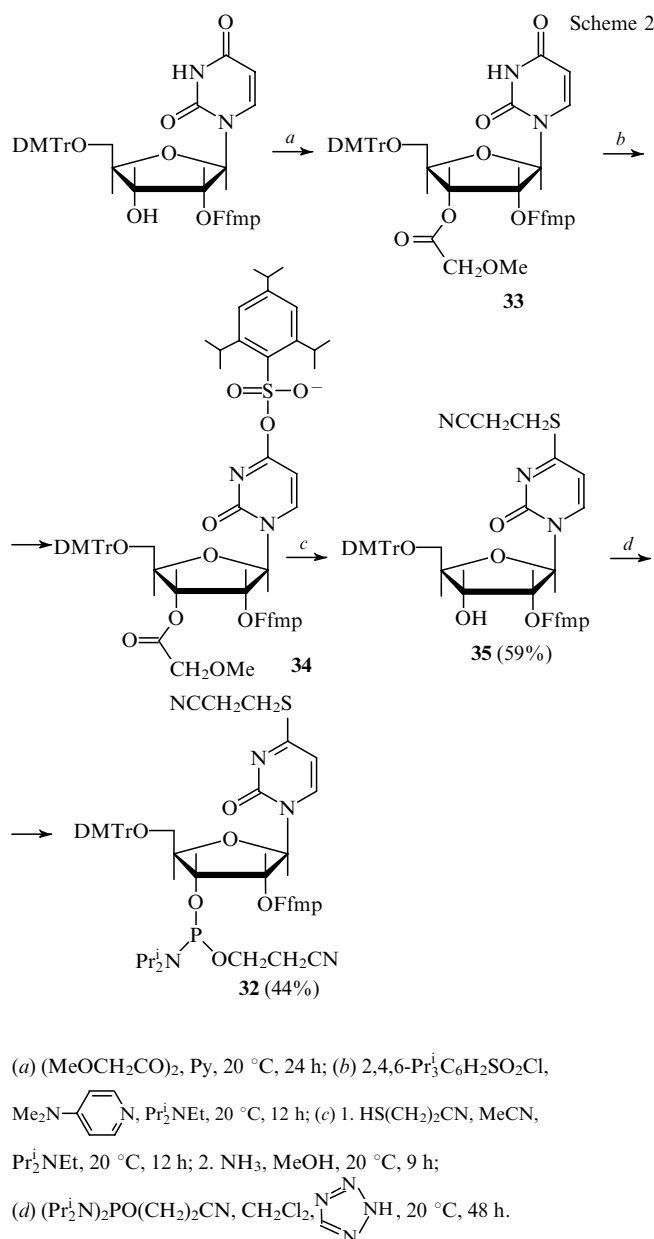
Halogeno or mercapto derivatives of oligoribonucleotides are also obtained using modified nucleoside triphosphates as substrates for T7 RNA polymerase in the polymerase-catalysed synthesis of RNA. Thus a 19-membered oligoribonucleotide **31** containing 5-bromouridine (5-BrU) at position (–5) was used to identify amino acid residues in the site of binding of the bacteriophage R17 membrane protein with genomic RNA.²⁵ The synthesis of compound **31** was carried out using 5-bromouridine 5'-triphosphate by a T7 RNA polymerase-catalysed synthesis on a synthetic DNA template.



The same approach was used to obtain oligoribonucleotides with a nucleotide sequence analogous to that of compound **31** but with U or C 5-iodo derivatives at position (–5).²⁶

A method for the synthesis of 4-(2-cyanoethyl)thiouridine **32** phosphoramidite has been proposed (Scheme 2).²⁷ This compound was further used in the chemical synthesis of modified RNA. The 2'-OH group of ribose was protected by a 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl group. The mercapto group of uridine was protected as a 2-cyanoethyl derivative.

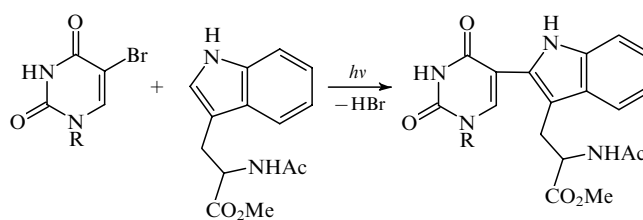
The reaction of 2'-O-[1-(2-fluorophenyl)-4-methoxypiperidin-4-yl]-5'-O-dimethoxytrityluridine with methoxyacetic anhydride in dry pyridine gave the derivative **33** in quantitative yield. To obtain the uridine derivative **35** with a cyanoethyl group at position 4, compound **33** was treated with 2,4,6-triisopropylbenzenesulfonyl chloride, after which the sulfonate **34** was introduced into reaction with 3-mercaptopropionitrile. The resulting compound was treated with ammonia in methanol to deprotect the 3'-hydroxy group of ribose. Phosphitylation of the 3'-OH group of the protected ribonucleoside **35** was carried out with 2-cyanoethyl bis(diisopropylphosphoramidite). After purification, compound **32** was obtained in 44% yield and further used in a solid-phase phosphoramidite synthesis to obtain photoactivated derivatives



of RNA containing 4-mercaptouridine in different positions of the recognition sites of the HIV Rev protein and the bacteriophage MS2 membrane protein.

b. The use of oligonucleotide halogeno and mercapto derivatives for cross-linking to proteins and nucleic acids

As has been mentioned above, UV irradiation of bromo(iodo) or mercapto derivatives of oligonucleotides generates reactive intermediates, which interact with reactive groups of proteins and nucleic acids. Using an oligonucleotide derivative containing 5-BrU as an example, it was shown that the mechanism of photoactivated reaction of halogeno derivatives with the protein amino groups depends on the wavelength.²⁸ Upon UV irradiation with $\lambda = 308$ nm, the 5-BrU molecule passes from the low-energy singlet state to the reactive triplet state n,π^* responsible for the binding of BrU–DNA with the associated protein, presumably through the initial electron transfer. The intermolecular covalent binding of BrU with amino acid residues, such as cysteine, glutathione, or tryptophan, is accompanied by elimination of HBr.



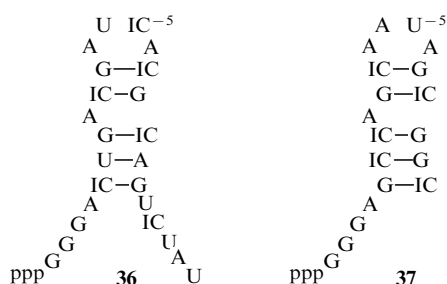
R is the oligonucleotide residue.

Upon UV irradiation with $\lambda = 254$ nm, the 5-BrU molecule passes into a high-energy singlet state π,π^* , which results in the cleavage of the C–Br bond to yield free radicals $\text{U}^\bullet$ and a Br atom. The highly reactive radical $\text{U}^\bullet$ either reacts with the reactive groups of the nearest environment (in particular, with the formation of a covalent bond with the amino groups of a protein) or passes into the triplet state, $^3\pi,\pi^*$.²⁹

Synthetic analogues of the promoter region of DNA containing several 5-BrdU residues were used to study covalently bound complexes of a series of transcription factors of the albumin gene (HNF1, APF, vAPF, α 1TEB, HPI) with the promoter regions of this gene.³⁰ Yet another aim of this study was to identify the polypeptide chains involved in the formation of a vAPF–APF complex and the nucleotide residues involved in the interaction with the protein. Complexes of DNA derivatives with the proteins were irradiated at $\lambda = 321$ nm. An analysis of cross-linking products revealed that the DNA–protein contact sites were distributed asymmetrically on a pseudopalindromic recognition site: the nucleotides crucial for the recognition were located in the middle of the pseudopalindromic sequence but the recognition site had other contacts of the protein with several nucleotides.

In order to investigate the formation of cross-linked complexes of a membrane protein with an operator of bacteriophage R17 transcription (R17 RNA) and to identify the amino acid residue responsible for the formation of the cross-linkage, Willis *et al.*²⁵ proposed to use a synthetic analogue of R17 RNA containing a 5-BrU residue at position (–5) (compound **30**). Its complex with the membrane protein was irradiated at $\lambda = 308$ nm for 5 min after which the protein concentration was increased and the complex was irradiated for an additional 5 min. The efficiency of formation of the cross-linked complex was 22%. The amino acid residue involved in this process was identified as Tyr85. It was found that cross-linking did not occur if Tyr85 was substituted by Ser.²⁵ These results are in good agreement with the above-described mechanism of the photoinduced reaction of oligonucleotides containing 5-BrU with the amino acid residues of the protein according to which 5-BrU derivatives cross-link only with aromatic amino acids upon irradiation at $\lambda = 308$ nm.²⁹

Earlier, it was found³¹ that oligonucleotides containing 5-IU residues are more efficient reagents for cross-linking to proteins than those containing 5-BrU. The efficiency of covalent photoaddition of iodine-containing reagents is usually 3 to 5 times higher than that of their bromo analogues. Therefore, the 5-BrU residue at position (–5) of compound **30** was substituted by the 5-IC residue.²⁶ Five additional 5-IC residues were introduced into various positions of RNA **36** in order to demonstrate the specificity of formation of the cross-linked complex.



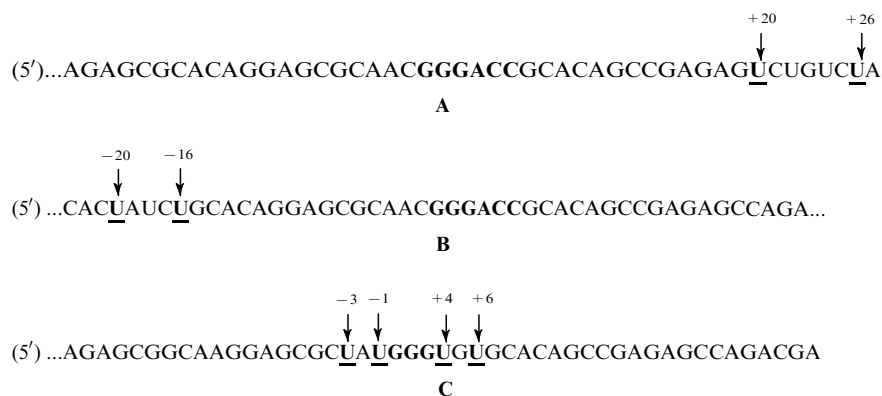


Figure 1. Model mRNA containing 4-mercaptouridine residues: A — mRNA 8'; B — mRNA 9'; C — mRNA 10'. The encoding sequences are bold-faced, and modified bases are underlined.

A complex of the membrane protein with compound **36** was irradiated with UV light ($\lambda = 325$ nm) for 2 h. The efficiency of cross-linking was 75%–95%. It is noteworthy that the formation of the cross-linked complex was accompanied by partial cleavage of the RNA chain. When an analogous RNA devoid of the 5-IC residue at position (–5) (compound **37**) was used, the cross-linked RNA–protein complex was not formed.

On irradiation at $\lambda > 300$ nm, oligonucleotides containing 4-mercaptouridine reacted by a free radical mechanism and cross-linked through reactive groups with proteins and nucleic acids.³² In the case of nucleic acids, the cross-linking was the most efficient between the adjacent uridine or adenine residues. This makes it possible to use mercapto derivatives of oligonucleotides for the studies of both nucleic acid–protein and nucleic acid–nucleic acid contacts. Thus a series of model mRNAs containing 4-mercaptouridine residues in various positions were synthesised to study cross-linking between mRNA and 18S RNA within a complex with the 80S ribosome (Fig. 1).³³ The synthetic mRNAs contained encoding sequences for glycine and/or tryptophan (GGG and ACC, respectively).

The mRNA–80S ribosome complex was irradiated with UV light ($\lambda = 320$ –365 nm) in the presence and in the absence of tRNA^{Gly} and/or tRNA^{Thr}. The efficiency of formation of a cross-linked mRNA–18S RNA complex depended on the presence of tRNA only for the mRNA 9' derivative and was 20% in the presence of tRNA and 40% in its absence. The efficiency of cross-linking was 8% and 14% for mRNA 8' and mRNA 10 derivatives, respectively. It was shown that a covalent bond is formed with U630 and U1111/A1112 of the 80S ribosome 18S rRNA.

Synthetic nucleic acid analogues having reactive thiol groups are widely employed in the studies of the structure and function of ribosomes. Thus a series of model RNAs have been synthesised to study the sites of binding of 5S RNA with the 50S subunit of the ribosome³⁴ in which 18% of uridine residues were statistically substituted by 4-mercaptouridine residues. The 5S RNA–ribosome 50S subunit complex was irradiated at $\lambda = 300$ nm for 10 min. The yield of the product of cross-linking of 5S RNA to the 23S ribosomal RNA was more than 75%. The structures of the products formed were not established, although it was shown that U89 of 5S RNA and U2477 of 23S RNA of 50S ribosomal subunits were cross-linked.

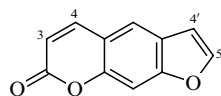
Thus, the indisputable advantage of halogeno and mercapto derivatives of nucleic acids is their high reactivity and the ability to operate at a zero distance, which makes possible the probing of direct nucleic acid–protein contacts. At the same time, the high reactivity of these intermediates may be the cause of nonspecific modification of proteins and other cell components and their partial destruction.²⁶ Moreover, the need for additional activation with light of definite wavelengths restricts the application of halogeno and mercapto derivatives of nucleic acids *in vivo*.

3. Psoralen derivatives of nucleic acids

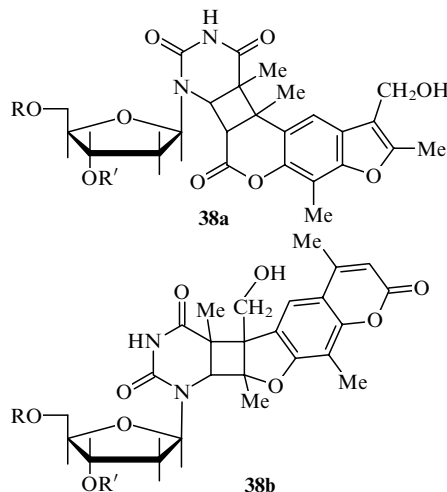
Nucleic acids that contain psoralen residues or its derivatives belong to the most efficient, selective photoreagents that are widely employed for affinity modification and structural analysis of nucleic acids.

a. Introduction of psoralen into oligonucleotides

Psoralens (7*H*-furo[3,2-*g*][1]benzopyran-7-ones)[†] are aromatic compounds with three linearly fused rings of α -pyrone, benzene, and furan. They contain two photoactivated double bonds, C(3) = C(4) in the pyrone ring and C(4') = C(5') in the furan ring.



Irradiation with long-wave UV light ($\lambda = 300$ –365 nm) can result in cycloaddition of both these bonds to the C(5) = C(6) bond of thymidine or uridine to form a cyclobutane ring. Thus psoralen derivatives **38a** and **38b** of a dodecanucleotide containing only one thymidine residue were obtained.^{35,36}

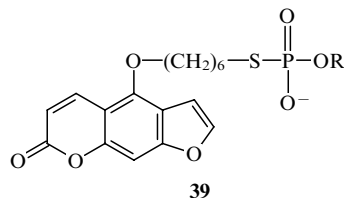


R = d(GAAGC); R' = d(ACGAGC).

Photochemical addition of psoralen gives reactive derivatives only if the C(4') = C(5') bond of the furan ring is involved in the reaction with the thymidine residue. In the case of thymidine cycloaddition to the C(3) = C(4) bond of the pyrone ring, the psoralen derivative formed is incapable of further photochemical

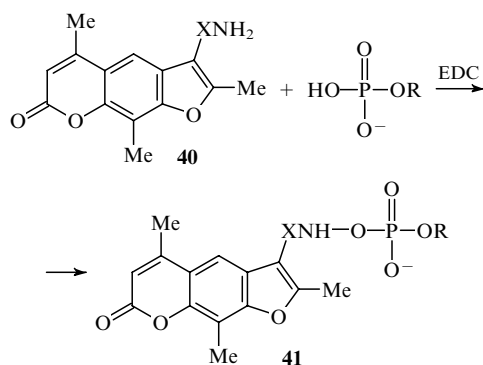
[†] Hereinafter the names used in the original publications are given.

addition.³⁷ Therefore, the introduction of psoralen into terminal phosphate groups of oligonucleotides has now become an especially widespread procedure, for it allows modifications that involve the reactive centres of the psoralen molecule. Thus a psoralen derivative of a 16-membered oligonucleotide **39** has been synthesised by alkylation of its 5'-terminal thiophosphate group with 5-(ω -iodohexyloxy)psoralen.³⁸



R = TTTTCTTTTCCCCCT.

4'-Aminoalkylamino-4,5',8-trimethylpsoralen **40** was attached to the 5'-phosphate group of a methylphosphonate analogue of the oligonucleotide using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (CDI) as the activating reagent.³⁹



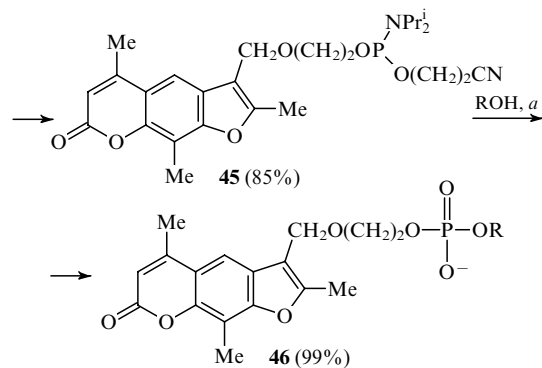
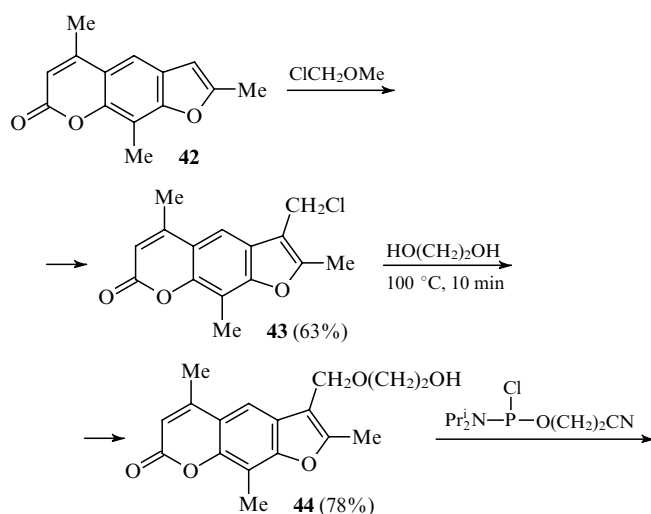
X = NH-CH₂; NH-(CH₂)_n-NHCH₂, n = 2, 4;

R is a methylphosphonate analogue of the oligodeoxyribonucleotide;

EDC is EtN=C=N(CH₂)₂CH₂NMe₂.

The reaction was performed in a lutidine hydrochloride buffer (pH 7.5) for 14 h at 20 °C. The yield of compound **41** was 85%.

The attachment of psoralen to the 5'-end of an oligonucleotide can also be carried out in the solid-phase oligonucleotide synthesis. Thus a 4,5',8-trimethylpsoralen residue **42** was incorporated into the oligonucleotide by phosphoramidite synthesis using psoralen β -cyanoethyl-*N,N*-diisopropylphosphoramidite **45** at the final stage.⁴⁰

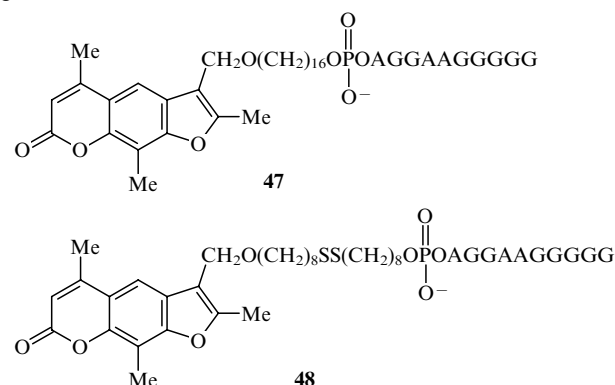


(a) 1. tetrazole; 2. I₂; 3. NH₃, 55 °C, 6 h;

R = d(TAGCCGCTATCGGTAGT).

The first step of this synthesis consisted in chloromethylation of 4,5',8-trimethylpsoralen **42** with chloromethyl methyl ether. Then, a linker group was introduced into the resulting compound **43**. Phosphitylation of 4'-(2-hydroxyethoxymethyl)-4,5',8-trimethylpsoralen **44** with β -cyanoethyl-*N,N*-diisopropylamidophosphochloridite was carried out in the presence of ethyl-diisopropylamine for 30 min at 20 °C. The oligonucleotide psoralen derivative **46** was obtained on an automated DNA synthesiser using a standard phosphoramidite protocol. The psoralen phosphoramidite **45** was attached to the 5'-end of the oligonucleotide at the last stage of this synthesis. Oxidation and deprotection with concentrated ammonia gave 5'-psoralen derivative **46** in 99% yield.

A similar strategy has been used to obtain derivatives of oligonucleotides **47** and **48**.⁴¹



Compound **48** with a disulfide bond, was synthesised using a mercaptoalkyl phosphoramidite that was introduced into an automated oligonucleotide synthesis prior to the attachment of the psoralen derivative.

Thus, psoralen derivatives of nucleic acids can be obtained both by photochemical cycloaddition of psoralen to the heterocyclic bases of nucleic acids and by chemical attachment of psoralen derivatives to terminal phosphate groups of nucleic acids. The latter approach has become more popular because the ability of psoralen for subsequent photochemical addition is fully preserved in this case. Moreover, photochemical modification of heterocyclic bases of nucleic acids with psoralen makes the *N*-glycosidic bond more labile and can sometimes result in the destruction of the polynucleotide chain.

b. Cross-linking of psoralen-containing oligonucleotides to biopolymers

Psoralen-containing oligonucleotides are mostly used for directed modification of nucleic acids. A detailed study of their cross-linking to complementary sites of nucleic acids has been carried out by Shi.³⁵ To this end, the dodecanucleotide GAAGCT*AC-GAGC derivatives containing a psoralen residue fused to thymidine both by its pyrone and furan rings (compounds **38a** and **38b**,

respectively) were used. Modified oligonucleotides **38a** and **38b** were hybridised with a complementary template and irradiated with monochromatic light of various wavelengths. It was shown that irradiation of the nucleic acid–oligonucleotide **38a** complex with light in a broad range of wavelengths resulted in the predominant splitting of the 4'-hydroxymethyl-4,5',8-trimethylpsoralen residue. In this case, the efficiency of cross-linking between complementary oligonucleotides was extremely low. With irradiation of the complementary nucleic acid–oligonucleotide **38b** complex at $\lambda < 313$ nm, both splitting of the psoralen residue and simultaneous formation of a covalent oligonucleotide–nucleic acid bond occur. Irradiation of the latter complex with $\lambda > 313$ nm results in highly efficient formation of a cross-linked complex, and psoralen is not split off. These results are in good agreement with other data on the stability of the psoralen monoadduct with thymidine. It was shown that thymidine fused with psoralen at the furan ring **38b** was more resistant to irradiation at $\lambda < 313$ nm than the compound of the type **38a** with the pyrone ring fusion. Introduction of a psoralen derivative of thymidine into an oligonucleotide only slightly increases the monoadduct resistance to photocleavage.⁴²

Psoralen-containing oligonucleotides have been used in studies of DNA transcription with the RNA polymerase of *E. coli*.³⁶ 4'-Hydroxymethyl-4,5',8-trimethylpsoralen was introduced into one of the chains of a 140-membered DNA duplex containing a promoter of *E. coli* RNA polymerase. Upon irradiation at $\lambda = 320$ –380 nm, psoralen fused with a particular thymidine residue in one of the duplex chains reacted with the closely situated thymidine residue of the complementary chain. The yield of the cross-linked DNA duplex was 80%. It was shown that transcription of this duplex was blocked at a distance of one nucleotide from the site of cross-linking.

Methylphosphonate analogues of oligonucleotides having psoralen derivatives at their 5'-ends and linked to the phosphate group of the oligonucleotide through various spacer groups were used for attachment to two 35-membered deoxyribonucleotides.³⁹



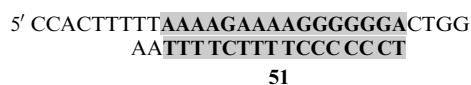
X = NHCH₂, NH(CH₂)_nNHCH₂, n = 2, 4;

Ps is the 4,5',8-trimethylpsoralen residue. The fragments of oligonucleotides containing internucleotide methylphosphonate groups are underlined.

The cross-linked complex was obtained by irradiation of the duplexes **49** and **50** with light of $\lambda = 365$ nm at 4 °C for 20 min. The yield of the photoaddition products strongly depended on the length of the spacer arm and reached maximum values (75% and 80% for systems **49** and **50**, respectively) at n = 4. Studies of the temperature dependence of the photoaddition reaction revealed that the efficiency of cross-linkage of DNA duplexes was determined by the stability of the complementary complex formed. Irradiation of photoaddition products at $\lambda = 254$ nm led to the cleavage of the cross-linked DNA duplexes and recovery of the original compounds. It was thus concluded that cross-linking of modified oligonucleotides is a result of formation of a cyclobutane ring between the C(5)–C(6) bond of thymine and the C(3)–C(4) bond of the pyrone ring of psoralen. The adduct with the furan ring of psoralen is not formed due to steric hindrances.

Psoralen attached to the terminal phosphate group of an oligonucleotide through C(5) retains its capacity to form a bisadduct. Therefore, this type of psoralen-containing oligonucleotides within a triplex can form a ternary cross-linked oligonucleotide complex. The structure of the triplex is stabilised by intercalation of psoralen residues into a double helix of DNA.

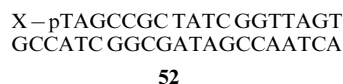
Thus psoralen-containing, 16-membered homopyrimidine oligonucleotide **39** was used for cross-linking to a double-helical region of DNA of the human immunodeficiency provirus **51**³⁸ (the site where the formation of a triplex structure takes place is bold-faced).



The sequence **51** contains a recognition site for the restriction endonuclease *DraI* (TTTAAA) overlapping with two or three nucleotides in the formation of a triplex with the oligonucleotide **39**. Plasmids pLTR and pBT1 containing one or two copies of sequence **51**, respectively, were incubated with the oligonucleotide **39** and irradiated with UV light ($\lambda > 310$ nm). The photomodified plasmids were used as substrates for the restriction enzyme *DraI*. It was found that photomodification with the psoralen derivative **39** selectively inhibited the enzymic splitting at the site overlapping with the triplex structure.

The ability of psoralen-containing oligonucleotides to form cross-linked triplex complexes has been used for site-specific insertion of mutations into animal cells in order to investigate their repair mechanism.⁴¹ To this end, the frequency and spectrum of mutations induced by various psoralen-containing oligonucleotides in several cell lines with various repair disturbances, viz., *xeroderma pigmentosum* variant (XPV) and *xeroderma pigmentosum* group A (XPA), were compared with the corresponding parameters of normal and *Fanconi anemia* (FA) cells. In these studies, compounds **47** and **48** were used, which form triplexes with the 167–176 region of the *supF* gene. It is noteworthy that the psoralen residue of compound **48** is linked with the oligonucleotide through a disulfide bond, which can be cleaved by dithiothreitol; this allows one to study mutagenesis in the absence of the site-directed oligonucleotide part of the probe. The triplex structure of compound **47** (or **48**) with the *supF* gene in the vector pSP189 was irradiated with long-wave UV or visible light. UV irradiation gave a cross-linked triplex in 65% yield, while upon irradiation with visible light the yield did not exceed 1%. The cross-linkage was formed between T166 and T167 residues. The DNA vector thus modified was transformed into the appropriate cultures of human cells. Analysis of mutagenesis in the line XPV revealed an unusually high frequency of mutations (more than 30%) with a unique spectrum that differed from those of XPA, FA, and normal cells. These data led Raha *et al.*⁴¹ to conclude that this approach is useful both for the description of repair defects in XPV cells and other genetic analyses of human cells.

The reactive oligonucleotide **46**, modified at the 5'-end with 4'-hydroxyethoxymethyl-4,5',8-trimethylpsoralen, was used to obtain a cross-linked DNA duplex within the complementary complex **52**. This DNA duplex was obtained in 75% yield upon UV irradiation of the complex **52** at $\lambda = 350$ nm at 20 °C.⁴⁰

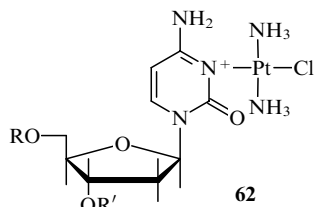


X is 4'-hydroxyethoxymethyl-4,5',8-trimethylpsoralen.

The glycosidic bond of the nucleotide involved in cross-linking of psoralen-containing oligonucleotides to nucleic acids becomes more labile. This property has been exploited in site-specific cleavage of DNA.³⁵ The cleavage site was mostly determined by the length of the spacer arm between the psoralen residue and the oligonucleotide end.

Thus, owing to their ability for selective cycloaddition to thymidine or uridine residues, psoralen-containing nucleic acids are widely employed for the study of structure and function of nucleic acids. The possibility of formation of bisadducts makes them helpful tools for the study of mechanisms of formation of triplex structures.

ion-exchange chromatography. However, when *cis*-aquahydroxydiammineplatinum (*cis*[(NH₃)₂Pt(OH)(H₂O)]NO₃) is used, modification affects all of the G, C, and A residues of the oligonucleotide. In this case, the covalent bond can also be formed between the nucleotides of the same chain. Reagents with one platinum residue can be prepared from oligothymidylates containing only one G, C, or A residue. Thus treatment of oligothymidylate having a single cytidine residue with a 10-fold excess of *cis*-aquahydroxydiammineplatinum nitrate⁵¹ gave compound **62**. The degree of conversion of the original oligonucleotide was 97%–99%:



R = d(TT), R' = TTTTTT.

The reaction was conducted in an aqueous medium (pH 7.0) for 24 h at 30 °C; the degree of conversion of the original compound and the homogeneity of the final product were estimated by microcolumn chromatography. Compound **62** was used for modification of DNA polymerase α of human placenta.

Thus, modern methods allow one to incorporate platinum both into heterocyclic bases and into a predetermined position of the sugar-phosphate backbone of nucleic acids. In the latter case, the synthesis of platinum-containing derivatives must be preceded by introduction of mercapto groups into the sugar-phosphate backbone.

2. Cross-linking of Pt-containing oligonucleotides with biopolymers

Bifunctional Pt-containing compounds are often used to obtain cross-linked nucleic acid–nucleic acid or nucleic acid–protein complexes.^{52,53} The synthesis of platinum-containing oligonucleotides makes it possible to increase considerably the efficiency and selectivity of modification of biopolymers by these reagents.

Cross-linking of Pt-containing oligonucleotides with biopolymers can be carried out in two ways: (1) by direct reaction of Pt-containing oligonucleotides with complementary sites of nucleic acids or DNA-recognising proteins and (2) by treatment of a preformed complex of a biopolymer with an oligonucleotide probe containing nucleophilic SH or NH₂ groups at predetermined positions with bifunctional Pt reagents. Thus treatment of a complementary complex **63** formed by a 322-membered DNA target and a 16-membered oligonucleotide probe carrying a cysteamine residue at its 5'-end with K₂PtCl₄ resulted in cross-linking. The efficiency of cross-linking varied from 10% to 50% depending on K₂PtCl₄ concentration.⁴⁶



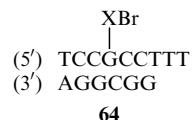
X = HSCH₂CH₂NH

The reaction involved the attachment of Pt coordinated with three chloride ions to the 5'-SH group of the oligonucleotide probe and subsequent modification of the DNA target.

A similar approach was used by Chu and Orgel⁵⁴ who carried out affinity modification of the transcription factors CREB and JUN using platinum-containing oligonucleotides. To this end, six internucleotide thiophosphate groups have been introduced into each CRE and TRE recognition site for the transcription factors CREB and JUN in covalently closed DNA duplexes. The complexes of oligonucleotide probes with the corresponding proteins were treated either with K₂PtCl₄ or with *trans*- or *cis*-diamminedichloroplatinum(II). The efficiency of cross-linking between oligonucleotides and proteins with K₂PtCl₄ or *trans*-**53** was from 30%

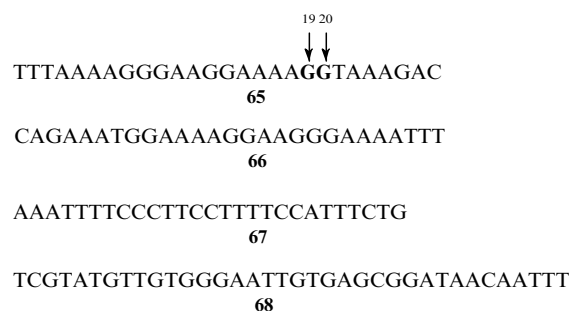
to 50% depending on the reagent concentration. Treatment of a DNA–protein complex with *cis*-**53** did not result in cross-linking. The use of analogous probes devoid of internucleotide thiophosphate groups resulted in several-fold lower efficiency of cross-linking. Presumably, this method⁵⁴ can be employed for the isolation of DNA-recognising proteins.

A Pt-containing nonanucleotide **61** (R = TCCGCCTTT) was used for modification of a complementary hexanucleotide GGCGGA within a two-helical complex **64**.⁴⁸ The yield of the cross-linked complex was 80%.



Unlike psoralen derivatives, treatment of guanine residues of template oligonucleotides with platinum-containing reagents favours stabilisation of the glycosidic bond. An analysis of products of partial scission of the template at purine bases allows one to identify particular guanine residues that have been modified. It was found that one of the two 5-terminal guanine residues of the template was involved in cross-linking.⁴⁸

A detailed study of cross-linking of oligonucleotides modified with the reagent **55** at the 5'-terminal or at internucleotide thiophosphate groups to complementary fragments of DNA was carried out by Gruff and Orgel.⁴⁷ The reaction was studied both within DNA duplexes and within ternary complexes using oligonucleotides **56–59** and **65–68**.



Using duplexes **65–56** as an example, it was shown that cross-linking was the most efficient (64% yield) when the reagent **55** (*n* = 6) was used. This reagent was chosen for subsequent experiments. The reaction was carried out for 60 min at 37 °C in the presence of NaClO₄. Modification affected residues G19 and G20 of the oligonucleotide **65** (marked bold). Under the same conditions, the efficiency of cross-linking in duplexes **58–68** and **59–68** was much lower (46% and 41%, respectively), which was attributed to the formation of intrachain cross-links in oligonucleotides **58** and **59** containing purine bases.⁴⁷ In the case of the oligonucleotide **57**, the nucleotide composition of which is identical with that of the oligonucleotide **58** but which contains a platinum reagent inside the chain (because the thiophosphate group is present in the middle of the sugar-phosphate backbone), the efficiency of cross-linking decreased to 37%. This low efficiency may be due to the involvement of the modified base in complementary interaction. A ternary complex was formed by oligonucleotides **66** and **67** and an analogue of a Pt-containing oligonucleotide **56** in which all cytidine residues had been substituted by 5-methylcytidine (oligonucleotide **69**). Such a substitution significantly stabilised the triplex structure. The reaction carried out at 25 °C for 60 min resulted in cross-linking of the oligonucleotide **69** with the chain **66** enriched with purine nucleotides and with 53%–68% efficiency. It was shown that the efficiency of this reaction strongly depended on the stability of the triplex structure. Thus a rise in temperature up to 37 °C sharply decreased the yield of cross-linked products. Replacement of the oligonucleotide probe **69** by **56** also decreased the yield down to several per cent.

5' AGCCAGA^UU^UGAGCAGC
 3' UCGGUCU—CUCGUCG
 ↑ ↑ ↑ ↑
 42-43 40-41 39-40 38-39
 75

used.³⁷

5' ACCTACC —O—P(=O)(O⁻)—NHCH₂—C(=O)—O—P(=O)(O⁻)—O—TGGTGGT
 3' TGGATGG ————— ACCACCA

↓ EDC

5' ACCTACC —O—P(=O)(O⁻)—NHCH₂—C(=O)—O—P(=O)(O⁻)—O—TGGTGGT
 3' TGGATGG ————— ACCACCA

$$\begin{array}{c} \text{ACCTCGGAAAGT}-\text{O}-\overset{\overset{\text{O}}{\parallel}}{\underset{\underset{\text{X}}{\mid}}{\text{P}}}-\text{NHCH}_2\overset{\overset{\text{O}}{\parallel}}{\text{C}}-\text{O}-\overset{\overset{\text{O}}{\parallel}}{\underset{\underset{\text{O}^-}{\mid}}{\text{P}}}-\text{O}-\text{CCCC TCT} \\ \text{GAGCCTTTCA}-\text{-----GGGGAGA} \end{array}$$
$$\begin{array}{c}
 \begin{array}{ccc}
 \begin{array}{c} \text{O} \\ \parallel \\ \text{R}'\text{O}-\text{P} \\ | \\ \text{X} \end{array} & \begin{array}{c} \text{O} \\ \parallel \\ -\text{O}-\text{P}-\text{OR}^2 \\ | \\ \text{O}^- \end{array} & \xrightarrow{-\text{H}^+} \begin{array}{c} \text{O} \\ \parallel \\ \text{R}'\text{O}-\text{P}-\text{O}^- \\ | \\ \text{X} \end{array} + \begin{array}{c} \text{O} \\ \parallel \\ \text{Nu}-\text{P}-\text{OR}^2 \\ | \\ \text{O}^- \end{array} \\
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 \\
 \begin{array}{ccc}
 \begin{array}{c} \text{O} \\ \parallel \\ \text{R}'\text{O}-\text{P} \\ | \\ \text{O}^- \end{array} & \begin{array}{c} \text{O} \\ \parallel \\ \text{NHCH}_2\text{C}-\text{O}-\text{P}-\text{OR}^2 \\ | \quad \quad | \\ \text{O}^- \quad \quad \text{O}^- \end{array} & \xrightarrow{\text{NuH}} \\
 & \text{NuH} \curvearrowright &
 \end{array} \\
 \\
 \begin{array}{ccc}
 \begin{array}{c} \text{O} \\ \parallel \\ \text{R}'\text{O}-\text{P} \\ | \\ \text{O}^- \end{array} & \begin{array}{c} \text{O} \\ \parallel \\ \text{NHCH}_2\text{C}-\text{Nu} \end{array} & + \begin{array}{c} \text{O} \\ \parallel \\ \text{HO}-\text{P}-\text{OR}^2 \\ | \\ \text{O}^- \end{array}
 \end{array}
 \end{array}$$

The active centre of the transcription factor HNF-1 was probed⁶¹ using a series of DNA duplexes containing an *O*-methyl-substituted pyrophosphate group in various positions (1–16) of the HNF-1 recognition site. These studies were carried out both with a gene-engineered protein, which represented a DNA-binding domain of HNF-1, and with proteins isolated from nuclear extracts of rat liver. Modified substrates were incubated with the protein or a nuclear extract at 4 °C or 20 °C for 10 min or 12 h. This reaction yielded cross-linked complexes both for the DNA-binding domain of HNF-1 and the HNF-1 of the nuclear extract. Cross-linking occurred only if a DNA duplex contained a reactive group in position 10. The efficiency of cross-linking was

40% of the non-covalent binding. It has been shown for the first time that cross-linking of a modified substrate with HNF-1 isolated from a nuclear extract occurred in a specific manner and was not accompanied by modification of other components of the nuclear extract. This finding holds much promise for the application of oligonucleotides with substituted pyrophosphate groups in various *in vivo* systems and for creation on their basis of new generations of therapeutic agents.

Compounds with a substituted pyrophosphate group were also used for establishing the contact site for the transcription factor NF- κ B and DNA.⁵⁸

RNA duplexes containing substituted pyrophosphate groups can also be used as reactive derivatives for affinity modification of biopolymers. The interaction of RNA duplexes TAR **75** with the Tat-protein and the Tat-peptide (37–72) of HIV-1 has been studied.⁶³ The RNA–protein complex was incubated for 18–24 h at 10 °C. Cross-linking with the Tat-peptide (37–72) was especially efficient when an RNA duplex containing a modified group in position 38–39 was used. The product yield was 50%. Analysis of the complex revealed that Lys51 of the main region of the Tat-peptide is involved in the formation of a covalent bond.

A first report concerning the successful application of a DNA duplex containing an acyl phosphate group for affinity modification of the p50 subunit of NF- κ B has been published recently.⁶⁴ The DNA duplex **76** containing a reactive acyl phosphate group in position 6 of the κ B region was used for cross-linking with the protein. The efficiency of cross-linking was 10%. Acyl phosphates are acylating reagents.⁵⁷ The group formed as a result of their interaction with nucleophilic amino acids of a protein is carboxamide, which unlike the phosphoramidate is relatively stable in acidic media. The application of nucleic acid analogues with an acyl phosphate group for affinity modification of DNA-recognising proteins may significantly facilitate both the isolation of protein–nucleic acid complexes and subsequent identification of amino acids that react with the reactive group.

Thus, reactive nucleic acids containing substituted pyrophosphate or acyl phosphate groups are successfully employed for the study of nucleic acid–protein interactions. It should be noted, however, that introduction of these groups into the sugar-phosphate backbone of nucleic acids increases the length of the internucleotide bond, which, in turn, may decrease the efficiency of its binding with the protein.⁶¹ This problem can be overcome through the use of nucleic acid duplexes containing reactive groups at other positions of the protein binding site.⁶¹

V. Prospects for the application of reactive oligonucleotides for directed *in vivo* modification of biopolymers

One of the most interesting applications of reactive oligonucleotides is the design on their basis of antiviral and antitumour drugs the effects of which are due to inhibition of gene expression in viral or oncogenic cells. The ability of reactive oligonucleotides to covalently bind to proteins of nucleic acid metabolism may suppress their activity and thus control the expression of the genetic material. It was found⁶⁷ that human tRNA₃^{Lys} containing 4-mercaptouridine residues efficiently interacts with HIV reverse transcriptase to form a cross-linked complex. This interaction results in the block of a region in reverse transcriptase that is responsible for the initiation of reverse transcription of HIV.

Of particular interest is the application of reactive oligonucleotide derivatives in various *in vivo* systems. The first studies in this area revealed a number of limitations related to weak penetrability of these reagents through the cellular membrane and their enhanced sensitivity with respect to cellular exonucleases. Besides, nonspecific modification of functional components of various cell structures by these reagents also presents some problem.⁶⁸ The permeability problem can be circumvented through the use of hydrophobic oligonucleotide derivatives (see

Ref. 69). Several approaches are now used to stabilise DNA fragments in the cell, such as construction of covalently closed dumbbell-like DNA duplexes,⁷⁰ cyclic DNAs,⁷¹ and DNA duplexes with covalently linked chains.⁷²

A serious limitation for the *in vivo* application of a vast number of reactive oligonucleotides is that an additional treatment (UV irradiation, heating, chemical reagents) are required for their activation. Therefore, the most promising reagents for *in vivo* application are apparently platinum derivatives and reactive nucleic acids containing substituted pyrophosphate or acyl phosphate groups. These compounds do not require additional activation; the mechanisms of their interaction with nucleic acid-recognising proteins have been studied in sufficiently great detail. Besides, they have already been used in nuclear cell extracts.^{54, 61} It should be noted, however, that modification of proteins with platinum derivatives of oligonucleotides in nuclear extracts is not always specific.⁵⁴ Besides, this procedure is inefficient unless mercapto derivatives of nucleic acids are used. At the same time, it has been shown⁶¹ that modification of the transcription factor HNF-1 in nuclear extracts of rat liver is highly specific and efficient. This circumstance gives every reason to believe that such compounds are promising for *in vivo* applications. In order to increase their resistance to cell exonucleases, it may be necessary to change their structure, *e.g.*, to design on their basis covalently closed DNA duplexes, or to synthesise DNA duplexes with covalently linked chains. The methods of their synthesis have already been developed^{61, 73–75} and the first encouraging results of the application of structures with substituted pyrophosphate groups for affinity modification of the proteins of nucleic acid metabolism have been obtained.⁷⁶

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^a — *Russ. J. Bioorg. Chem. (Engl. Transl.)*

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1,2,4-Triazine *N*-oxides and their annelated derivatives

D N Kozhevnikov, V L Rusinov, O N Chupakhin

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Abstract. This review deals with the synthesis and properties of 1,2,4-triazine *N*-oxides and their annelated derivatives. Methods for the incorporation of the *N*-oxide group in the 1,2,4-triazine ring by direct oxidation and cyclisation involving nitro, nitroso, and isonitroso groups are discussed. Reactions of 1,2,4-triazine *N*-oxides with electrophiles, nucleophiles, and dienophiles are considered. The effect of the *N*-oxide group on the chemical shifts in the ^1H , ^{13}C , and ^{14}N NMR spectra and the specific features of decomposition of 1,2,4-triazine *N*-oxides under electron impact are analysed. The bibliography includes 107 references.

I. Introduction

The present review discusses methods for the synthesis of 1,2,4-triazine *N*-oxides and reactions of these compounds. 1,2,4-Triazine is a heterocycle incorporated in many natural and synthetic compounds that possess biological activity and many practically useful properties.

The presence of the *N*-oxide group in the azine ring makes it sensitive both to nucleophilic and electrophilic attack and expands substantially the synthetic prospects for modifying nitrogen-containing heterocycles.¹ This is the reason for the ever increasing interest of investigators in heterocyclic *N*-oxides. A series of reviews on the chemistry of pyridine *N*-oxides,² pyrimidine *N*-oxides,³ and quinoxaline *N*-oxides⁴ have been published in the 90s. A monograph⁵ and several reviews^{6–9} on 1,2,4-triazines include special chapters on the chemistry of triazine *N*-oxides. However, data on the methods for the synthesis, reactivity, and properties of these compounds have not been systematised to date. The goal of this review is to bridge this gap.

II. Methods for the synthesis of 1,2,4-triazine *N*-oxides

Two main approaches are used to synthesise azines containing the *N*-oxide fragment. First, oxidation of nitrogen atoms of the ring with organic peracids or hydrogen peroxide in acidic media and, second, closing the azine ring with the participation of nitro,

nitroso, or isonitroso groups to give an *N*-oxide group.¹ Both of these methods are used for the synthesis of 1,2,4-triazine *N*-oxides.

1. Synthesis of 1,2,4-triazine 1- and 2-oxides by oxidation of 1,2,4-triazines

N-Oxides are formed rather readily in reactions of 1,2,4-triazines with organic peracids or hydrogen peroxide in the presence of carboxylic acids. In this case, only two of the three possible isomers are formed, namely, 1- and 2-oxides. The ratio of these isomers depends on the type of substituents in the starting 1,2,4-triazine.

For example, oxidation of 3-amino-1,2,4-triazines **1** gives mainly 2-oxides **2**. 3-Alkoxy-1,2,4-triazines **1** react with organic peracids to give solely 1,2,4-triazine 1-oxides **3**.^{11–14}

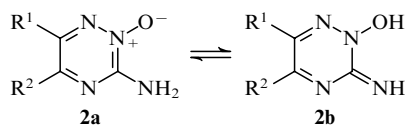
			Oxidising agent	Yield (%)		Ref.
R ¹	R ²	R ³		2	3	
H	H	NH ₂	<i>m</i> -ClC ₆ H ₄ CO ₃ H	80	0	10
H	Me	NH ₂	<i>m</i> -ClC ₆ H ₄ CO ₃ H	80	0	10
H	H	NH(CH ₂) ₂ Cl	<i>m</i> -ClC ₆ H ₄ CO ₃ H	51	0	10
H	Me	NH(CH ₂) ₂ Cl	<i>m</i> -ClC ₆ H ₄ CO ₃ H	77	0	10
H	Ph	NH(CH ₂) ₂ Cl	<i>m</i> -ClC ₆ H ₄ CO ₃ H	35	0	10
H	H	OMe	<i>m</i> -ClC ₆ H ₄ CO ₃ H	0	30	11
Me	Me	NH ₂	H ₂ O ₂ /AcOH	30	0	12
H	Ph	NH ₂	H ₂ O ₂ /AcOH	37	0	13
H	Ph	NHCOMe	H ₂ O ₂ /AcOH	45	0	13
H	Ph	NHCOEt	H ₂ O ₂ /AcOH	41	0	13
Me	Me	H	PhCO ₃ H	0	30	14
Ph	Ph	H	PhCO ₃ H	0	17	14
H	Ph	H	PhCO ₃ H	0	26	14
H	H	OMe	PhCO ₃ H	0	15	14
Ph	Ph	OMe	PhCO ₃ H	0	23	14
H	Me	OMe	PhCO ₃ H	0	26	14
H	Ph	OMe	PhCO ₃ H	0	39	14

Obviously, the possibility of amino–imino tautomerism **2a** ⇌ **2b** in 3-amino-1,2,4-triazine *N*-oxides stabilises the products of oxidation at position 2 of the triazine system.¹⁰

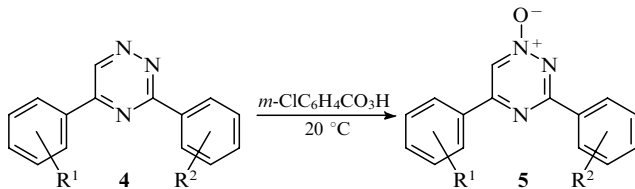
D N Kozhevnikov, V L Rusinov, O N Chupakhin Ural State Technical University, ul. Mira 19, 620002 Ekaterinburg, Russian Federation. Fax (7-343) 274 04 58. Tel. (7-343) 274 04 58 (D N Kozhevnikov), (7-343) 274 44 26. E-mail: azine@htf.rcupi.e-burg.su (O N Chupakhin)

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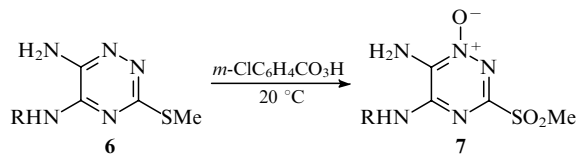
Oxidation of 3,5-diaryl-1,2,4-triazines **4** with *m*-chloroperbenzoic acid gives 1,2,4-triazine 1-oxides **5** in 75%–98% yields.¹⁵



$\text{R}^1 = \text{H}, 2\text{-Me}, 3\text{-Me}, 4\text{-Me}, 2\text{-Cl}, 3\text{-Cl}, 4\text{-Cl}, 3\text{-CF}_3$;

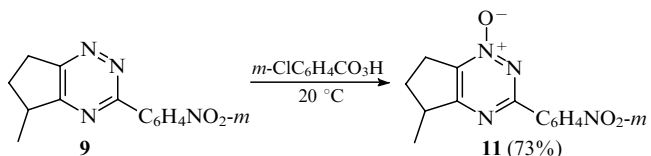
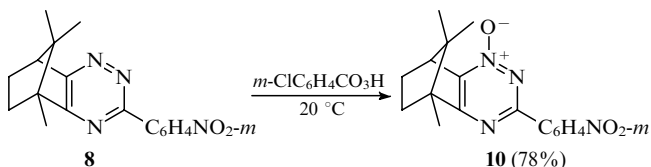
$\text{R}^2 = \text{H}, 4\text{-Br}, 2\text{-F}, 3\text{-F}, 4\text{-F}, 4\text{-Cl}, 4\text{-CF}_3$.

5,6-Diamino-3-methylsulfonyl-1,2,4-triazine 1-oxides **7** were prepared under the same conditions from 5,6-diamino-3-methylthio-1,2,4-triazines **6** in 60%–80% yields.¹⁶

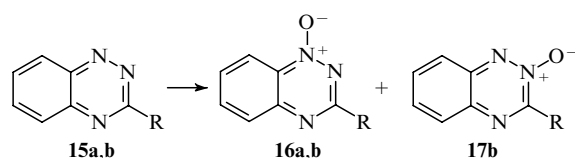
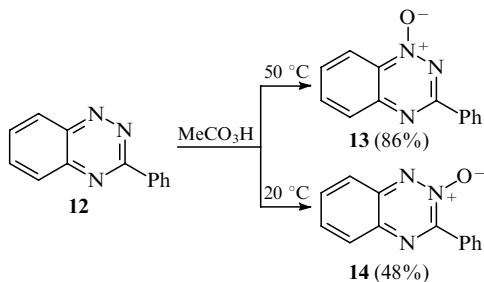


$\text{R} = \text{H}, \text{CH}_2\text{Ph}$.

Oxidation of 1,2,4-triazines containing the camphor (compound **8**) or methylcyclopentane fragments (compound **9**)¹⁷ with *m*-chloroperbenzoic acid affords solely triazine 1-oxides **10** and **11**.



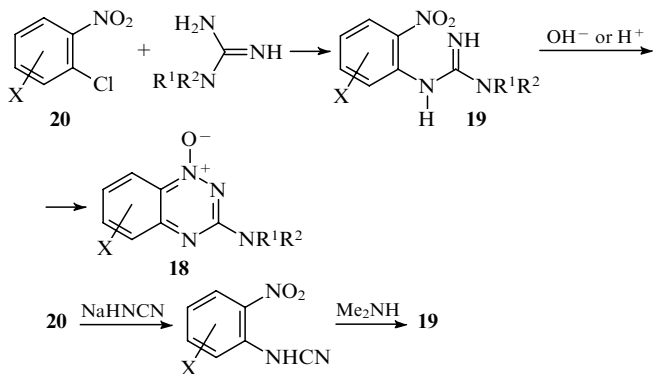
The reaction pathway also depends on the temperature. The reaction of 3-phenyl-1,2,4-benzotriazine **12** with peracetic acid affords 3-phenyl-1,2,4-benzotriazine 1-oxide **13** at 50 °C and 2-oxide **14** at 20 °C.¹⁸ Only the 1-oxide **16a** was obtained in 28% yield in the oxidation of 1,2,4-benzotriazine **15a**. Oxidation of 3-methyl-1,2,4-benzotriazine **15b** under the same conditions gives a mixture of 3-methyl-1,2,4-benzotriazine 1-oxide **16b** and 2-oxide **17b** in 25% and 10% yields, respectively.



$\text{R} = \text{H}$ (**a**), Me (**b**).

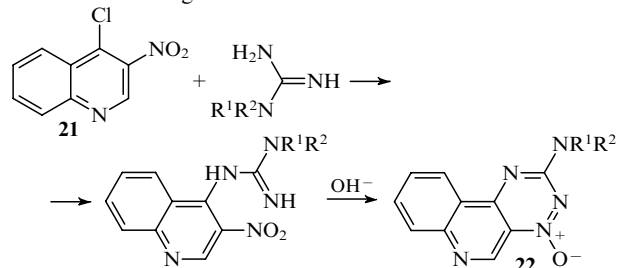
2. Synthesis of 1,2,4-triazine 1-oxides by cyclisation involving a nitro group

Aromatic and heteroaromatic nitro-compounds containing a guanidine fragment at the *ortho*-position relative to the nitro group readily undergo cyclisation in alkaline or acidic media to give benzo- or hetero-annulated 1,2,4-triazine 1-oxides. For example, 3-amino-1,2,4-benzotriazine 1-oxide **18** was obtained in 1913 by treatment of 2-nitrophenylguanidine **19** with an alkali.¹⁹ Subsequently, this approach was used to synthesise a number of 3-amino-1,2,4-benzotriazine 1-oxides of the type **18**.^{20–27} It is noteworthy that compound **19** can be obtained either by the reaction of guanidine with 2-nitrochlorobenzene **20** or by treatment of compound **20** with sodium cyanamide and dimethylamine (in the latter case, compounds **19** and **20** with $\text{R}^1 = \text{R}^2 = \text{Me}$ are formed).



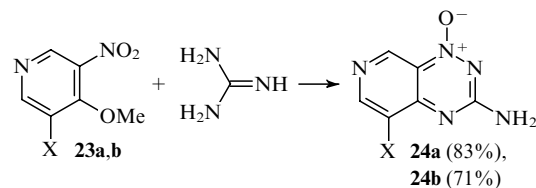
$\text{X} = \text{H}, \text{Me}, \text{Cl}, \text{Br}, \text{NO}_2, \text{OMe}, \text{CN}$.

In a similar way, 3-amino-1,2,4-triazino[6,5-*c*]quinoline 4-oxides **22** were synthesised in 62%–95% yields by the reaction of 4-chloro-3-nitroquinoline **21** with guanidine followed by cyclisation of substituted guanidines formed in an alkaline medium.²⁸

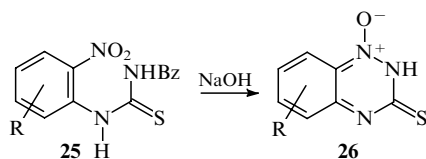


$\text{R}^1 = \text{H}, \text{Me}; \text{R}^2 = \text{H}, \text{Me}, \text{Et}, \text{Bu}^n, n\text{-C}_{10}\text{H}_{21}, \text{Bn}, (\text{CH}_2)_2\text{NEt}_2$.

The reaction of 4-methoxy-3-nitropyridines **23a,b** with guanidine under similar conditions affords 3-aminopyrido[3,4-*e*]-1,2,4-triazine 1-oxides **24a,b**.²⁹

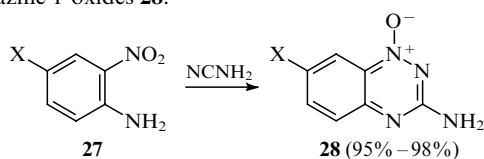


Cyclisation of *N*-(2-nitrophenyl)-*N'*-benzoylthiourea and its derivatives (compounds **25**) in an alkaline medium affords the corresponding 1,2,4-benzotriazine-3(2*H*)-thione 1-oxides **26**.³⁰



R = H (77%), 5-Cl (72%), 7-Cl (80%), 6-SH (40%), 7-Me (72%), 7-OMe (75%).

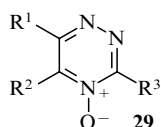
The reaction of *o*-nitroaniline and its 4-substituted derivatives (compounds **27**) with cyanamide gives 3-amino-1,2,4-benzotriazine 1-oxides **28**.²²



X = H, Me, OMe, Br, Cl, OPh, CN, NO₂.

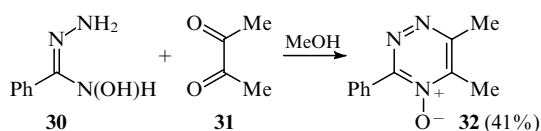
3. Preparation of 1,2,4-triazine 4-oxides by cyclisation involving a nitroso or isonitroso group

Unlike 1- and 2-oxides, 1,2,4-triazine 4-oxides **29** are not formed upon direct oxidation of the corresponding 1,2,4-triazines.

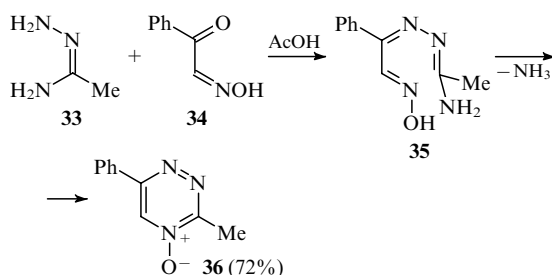


Therefore, the only possibility to prepare 1,2,4-triazines with the *N*-oxide group at position 4 is to synthesise the triazine cycle from compounds with nitroso or isonitroso groups. The synthesis can be carried out in several ways.

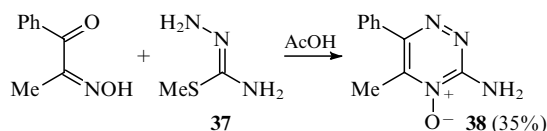
The reaction of hydroxyamidrazone **30** with dimethylglyoxal **31** in methanol affords 5,6-dimethyl-3-phenyl-1,2,4-triazine 4-oxide **32**.³¹



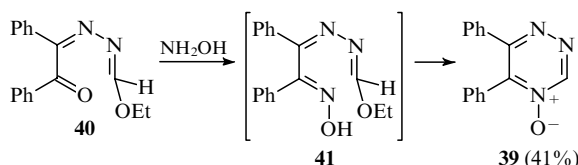
The condensation of amidrazone **33** with phenylglyoxal monooxime **34** occurs through the formation of hydrazone **35**. The elimination of an ammonia molecule from compound **35** gives 3-methyl-6-phenyl-1,2,4-triazine 4-oxide **36** in a good yield.³¹



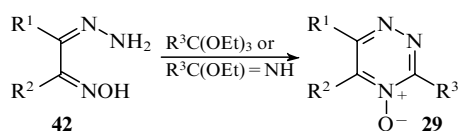
If aminoguanidine or *S*-methylisothiosemicarbazide **37** are used instead of amidrazone, 3-amino-1,2,4-triazine 4-oxides are formed. 3-Amino-5-methyl-6-phenyl-1,2,4-triazine 4-oxide **38** was synthesised in this way.^{32,33}



5,6-Diphenyl-1,2,4-triazine 4-oxide **39** was obtained by the reaction of diphenylglyoxal mono-2-ethoxymethylenhydrazone **40** with hydroxylamine.³¹ Obviously, formation of the intermediate **41** followed by its cyclisation to 1,2,4-triazine 4-oxide **39** occurs in this case.

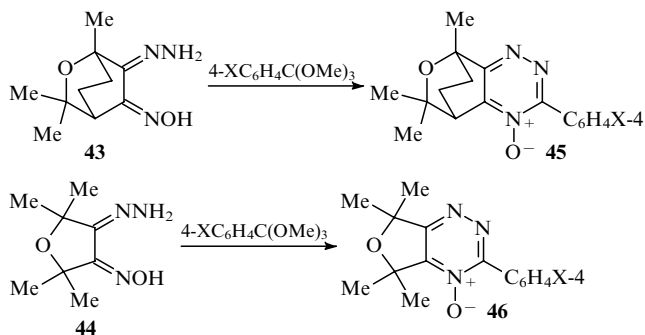


A more promising method for the synthesis of 1,2,4-triazine 4-oxides is the cyclisation of α -hydrazonooximes **42** with ortho-carboxylates or iminoesters. Rather a wide range of 1,2,4-triazine 4-oxides **29** was synthesized using this method.^{31,34-38}



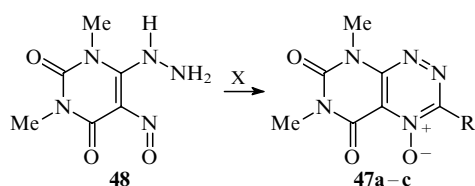
R ¹	R ²	R ³	Yield of 29 (%)	Ref.
Reagent R ³ C(OEt) ₃				
Me	H	Me	40	34
Me	Me	Me	80	34
Ph	Ph	Me	70	34
Me	H	Ph	53	34
Ph	Me	Me	70	34
Ph	Me	Et	60	34
Ph	Me	Ph	70	34
2-NO ₂ C ₆ H ₄	H	H	89	36
4-NO ₂ C ₆ H ₄	H	H	84	34
4-NO ₂ C ₆ H ₄	H	H	89	36
4-MeOC ₆ H ₄	H	H	80	34
Ph	H	H	86	31
Ph	H	Ph	57	31
Ph	Me	H	27	31
Me	Me	H	51	31
Me	H	H	23	31
Bu ^t	H	H	59	38
Bu ^t	H	Me	65	38
Bu ^t	H	Ph	43	38
Reagent R ³ C(OEt)=NH				
4-MeOC ₆ H ₄	H	4-NO ₂ C ₆ H ₄	16	34
Ph	Me	4-NO ₂ C ₆ H ₄	25	34
4-NO ₂ C ₆ H ₄	H	4-MeOC ₆ H ₄	16	34
Ph	H	4-MeOC ₆ H ₄	45	34
Ph	H	4-NO ₂ C ₆ H ₄	54	34
Ph	H	Me	51	31

Similarly, reactions of 5-isonitroso-1,3,3-trimethyl-2-oxabicyclo[2.3.3]octan-6-one hydrazone **43** and 4-isonitroso-2,2,5,5-tetramethyltetrahydrofuran-3-one **44** with the corresponding orthobenzoates afford 3-aryl-5,8-dihydro-6,6,8-trimethyl-5,8-ethanopyrano[4,3-*e*]-1,2,4-triazine 4-oxides **45** and 3-aryl-5,7-dihydro-5,5,7,7-tetramethylfurano[3,4-*e*]-1,2,4-triazine 4-oxides **46**.³⁹



X = Me, OMe, NO₂, CF₃, Cl, Br, F.

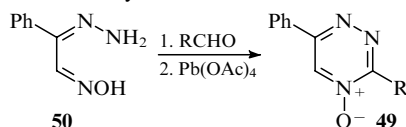
Annelated 1,2,4-triazine 4-oxides, *viz.*, 3-R-fervenulin 4-oxides **47**, were synthesised from 6-hydrazino-1,3-dimethyl-5-nitrosouracil **48**.^{40–42} Orthoesters, formic acid, or DMF in the presence of POCl₃ or dimethyl sulfate can be used as cyclisation agents.



X is cyclisation agent; R = H (**a**), Me (**b**), Et (**c**).

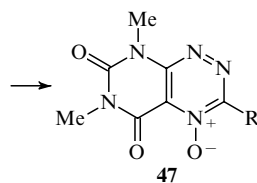
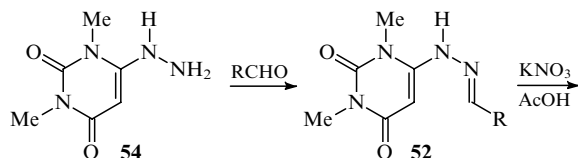
Compound	Cyclisation agent (X)	Yield of 47 (%)	Ref.
47a	HC(OEt) ₃	71	40–42
47b	MeC(OEt) ₃	76	40–42
47c	EtC(OEt) ₃	85	40
47a	HCOOH	54	40
47a	DMF–POCl ₃	72	40
47a	DMF–Me ₂ SO ₄	43	40

A new, rather simple method for the synthesis of 1,2,4-triazine 4-oxides **49** was suggested recently. It involves the condensation of isonitrosoacetophenone hydrazone **50** with aldehydes followed by oxidation of the condensation product with lead tetraacetate. This is a simple way to obtain 1,2,4-triazine 4-oxides with almost any aliphatic, aromatic, and heteroaromatic substituents at position 3 of the triazine cycle.⁴³

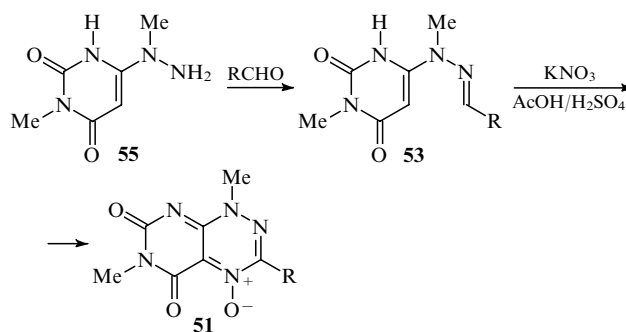


R = Me, Et, Prⁱ, C₇H₁₅, Ph, 4-NO₂C₆H₄, 4-BrC₆H₄,

To prepare fervenulin 4-oxides **47** or toxoflavine 4-oxides **51**, it is convenient to use the reaction of 1,3-dimethyl-2,4-dioxypyrimidin-6-yl hydrazone **52** or *N*-(3-methyl-2,4-dioxypyrimidin-6-yl) *N*-methylhydrazone **53** with potassium nitrate in acetic acid.^{44–48} Sometimes, diethylazo diformate is used instead of potassium nitrate.⁴⁹ In this case, cyclisation occurs simultaneously with the formation of the NO group. Compounds **52** and **53** were synthesised from the corresponding hydrazines **54** and **55** and aldehydes.

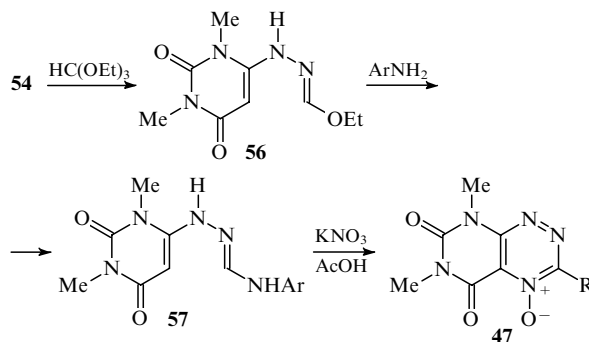


R	Yield of 47 (%)	Ref.
Ph	68	44
	54	49
4-ClC ₆ H ₄	50	44
	43	49
3,4-Cl ₂ C ₆ H ₃	65	44
	61	49
4-MeOC ₆ H ₄	63	49
4-Me ₂ NC ₆ H ₄	58	49
4-NO ₂ C ₆ H ₄	45	44



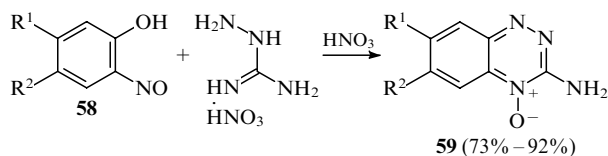
R	Yield of 51 (%)	Ref.
H	56	48
Me	63	49
Ph	51	48
4-ClC ₆ H ₄	46	48
3,4-Cl ₂ C ₆ H ₃	67	48
4-MeC ₆ H ₄	54	48
4-Me ₂ NC ₆ H ₄	50	49
PhCH=CH	46	48
	61	48

3-Anilinofervenulin 4-oxides **47** (R = ArNH) were obtained by the reaction of 6-hydrazino-1,3-dimethyluracil **54** with triethyl orthoformate followed by substitution of the ethoxy group in the resulting hydrazide **56** with an aniline residue and further cyclisation of compound **57** under nitrosation conditions.⁴⁶



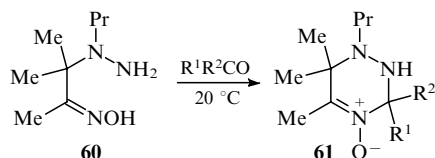
R = ArNH = PhNH (51%), 4-ClC₆H₄NH (63%), 4-BrC₆H₄NH (49%), 4-MeOC₆H₄NH (47%), 4-MeC₆H₄NH (56%).

2-Nitrosophenols **58** react with aminoguanidine nitrate in the presence of nitric acid. This method gave 3-amino-1,2,4-benzotriazine 4-oxides **59**.⁵⁰



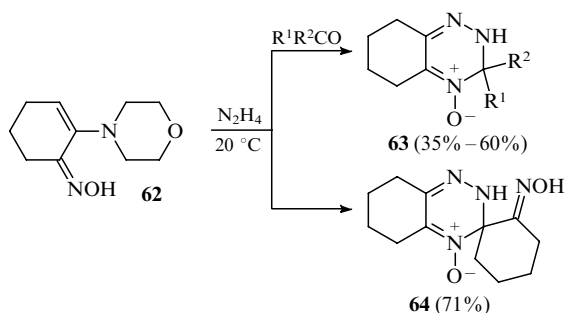
$R^1 = \text{Cl, Br, Me; } R^2 = \text{H, Me.}$

Reaction of 3-hydrazino-3-methylbutan-2-one oxime **60** with aldehydes and ketones affords 3- R^1 -3- R^2 -1,3,4,6-tetrahydro-5,6,6-trimethyl-1,2,4-triazine 4-oxides **61**.⁵¹



$R^1 = \text{H, Me; } R^2 = \text{H, Me, Pr}^i.$

Condensation of 1-morpholino-6-oximinocyclohexene **62** with hydrazine hydrate and ketones gives 2,3,5,6,7,8-hexahydro-1,2,4-benzotriazine 4-oxides **63**. In the absence of a carbonyl compound, this reaction leads to spiro compound **64**.⁵²

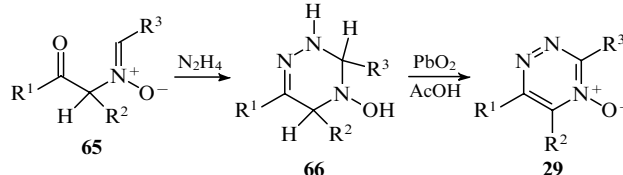


$R^1, R^2 = \text{Me, CH}_2\text{Ph; } R^1 - R^2 = (\text{CH}_2)_5, (\text{CH}_2)_6.$

4. Other methods for the synthesis of 1,2,4-triazine 4-oxides

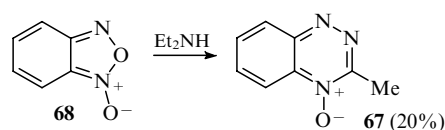
There is a method for the synthesis of 1,2,4-triazine 4-oxides that is fundamentally different from those discussed above.⁵³ The reaction of nitrones **65** with an excess of hydrazine afforded 4-hydroxy-2,3,4,5-tetrahydro-1,2,4-triazines **66**. Subsequent oxida-

tion with Pb(IV) oxide resulted in the corresponding triazine 4-oxides **29**.



R^1	R^2	R^3	Yield of 29 (%)
Ph	Me	Et	57
Ph	Me	Ph	70
Me	Me	Ph	52
Ph	H	Ph	51

3-Methyl-1,2,4-benzotriazine 4-oxide **67** was obtained by the reaction of benzofurazan oxide **68** with diethylamine.^{54, 55}



III. Physicochemical characteristics of 1,2,4-triazine *N*-oxides

The incorporation of an *N*-oxide fragment in the 1,2,4-triazine molecule changes substantially the ¹H, ¹³C, and ¹⁵N NMR spectra.

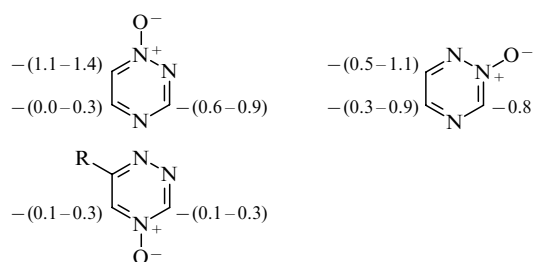
In ¹H NMR spectra of 1,2,4-triazine 1-oxides, the signals of the protons at positions 3 and 6 are observed at 9.00 and 8.04 ppm, *i.e.*, they are shifted upfield by 0.6–0.7 and 1.1–1.2 ppm, respectively, in comparison with those in the 1,2,4-triazines, but the signal of the H(5) proton (8.57 ppm) remains almost unchanged.^{10, 14, 56}

A comparison of the ¹H NMR spectra of 1,2,4-triazine 4-oxides with those of the corresponding 1,2,4-triazines shows that the signals of the H(3) and H(6) protons have an almost similar upfield shift ($\Delta\delta = -0.8$ ppm), and their chemical shifts are 8.82 and 8.42 ppm, respectively. The signal of the H(5) proton is also shifted upfield by 0.3 ppm ($\delta = 8.00$ ppm) (Table 1).¹⁰

Table 1 Chemical shifts of cyclic protons in the ¹H NMR spectra of 1,2,4-triazines and their *N*-oxides in CDCl₃.

Compound	δ /ppm			$\Delta\delta$ /ppm			Ref.
	H(3)	H(5)	H(6)	H(3)	H(5)	H(6)	
1,2,4-Triazine	9.63	8.53	9.24				10
1,2,4-Triazine 1-oxide	9.00	8.57	8.04	−0.63	0.04	−1.20	10, 14
1,2,4-Triazine 2-oxide	8.82	8.00	8.42	−0.81	−0.53	−0.82	10
3-Methoxy-1,2,4-triazine		8.56	9.16				56
3-Methoxy-1,2,4-triazine 1-oxide		8.37	7.83		−0.19	−1.33	14
3-Methoxy-1,2,4-triazine 2-oxide		7.70	8.12		−0.86	−1.04	10
3-Amino-1,2,4-triazine ^a		8.53	8.88				10
3-Amino-1,2,4-triazine 2-oxide ^a		8.19	8.23		−0.34	−0.65	10
3-(<i>N,N</i> -Dimethylamino)-1,2,4-triazine		8.14	8.15				10
3-(<i>N,N</i> -Dimethylamino)-1,2,4-triazine 1-oxide		7.76	7.86		−0.38	−0.65	10
3-Morpholino-1,2,4-triazine		8.14	8.54				57
3-Morpholino-1,2,4-triazine 2-oxide		7.81	8.54		−0.33	−0.52	10
6-Methyl-1,2,4-triazine	9.55	8.55					31
6-Methyl-1,2,4-triazine 4-oxide	9.28	8.22		−0.27	−0.33		31
6-Phenyl-1,2,4-triazine	9.52	8.91					31
6-Phenyl-1,2,4-triazine 4-oxide	9.31	8.60		−0.21	−0.31		31

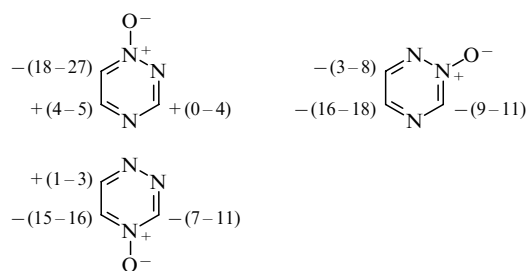
^a In [²H₆]DMSO.



The incorporation of an *N*-oxide group at position 4 of the triazine system shifts the signals of the H(3) and H(5) protons upfield by 0.1–0.3 ppm (the 9.28–9.47 and 8.55–8.90 ppm regions). It should be noted that, unlike the case of 1,2,4-triazines, these signals in 1,2,4-triazine 4-oxides appear as doublets ($J = 1.8$ Hz) (see Table 1).³¹

The ¹³C NMR spectra are also changed upon the introduction of the *N*-oxide fragment. In 1,2,4-triazine 4-oxides, the signals of the carbon atoms in the *ortho*- and *para*-positions with respect to the N–O fragment are shifted upfield by 18–20 ppm for 1-oxides, 9–18 ppm for 2-oxides, and 10–15 ppm for 4-oxides in comparison with those of the corresponding 1,2,4-triazines,^{39, 58–62} but the signal of the carbon atom in the *meta*-position is almost not shifted (Table 2).^{10, 39}

Thus, comparison of the ¹³C NMR spectra of 1,2,4-triazines and their oxides allows one to determine easily the position of the *N*-oxide group.



¹⁵N NMR spectroscopic data also allow the determination of the position of the *N*-oxide group. On going from 1,2,4-triazines to their 1-oxides, the maximum upfield shift is observed for the nitrogen atom in position 1 [$\Delta\delta = -(83-87)$ ppm]. The signals of the N(2) and N(4) atoms are shifted upfield to a much smaller extent [$\Delta\delta = -(39-46)$ ppm and $\Delta\delta = -(22-24)$ ppm, respectively]. For 1,2,4-triazine 2-oxides, the situation is somewhat different. The signals of the N(1) and N(2) atoms are shifted upfield by almost the same value [$\Delta\delta = -(70-75)$ ppm], but the signal of the nitrogen atom in position 4 is almost not shifted [$\Delta\delta = -(13-23)$ ppm] (Table 3).^{63–65}

The IR spectra of 1,2,4-triazine *N*-oxides,⁵³ as well as those of *N*-oxides of other azines,¹ contain a characteristic band of stretching vibration of the N–O group in the region near 1250 cm^{–1}.

The absorption maximum in the UV spectrum of 3,4-diphenyl-1,2,4-triazine 4-oxide is around 286 nm ($\log \varepsilon = 4.57$).⁵³

Table 3 Signals of cyclic nitrogen atoms in the ¹⁵N NMR spectra of 1,2,4-triazines and their *N*-oxides⁶³ in [²H₆]DMSO relative to MeNO₂.

Compound	δ / ppm			$\Delta\delta$ / ppm		
	N(1)	N(2)	N(4)	N(1)	N(2)	N(4)
1,2,4-Triazine	40.0	2.0	–62.0			
1,2,4-Triazine 1-oxide	–43.0	–	–	–83	–	–
3-Methoxy-1,2,4-triazine	36.0	–58.0	–124.4			
3-Methoxy-1,2,4-triazine 1-oxide	–50.0	–97.1	–148.0	–86.0	–38.9	–23.6
3-Amino-1,2,4-triazine	35.7	–61.0	–130.0			
3-Amino-1,2,4-triazine 1-oxide	–51.1	–107.0	–152.0	–86.8	–46.0	–22.0
3-Amino-1,2,4-triazine 2-oxide	–39.0	–137.0	–153.0	–74.7	–76.0	–23.0

Table 2 Chemical shifts of carbon atoms in the ¹³C NMR spectra of 1,2,4-triazine *N*-oxides in [²H₆]DMSO.

Compound	δ / ppm			$\Delta\delta$ / ppm			Ref.
	C(3)	C(5)	C(6)	C(3)	C(5)	C(6)	
1,2,4-Triazine 1-oxide ^a	158.5	152.7	129.7	–0.4	3.1	–21.1	60
1,2,4-Triazine 2-oxide ^a	143.5	132.5	146.0	–14.6	–17.1	–4.8	60
3-Methoxy-1,2,4-triazine 1-oxide ^a	166.5	154.0	124.5	2.5	4.0	–18.5	10
3-Methoxy-1,2,4-triazine 2-oxide ^a	152.5	130.0	135.5	–11.5	–20.0	–7.5	10
3-Amino-1,2,4-triazine 1-oxide	165.0	155.9	120.7	1.7	6.1	–19.9	60
3-Amino-1,2,4-triazine 2-oxide	151.6	132.4	134.9	–11.7	–17.4	–5.7	60
3-(<i>N,N</i> -Dimethylamino)-1,2,4-triazine 1-oxide ^a	161.0	152.0	120.0	1.0	4.0	–18.0	10
3-(<i>N,N</i> -Dimethylamino)-1,2,4-triazine 2-oxide ^a	151.0	132.0	133.0	–9.0	–16.0	–5.0	10
3-Amino-5,6-dimethyl-1,2,4-triazine 1-oxide	166.0	164.3	119.4	3.9	5.4	–27.7	60
3-Amino-5,6-dimethyl-1,2,4-triazine 2-oxide	148.9	140.2	144.2	–13.2	–18.7	–2.9	60
3-Amino-5,6-dimethyl-1,2,4-triazine 4-oxide	154.4	143.0	148.7	–7.7	–15.9	1.6	60
5-Methyl-1,2,4-triazine 1-oxide ^a	158.7	166.1	129.1	1.7	5.6	–21.8	60
6-Phenyl-1,2,4-triazine 1-oxide	149.9	132.0	157.5	–	–	–	60
3-Methyl-6-phenyl-1,2,4-triazine 4-oxide	159.4	131.4	156.4	–	–	–	60
3,6-Diphenyl-1,2,4-triazine 4-oxide	156.2	132.8	155.6	–	–	–	60
3-Ethyl-6-phenyl-1,2,4-triazine 4-oxide	161.9	131.4	156.3	–	–	–	60
5-Ethyl-5-(indol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	161.0	135.5	156.7	–	–	–	62
5-(1-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.0	139.4	157.3	–	–	–	62
3-Ethyl-5-(1-methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	160.8	136.0	135.8	–	–	–	62
5-(1-Methylindol-3-yl)-3,6-diphenyl-1,2,4-triazine 4-oxide	156.1	136.1	156.0	–	–	–	62
5-(2-Methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	149.9	142.8	160.9	–	–	–	62
3-Methyl-5-(2-methylindol-3-yl)-6-phenyl-1,2,4-triazine 4-oxide	157.9	140.2	158.9	–	–	–	62

^a In CDCl₃.

A molecular ion peak (often with the maximum intensity) and intense $[M - 16]^+$ and $[M - 17]^+$ peaks typical of this class of compounds are observed in the mass spectra of 1,2,4-triazine 1- and 2-oxides. The fragmentation of 1,2,4-triazine 1- and 2-oxides is similar, which prevents an unambiguous determination of the position of the *N*-oxide group.^{62, 66, 67} However, a somewhat different picture is observed in the case of 1,2,4-triazine 4-oxides. The characteristic feature of their mass spectra is the existence of an intense molecular ion peak and a very weak $[M - 16]^+$ peak.³¹

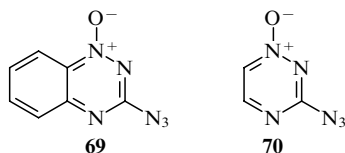
The X-ray diffraction data for 3,6-diphenyl-5-(indol-3-yl)-1,2,4-triazine 4-oxide⁶² showed that the 1,2,4-triazine 4-oxide fragment and the substituents are non-coplanar, the slopes of the corresponding planes being within 30–50°.

IV. Chemical properties of 1,2,4-triazine-*N*-oxides

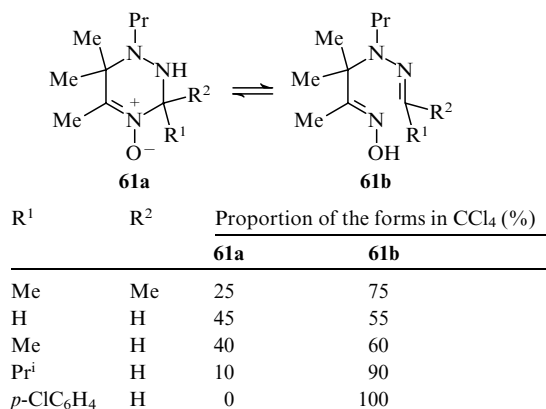
1. Tautomerism

The amino–imino tautomerism is typical of 3-amino-1,2,4-triazine 4-oxides **2a**. This is the reason for the formation of 2-oxides in the oxidation of 3-amino-1,2,4-triazines **1**.¹⁰

3-Azido-1,2,4-benzotriazine 1-oxides **69** exist only in the form of azides, both in the crystal state and in solution. This is also true for 3-azido-1,2,4-triazine 1-oxides **70**, which have not been found in the tetrazole form in any aggregation state.^{68–70}



Ring–chain tautomerism is observed for the series of 1,2,3,6-tetrahydro-1,2,4-triazine 4-oxides **61**.⁵¹ These compounds exist solely as hydrazones **61b** both in solution and in the crystal form. In aprotic non-polar solvents (*e.g.*, CCl₄), the fraction of the cyclic form **61a** is as high as 45%, depending on the nature of the substituents R¹ and R².



Ring–chain transformations are also observed for 3,4-dihydro-4-hydroxy-1,2,4-triazines **71**. For example, compounds **71** in DMSO-*d*₆ exist both in a cyclic form **71a** and in an open form **71b**. It was found that aliphatic substituents at position 3 of 3,4-dihydro-1,2,4-triazine **71** shift the equilibrium towards the cyclic form **71a**, while aromatic and heteroaromatic substituents, towards the open form **71b** (Table 4). An increase in temperature increases the fraction of hydrazone **71b**. Analysis of high-resolution mass spectra of these compounds made it possible to find out that the cyclic form **71a** prevails (70%–90%) in the gas phase.⁷¹

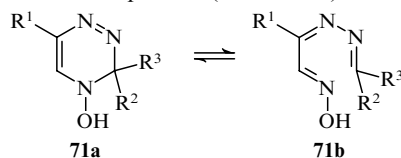
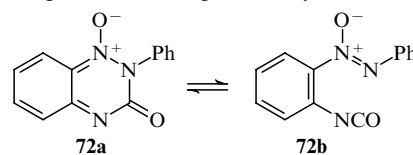


Table 4. Ratio of the cyclic (**71a**) to the open (**71b**) forms of 3,4-dihydro-4-hydroxy-6-phenyl-1,2,4-triazine **71** in [2H₆]DMSO and in gas phase.⁷¹

R ¹	R ²	R ³	Isomer ratio (%)			
			solution		gas phase	
			71a	71b	71a	71b
Ph	H	Me	100	0	72	22
Ph	H	Et	100	0		
Ph	H	Pr ⁱ	100	0	90	10
Ph	H	C ₇ H ₁₅	90	10	80	20
Ph	H	Ph	23	77	82	18
Ph	H	2-NO ₂ C ₆ H ₄	5	95		
Ph	H	4-NO ₂ C ₆ H ₄	8	92		
Ph	H	4-HOC ₆ H ₄	7	93	75	25
Ph	H	3,4-(HO) ₂ C ₆ H ₃	35	65	85	15
Ph	H	4-BrC ₆ H ₄	15	85	11	89
Ph	H	4-NMe ₂ C ₆ H ₄	0	100		
Ph	H	CO ₂ H	100	0		
Ph	H		7	93		
Ph	Me	Me	90	10		
Ph	Me	Ph	50	50		
Ph	Me	CH ₂ CO ₂ Et	0	100		
Ph	–(CH ₂) ₄ –		96	4		
Ph	–(CH ₂) ₅ –		82	18		
Me	H	4-NO ₂ C ₆ H ₄	0	100		
Me	H	4-HOC ₆ H ₄	0	100		
Me	H	4-NMe ₂ C ₆ H ₄	0	100		

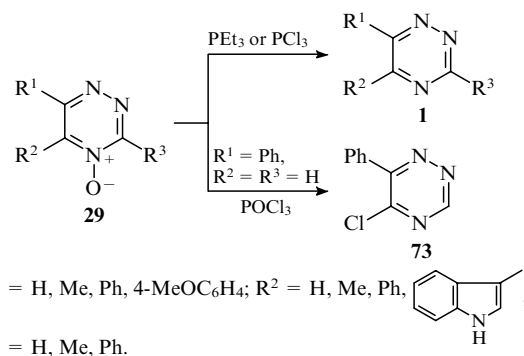
2-Phenyl-1,2,4-benzotriazin-3(2*H*)-one 1-oxide **72**, which exists in the cyclic form **72a** when in the crystal, undergoes ring opening in solution to give 2-isocyanatoazoxybenzene **72b**.⁷²



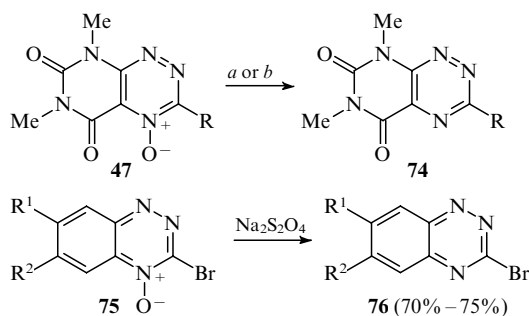
2. Deoxygenation

Elimination of oxygen (deoxygenation) occurs in 1,2,4-triazine *N*-oxides, as well as in other azine *N*-oxides, upon treatment with reducing agents.

The reaction of 1,2,4-triazine *N*-oxides **29** with triethylphosphine or PCl₃ resulted in the corresponding 1,2,4-triazines **1** (in 65%–95% yield), which were impossible to synthesise by other methods.^{31, 35} If POCl₃ is used in this reaction, deoxygenation is accompanied by chlorination of 1,2,4-triazine. For example, 5-chloro-6-phenyl-1,2,4-triazine **73** was obtained in 37% yield from 6-phenyl-1,2,4-triazine 4-oxide.⁷³

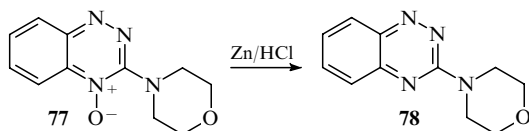


Sodium dithionite can be used for the reduction of 1,2,4-triazine 4-oxides. This method has been used in the synthesis of fervenulins **74** from fervenulin 4-oxides **47**⁴¹ and 3-bromo-1,2,4-benzotriazines **76** from 3-bromo-1,2,4-benzotriazine 4-oxides **75**.⁶⁹ Boiling of fervenulin 4-oxide **47** in DMF results in its thermal deoxygenation to form fervenulin **74**.⁴⁰

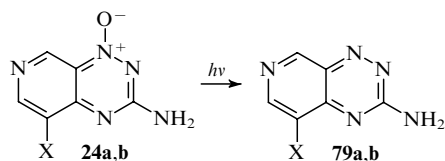


(a): Na₂S₂O₄ (55%–90%); (b): DMF, 150 °C (60%).

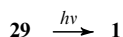
The reaction of 3-morpholino-1,2,4-benzotriazine 4-oxide **77** with zinc in hydrochloric acid afforded 3-morpholino-1,2,4-benzotriazine **78**.⁷⁴



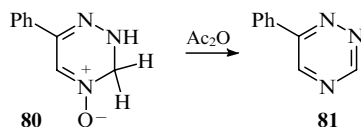
UV irradiation of 3-aminopyrido[4,3-*e*]-1,2,4-triazine 1-oxides **24a,b** or 1,2,4-triazine 4-oxides **29** is also accompanied by the loss of the *N*-oxide group^{75,76} and gives the corresponding 3-aminopyrido[4,3-*e*]-1,2,4-triazines **79a,b** or 1,2,4-triazines **1**.



X = H (**a**), Cl (**b**).



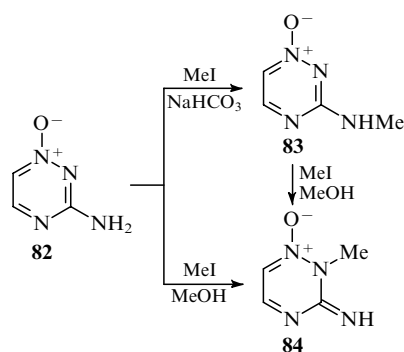
The reaction of 2,3-dihydro-6-phenyl-1,2,4-triazine 4-oxide **80** with acetic anhydride leads to deoxygenation and aromatisation of the former to give 6-phenyl-1,2,4-triazine **81**.⁷⁷



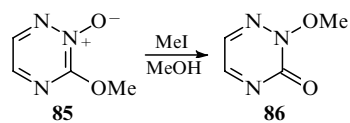
3. Reaction with electrophilic agents

a. Alkylation

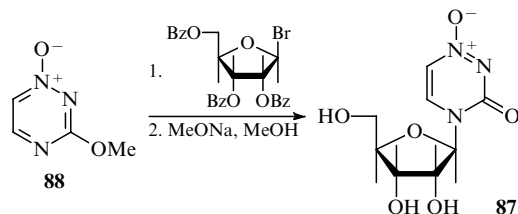
The reaction of 3-amino-1,2,4-triazine 1-oxide **82** with methyl iodide in the presence of sodium bicarbonate results in methylation of the amino group to give 3-methylamino-1,2,4-triazine 1-oxide **83**. In neutral media, the N(3) atom of the cycle in 1,2,4-triazine 1-oxide **82** undergoes methylation resulting in 3-imino-2-methyl-1,2,4-triazine 1-oxide **84**. It is interesting that 1-oxide **83** undergoes rearrangement to 1-oxide **84** in methanol in the presence of methyl iodide.



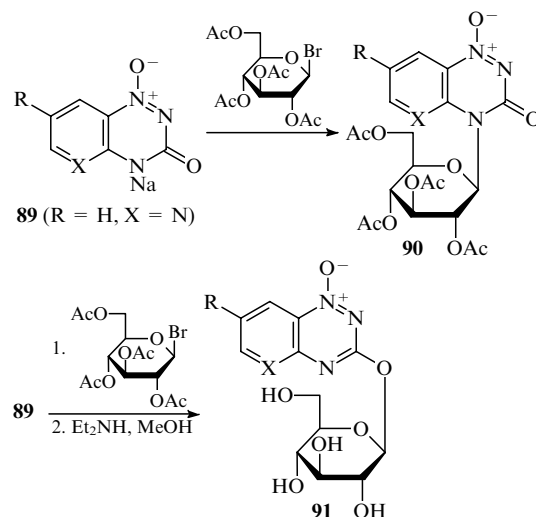
3-Methoxy-1,2,4-triazine 1-oxide **85** undergoes the same rearrangement under the same conditions and transforms into 2-methoxy-1,2,4-triazin-3-one **86**.⁷⁸



An abnormal nucleoside, 4-(β-D-ribofuranosyl)-1,2,4-triazin-3(4*H*)-one 1-oxide **87**, was obtained in 38% yield by the reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl bromide with 3-methoxy-1,2,4-triazine 1-oxide **88** followed by the removal of the benzoyl protective groups with sodium methoxide.¹¹

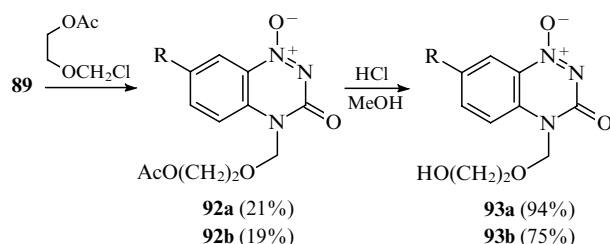


The reaction of the sodium salt of pyrido[2,3-*e*]-1,2,4-triazine-3(4*H*)-one 1-oxide **89** (X = N) or 1,2,4-benzotriazine-3(4*H*)-one 1-oxides **89** (X = CH) with acetobromoglucose allows one to obtain the tetraacetyl derivatives of β-D-glucopyranosides **90**, the deacetylation of which affords nucleosides **91**.⁷⁹



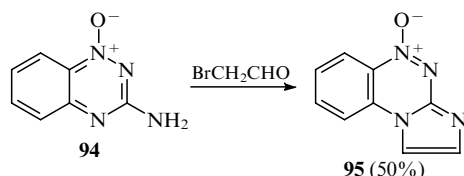
R = Me; X = CH.

The reaction of compounds **89** (X = CH; R = H, Me) with 2-chloromethoxyethyl acetate results in *N*-alkylation products **92a,b**. Their subsequent hydrolysis affords 4-(2-hydroxyethoxymethyl)-1,2,4-benzotriazin-3(4*H*)-one 1-oxides **93a,b**.⁷⁹

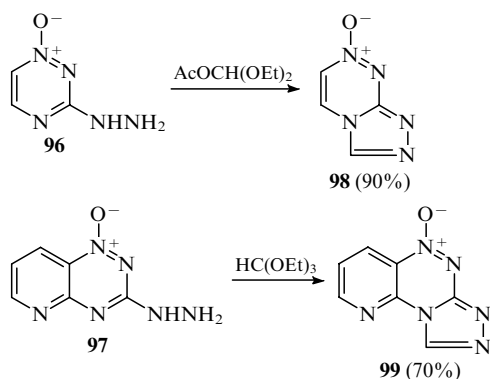


R = H (a), Me (b).

3-Amino-1,2,4-benzotriazine 1-oxide **94** undergoes the Chichibabin reaction with bromoacetaldehyde to give imidazo[2,1-*c*]-1,2,4-benzotriazine 1-oxide **95**.⁸⁰

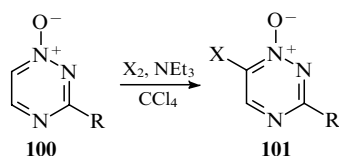


Reactions of 3-hydrazino-1,2,4-triazine 1-oxide **96** or 3-hydrazinopyrido[2,3-*c*]-1,2,4-triazine 1-oxide **97** with diethoxymethyl acetate or triethyl orthoformate followed by cyclisation afford the corresponding pyrazolo[3,4-*c*]-1,2,4-triazine 6-oxides **98** and **99**.^{81–83}



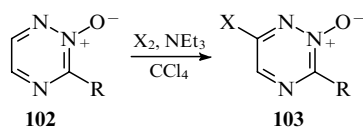
b. Electrophilic substitution of hydrogen

Halogenation of 3-*R*-1,2,4-triazine 1- and 2-oxides has been described.^{67,84} The reaction of 3-methoxy and 3-amino(alkylamino)-1,2,4-triazine 1-oxides **100** with chlorine or bromine in CCl_4 in the presence of triethylamine results in the corresponding 6-chloro- or 6-bromo-1,2,4-triazine 1-oxides **101**.



X = Cl, Br; R = OMe, NH_2 , NHMe , NMe_2 .

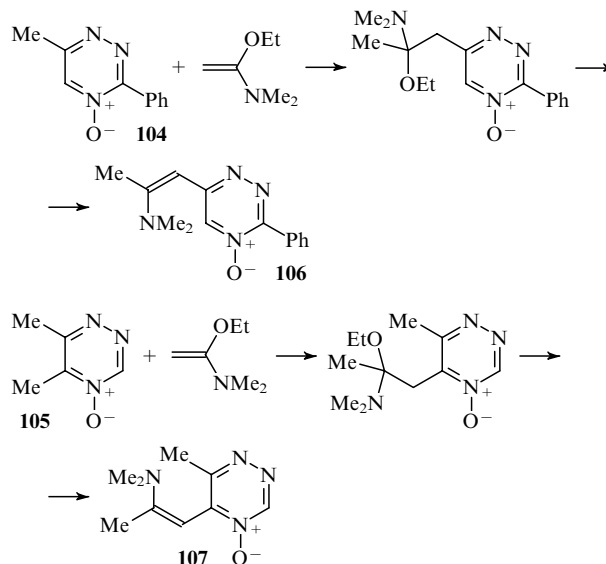
Halogenation of 3-methoxy- and 3-methyl(dimethyl)amino-1,2,4-triazine 2-oxides **102** occurs in a similar way to give 6-halo-derivatives **103**.



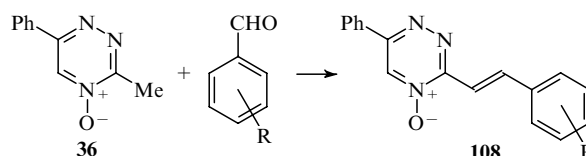
X = Cl, Br; R = OMe, NHMe , NMe_2 .

c. Other reactions

1-(Dimethylamino)-1-ethoxyethylene acts as an electrophilic agent in the reactions with 1,2,4-triazine 4-oxides **104** and **105** containing a methyl group at position 5 and/or 6. The addition of an olefin to the methyl group followed by elimination of ethanol results in the corresponding (2-dimethylamino)-1-propenyl-1,2,4-triazine 4-oxides **106** and **107**.⁸⁵

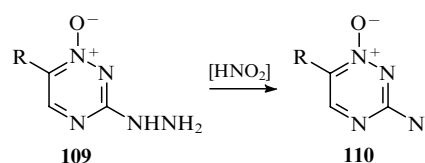


The reactivity of the hydrogen atoms of the methyl group in 1,2,4-triazine 4-oxide **36** allows one to make this compound react with nitrobenzaldehydes. This reaction gave 3-[2-(*R*-nitrophenyl)-vinyl]-6-phenyl-1,2,4-triazine 4-oxides **108**.⁷⁶



R = 2- NO_2 (27%), 3- NO_2 (47%), 4- NO_2 (48%).

The reaction of 3-hydrazino-1,2,4-triazine 1-oxides **109** with nitrous acid affords 3-azido-1,2,4-triazine 1-oxides **110**.^{68,84}

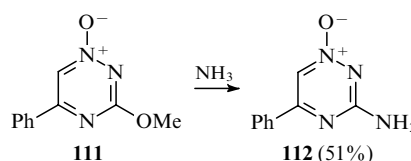


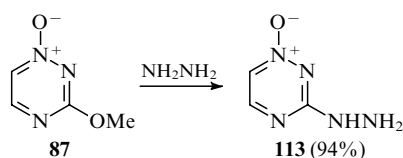
R = H (80%), Me (82%), Ph (85%).

4. Reactions with nucleophilic agents

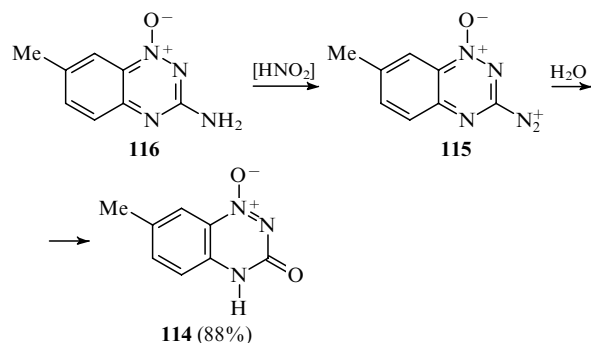
a. Nucleophilic substitution of readily leaving groups

Substitution of nucleofugal groups is a widespread method for the modification of 1,2,4-triazine *N*-oxides. The reaction of 3-methoxy-5-phenyl-1,2,4-triazine 1-oxide **111** with ammonia afforded 3-amino-5-phenyl-1,2,4-triazine 1-oxide **112**. The reaction of 3-methoxy-1,2,4-triazine 1-oxide **87** with hydrazine results in 3-hydrazino-1,2,4-triazine 1-oxide **113**.¹⁴

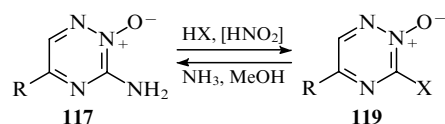




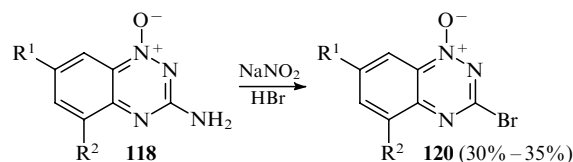
7-Methyl-1,2,4-benzotriazin-3(4*H*)-one 1-oxide **114** can be obtained in a good yield by replacement of the diazo group by OH in 3-diazo-7-methyl-1,2,4-benzotriazine 1-oxide **115**, which is formed upon the reaction of the corresponding amino derivative **116** with nitrous acid.⁷⁹



Similarly, diazotisation of 3-amino-1,2,4-triazine 2-oxides **117** or 1-oxides **118** results in the replacement of the diazo group by a halogen on treatment with hydrochloric or hydrobromic acids and affords the corresponding 2-oxides **119**¹⁰ or 1-oxides **120**.⁶⁹

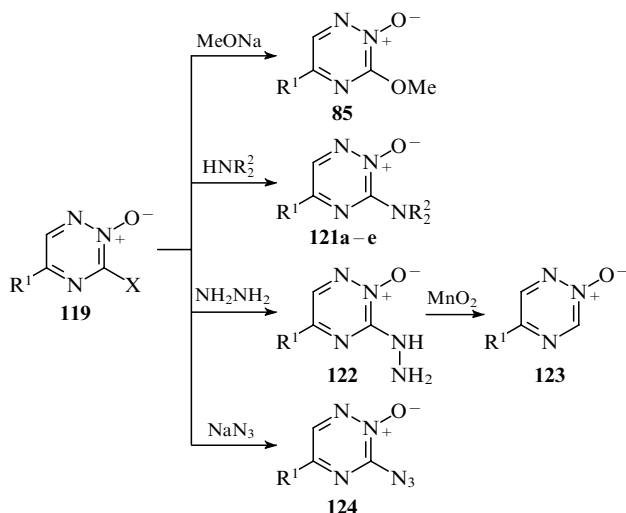


X = Cl: R = H (34%), Me (32%), Ph (26%); X = Br, R = H (47%).



R¹, R² = H, Me.

In turn, the halogen atom can be replaced by a different functional group. 3-Methoxy-1,2,4-triazine 2-oxide **85** (R = H) was obtained by the reaction of 3-bromo-1,2,4-triazine 2-oxide **119** with sodium methoxide. When secondary amines are used as nucleophiles, 3-amino-derivatives of 1,2,4-triazine 2-oxides **121a–e** are formed. 3-Hydrazino-1,2,4-triazine 2-oxide

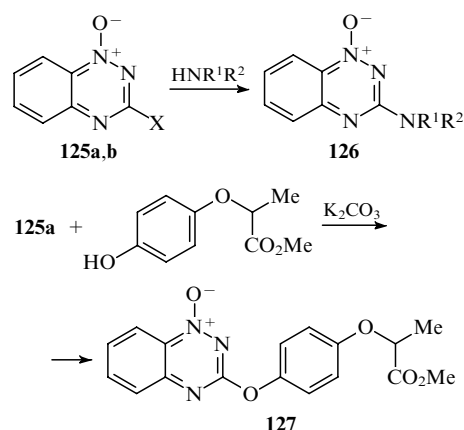


R¹ = H, Me; X = Br.

Compound	R ¹	NR ₂ ²	Yield (%)	Ref.
85	H		10	10
121a	H		95	10
121b	Me		90	10
121c	H		93	10
121d	H		95	10
121e	H	NMe ₂	93	10
122	H		69	10
123	H		27	10
124	H		86	68

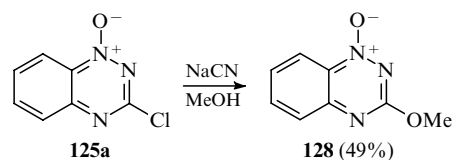
122 was synthesised by the replacement of bromine in 2-oxide **119** by hydrazine. The subsequent oxidation of compound **122** with Mn(IV) oxide afforded 1,2,4-triazine 2-oxide **123**,¹⁰ but the reaction of compound **119** with sodium azide gave 3-azido-1,2,4-triazine 2-oxide **124**.⁶⁸

Reactions of 3-chloro- or 3-methylthio-1,2,4-benzotriazine 1-oxides **125a,b** with amines result in 3-amino-derivatives of 1,2,4-benzotriazine 1-oxides **126**.^{24, 74, 86, 87} Replacement of the halogen in 3-chloro-1,2,4-benzotriazine 1-oxide **125a** upon the reaction with methyl 2-(4-hydroxyphenoxy)propionate proceeds in a similar way. For example, compound **127** was synthesised by this method.^{88, 89}



X = Cl (a), SMe (b).

Replacement of chlorine in the 3-chloro-derivative **125a** on treatment with sodium cyanide in methanol affords 3-methoxy-1,2,4-benzotriazine 1-oxide **128**.⁹⁰

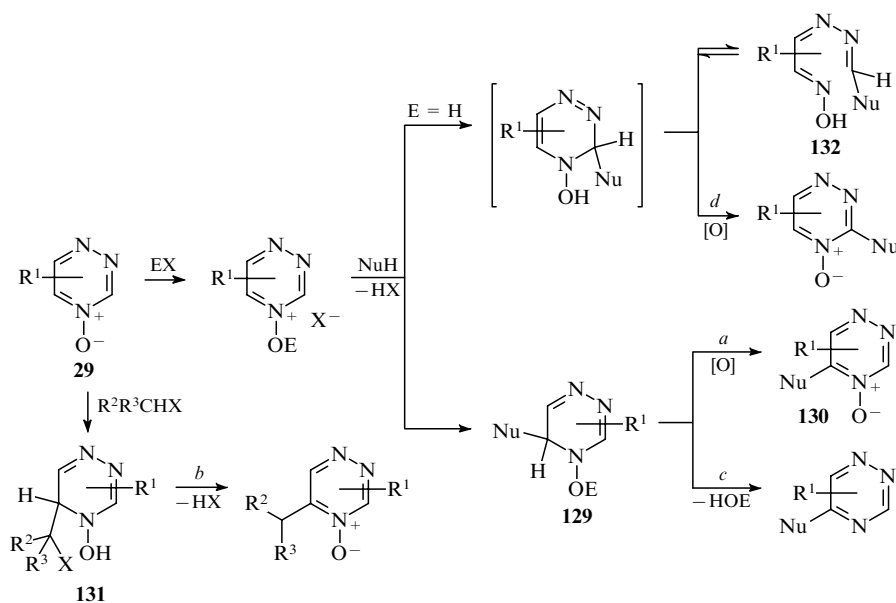


b. Nucleophilic substitution of hydrogen

The mechanism of the nucleophilic substitution of hydrogen (S_NH) in 1,2,4-triazine *N*-oxides has been studied in most detail using 1,2,4-triazine 4-oxides **29** as an example. This mechanism is common to all 1,2,4-triazine 4-oxides. The reactions of nucleophilic substitution of hydrogen in 4-oxides **29** occur according to the 'addition–elimination' scheme; the process can stop at the step of addition to form adducts **129**. Due to the low probability of the elimination of such a particle as a hydride ion,⁹¹ aromatisation of these adducts can follow several paths.

Oxidative aromatisation leads to products of the S_NH-reaction of the type **130** [Scheme 1, pathway (a)]. Auto-aromatisation of the σ^H-adducts in two directions is also possible. For example,

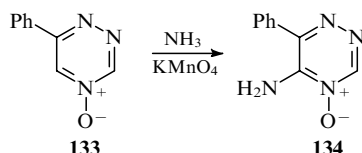
Scheme 1



1,2-elimination of HX is possible in nucleophiles carrying a vicarious nucleofugal group X. In this case, a hydrogen atom is eliminated from the substrate and the X group is eliminated from the reactive fragment of the σ^H -adduct **131** [Scheme 1, pathway (b)]. Makosza⁹² named such reactions vicarious nucleophilic substitution.

Another variant of auto-aromatisation is the elimination of the HOE molecule from the σ^H -adduct **129** which is formed from the cationic derivatives of 1,2,4-triazine *N*-oxides [Scheme 1, pathway (c)]. In this case, S_NH-substitution is accompanied by the loss of an oxygen atom. It should be noted that both the hydrogen atom and the vicarious OE group are eliminated from the substrate fragment of the intermediate. Conceptually, mediated (vicarious) nucleophilic substitution of hydrogen atom is observed in this case. Sometimes, the σ^H -adducts exist in a non-cyclic form. The ring opens readily after the addition of a nucleophile to the 1,2,4-triazine 4-oxide. This process is reversible and the equilibrium is shifted towards the open form **132** [Scheme 1, pathway (d)]. In this way, the σ^H -adduct is eliminated from the reaction; however, it exists in quasi-steady-state concentrations and can be easily oxidised to the corresponding 1,2,4-triazine 4-oxide.

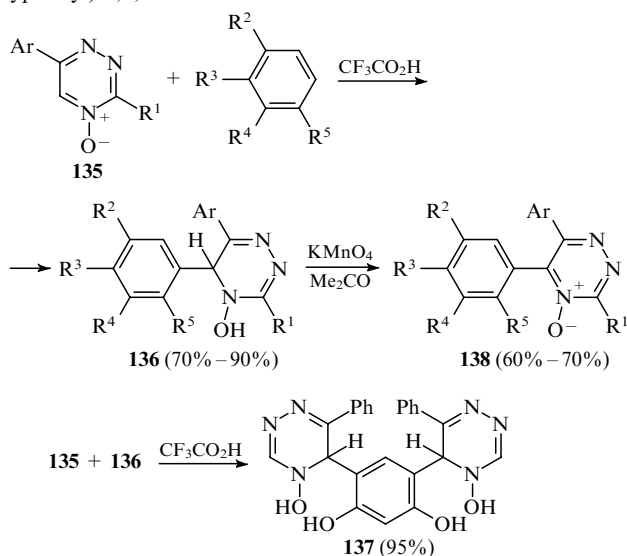
Oxidative aromatisation [see Scheme 1, path (a)] is achieved by the amination of 6-phenyl-1,2,4-triazine 4-oxide **133** with liquid ammonia in the presence of potassium permanganate as the oxidising agent. The reaction affords 5-amino-6-phenyl-1,2,4-triazine 4-oxide **134**.⁹³



The reaction of 6-aryl-1,2,4-triazine 4-oxides **135** with phenol, 2,6-dimethylphenol, resorcinol and phenetol in the presence of trifluoroacetic acid results in stable σ^H -adducts, 6-aryl-2,4-dihydro-4-hydroxy-5-Nu-1,2,4-triazines **136** (Nu = 2-hydroxy-, 2-ethoxy-, 4-ethoxy- or 2,4-dihydroxyphenyl). The reaction of resorcinol (R² = R⁴ = OH, R³ = R⁵ = H) with a twofold excess of triazine *N*-oxide **135** (R¹ = H, Ar = Ph) affords 4,6-bis(4-hydroxy-6-phenyl-1,2,4-triazin-5-yl)resorcinol **137**.⁹⁴

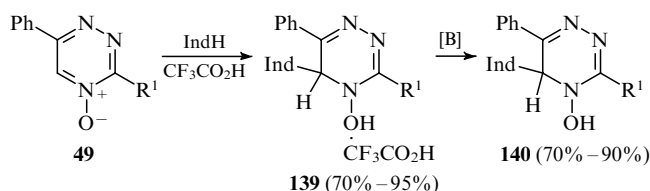
The formation of σ^H -adducts in S_NH-reactions of azine *N*-oxides was confirmed directly for the first time by the isolation and identification of compounds **136**. Before that, it was only postulated in the discussions of the mechanism of such reactions.

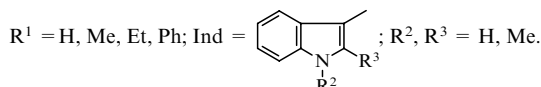
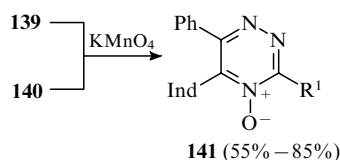
Dihydro-1,2,4-triazines **136** are rather stable compounds. Boiling in butanol, DMF, or trifluoroacetic acid does not result in their thermal dehydration [see Scheme 1, pathway (c)]. At the same time, their oxidative aromatisation [pathway (b)] occurs readily and in high yields. For example, compounds **136** react with potassium permanganate in acetone to form 6-aryl-5-(4-hydroxyphenyl)-1,2,4-triazine 4-oxides **138**.⁹⁴



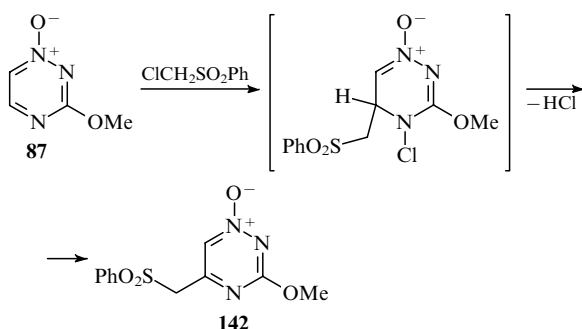
Ar = Ph, *p*-ClC₆H₄; R¹ = H, Me; R², R³, R⁴, R⁵ = H, OH, OEt.

3-R¹-6-phenyl-1,2,4-triazine 4-oxides **49** react with indole or its 1- or 2-methyl derivatives in a similar way. When the reaction is carried out in the presence of trifluoroacetic acid, stable 4-hydroxy-5-(indol-3-yl)-6-phenyl-4,5-dihydro-1,2,4-triazines are formed.⁶² They were isolated both as trifluoroacetates **139** and as free bases **140**. Oxidative aromatisation of the σ^H -adducts obtained with potassium permanganate in acetone affords 3-R¹-5-(indol-3-yl)-6-phenyl-1,2,4-triazine 4-oxides **141**.⁶²





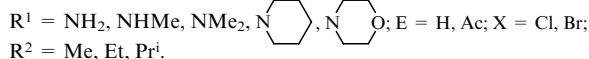
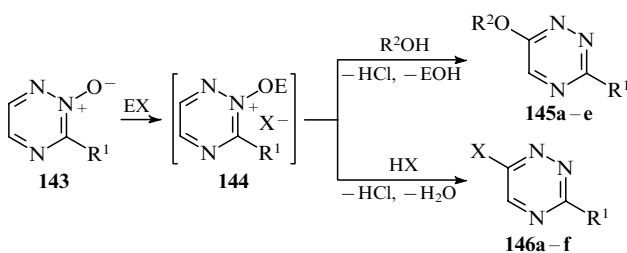
The reaction of 3-methoxy-1,2,4-triazine 1-oxide **87** with chloromethyl phenyl sulfone gives an intermediate adduct, whose further aromatisation [see Scheme 1, path (b)] leads to 3-methoxy-5-(phenylsulfonyl)-1,2,4-triazine 1-oxide **142** in 70% yield.⁹⁵



Another variant of auto-aromatisation occurs in the reaction of 3-amino-1,2,4-triazine 2-oxides **143** with alcohols in the presence of HCl or acetyl chloride. Elimination of water or acetic acid from the adduct **144** results in 3-amino-6-alkoxy-1,2,4-triazines **145a–e**.⁸⁴

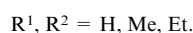
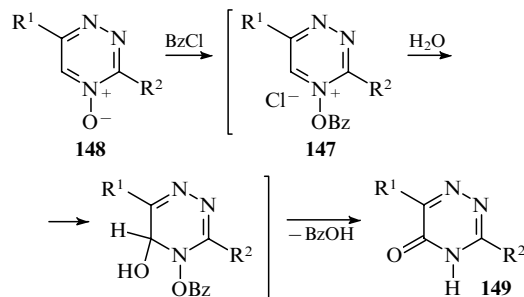
It should be noted that 1,2,4-triazine 1-oxides do not react with alcohols under these conditions.⁸⁴

6-Chloro(bromo)-3-amino-1,2,4-triazines **146a–f** were obtained on passing gaseous hydrogen chloride or hydrogen bromide through a solution of 3-amino-1,2,4-triazine 2-oxide **143**.⁶⁷

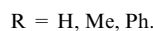
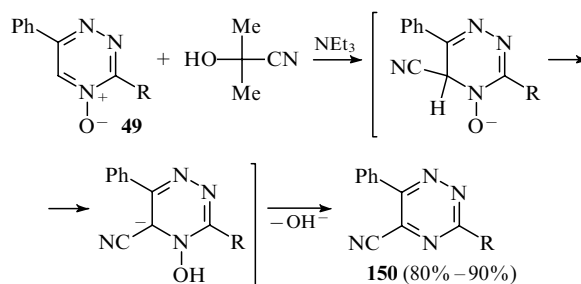


Compound	R^1	$R^2\text{O}$	X	Yield (%)	Ref.
145a	NH ₂	OMe		71	84
145b	NH ₂	OEt		64	84
145c	NHMe	OMe		50	84
145d	NMe ₂	OMe		51	84
145e	NH ₂	OPr ⁱ		65	84
146a	NHMe		Cl	85	68
146b	NMe ₂		Cl	64	67
146c			Cl	80	67
146d			Cl	50	67
146e	NHMe		Br	25	67
146f	NMe ₂		Br	41	67

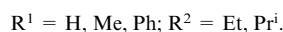
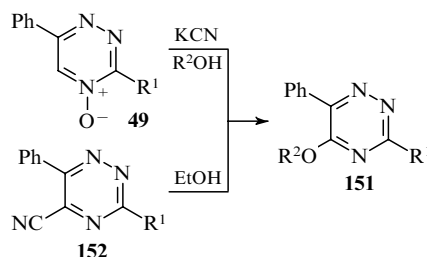
Acyl salts of 1,2,4-triazine 4-oxides **147** synthesised by the reaction of benzoyl chloride with the corresponding 1,2,4-triazine 4-oxides **148** react with water according to pathway (c) (Scheme 1). It is evident that after addition of the nucleophile at position 5 of the triazine ring, auto-aromatisation of the adduct occurs with elimination of benzoic acid and formation of 1,2,4-triazin-5-ones **149**.⁷⁶



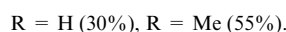
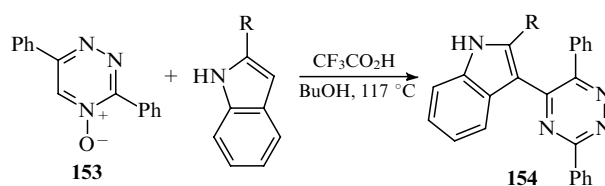
The reaction of 1,2,4-triazine 4-oxides **49** with acetone cyanohydrin in the presence of triethylamine affords 5-cyano-1,2,4-triazines **150**.⁹⁶



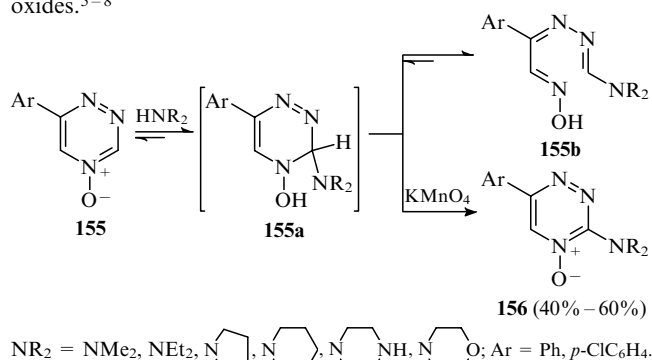
If potassium cyanide in alcohols (ethanol, propanol, isopropanol) is used as a cyanating agent, 5-alkoxy-1,2,4-triazines **151** are formed in 80%–90% yields. Their formation can be explained by replacement of the cyano group by an alkoxy. In fact, 5-cyano-1,2,4-triazines **152** slowly react with ethanol at room temperature to give 3- R^1 -6-phenyl-5-ethoxy-1,2,4-triazines **151**.⁹⁶



The reaction of 1,2,4-triazine 4-oxide **153** with indole or 2-methylindole in boiling butanol in the presence of trifluoroacetic acid is accompanied by auto-aromatisation of the products of addition of the nucleophile to the 1,2,4-triazine 4-oxide and results in 5-(indol-3-yl)- and 5-(2-methylindol-3-yl)-3,6-diphenyl-1,2,4-triazines **154**.⁹⁷

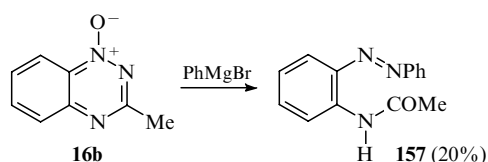


The reaction of 6-aryl-1,2,4-triazine 4-oxides **155** with dialkylamines or cycloalkylamines occurs by pathway (d) (Scheme 1).⁹⁸ The adducts **155a**, which are in equilibrium with the open-chain form, *N,N*-disubstituted 3-aryl-1,4,5-triaza-1,3,5-hexatrien-1-ols **155b**, are formed in the first step. In this case, the equilibrium is shifted towards the compounds **155b**. In spite of the low concentration of the form **155a**, oxidation of the compounds **155** with potassium permanganate in solution affords 3-amino-6-aryl-1,2,4-triazine 4-oxides **156**. It is noteworthy that it is possible to withdraw the cyclic tautomer from the reaction zone, which allows one to obtain the products of hydrogen substitution at position 3 of the triazine system when the position 5 is free. Such a substitution has been carried out for the first time. Note that all the experimental data obtained until now have indicated that position 5 is the most reactive in 1,2,4-triazines and their oxides.^{5–8}

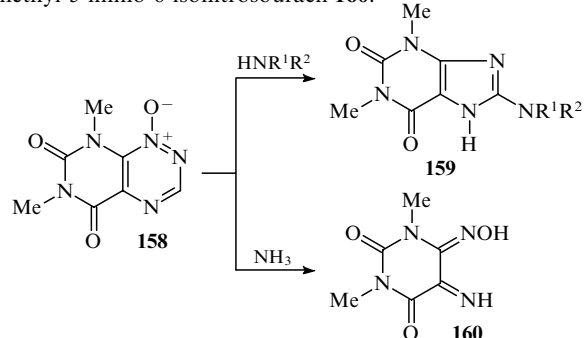


c. Reaction of 1,2,4-triazine *N*-oxides with nucleophiles accompanied by destruction of the ring

In addition to the formation of nucleophilic substitution products, the reaction of 1,2,4-triazine *N*-oxides with nucleophiles results in the opening, narrowing, or fragmentation of the 1,2,4-triazine ring. For example, the reaction of 3-methyl-1,2,4-benzotriazine 1-oxide **16b** with phenylmagnesium bromide affords 2-phenylazoacetanilide **157**.⁹⁹

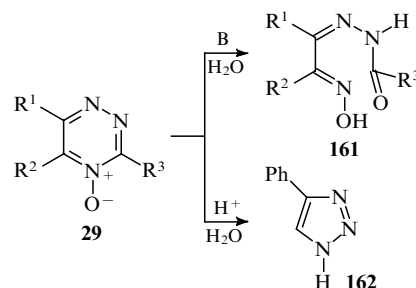


The reaction of fervenulin 1-oxides **158** with secondary amines results in narrowing of the triazine ring and formation of 2-amino-5,7-dimethylimidazo[4,5-*e*]pyrimidine-4,6(5*H*,7*H*)-diones **159**. The reaction of the same *N*-oxide with ammonia affords 1,3-dimethyl-5-imino-6-isonitrosouracil **160**.¹⁰⁰

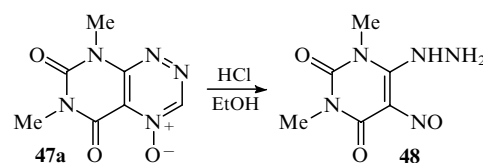


1,2,4-Triazine 4-oxides undergo hydrolysis both in acidic and basic media. For example, in the presence of 2 M KOH, opening of the triazine ring in 1,2,4-triazine 4-oxides **29** occurs with the formation of *N'*-(2-hydroxyiminoethylidene)hydrazides of carboxylic acids **161**. Hydrolysis of the 4-oxides **29** in acid media

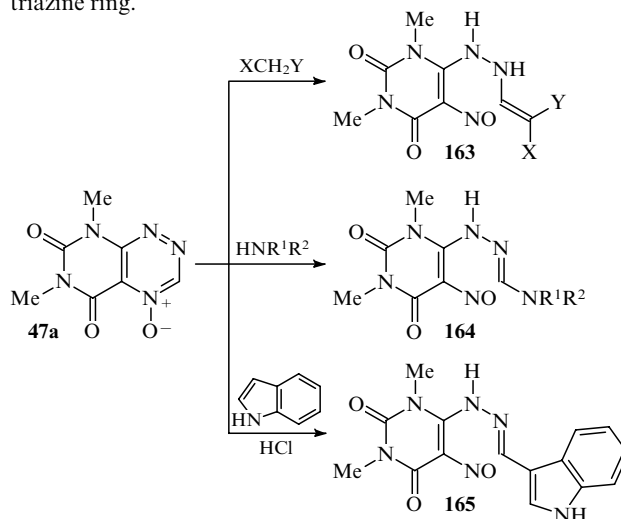
results in narrowing of the 1,2,4-triazine ring to 1,2,3-triazole, in particular, in the formation of the compound **162**.⁷⁶



The reaction of fervenulin 4-oxide **47a** with hydrogen chloride in ethanolic solution leads to the opening of the triazine ring and the formation of 1,3-dimethyl-5-nitroso-6-hydrazouracil **48**. In fact, this reaction is reverse to that for the synthesis of the fervenulin 4-oxide.^{40, 101}



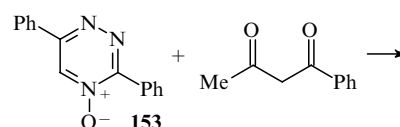
Reactions of the fervenulin 4-oxide **47a** with CH-active compounds are also accompanied by the destruction of the triazine ring.

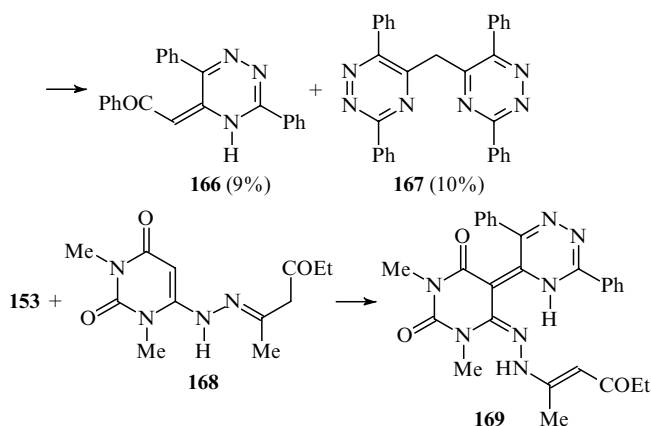


$\text{X}, \text{Y} = \text{CO}_2\text{Et}, \text{COMe}; \text{X} = \text{NO}_2, \text{Y} = \text{CO}_2\text{Et}.$

In this case, 1,3-dimethyl-5-nitroso-6-(*N'*-ethen-1-ylhydrazino)uracils **163** are formed.¹⁰² Fervenulin 4-oxide **47a** reacts with amines or indoles in a similar way. The nucleophilic attack is accompanied by opening of the 1,2,4-triazine ring and formation of 6-aminomethylenehydrazino-1,3-dimethyl-5-nitrosouracil **164**¹⁰³ or 1,3-dimethyl-5-nitroso-6-[*N'*-(indol-3-yl)methylidenehydrazino]uracil **165**.^{104, 105}

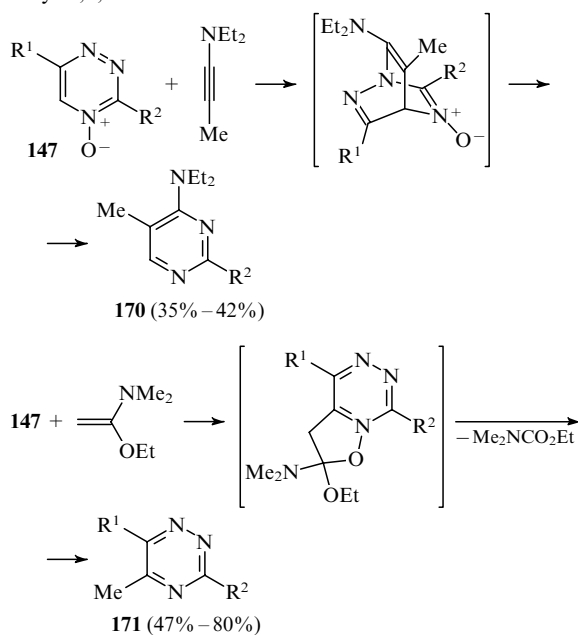
The reaction of 3,6-diphenyl-1,2,4-triazine 4-oxide **153** with benzoylacetone under basic catalysis conditions (DMSO, NEt_3) affords 1,2,4-triazine **166** in 9% yield and bis(1,2,4-triazin-5-ylmethane) **167**.⁹⁷ According to literature data,⁹⁷ the 1,3-dimethyluracil derivative **168** with two reactive centres reacts with the *N*-oxide **153** at the uracil fragment only to form compound **169**.



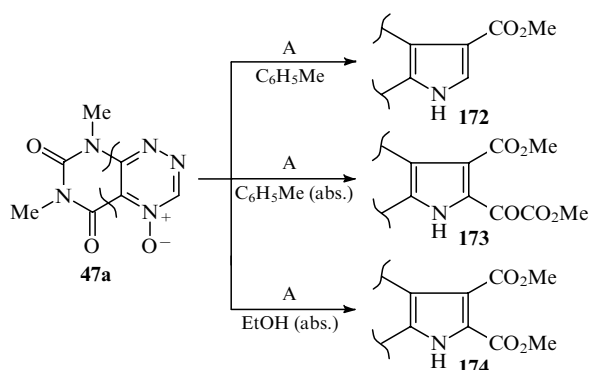


5. Reactions with dienophiles

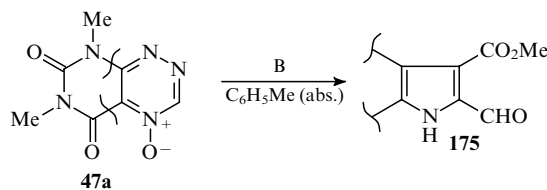
The direction of the reaction of 1,2,4-triazine *N*-oxides with dienophiles differs substantially from that for 1,2,4-triazines. 1,2,4-Triazine 4-oxides **147** act as 1,3-dienes only in the reaction with *N,N*-diethyl-*N*-(1-propynyl)amine giving 2-*R*²-5-methyl-4-(dimethylamino)pyrimidines **170**. The reaction of these 1,2,4-triazine 4-oxides with 1-(dimethylamino)-1-ethoxyethylene occurs as 1,3-dipolar cycloaddition to produce the corresponding 5-methyl-1,2,4-triazines **171**.⁸⁵



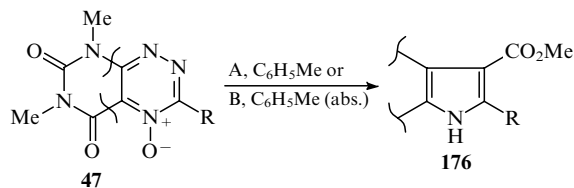
The reaction of the fervenulin 4-oxide **47a**, which is not substituted at position 3, with dimethyl acetylenedicarboxylate in various solvents affords compounds **172–174**.



If methyl propionate is used as the reagent, 6-formyl-7-(methoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-dione **175** is formed.

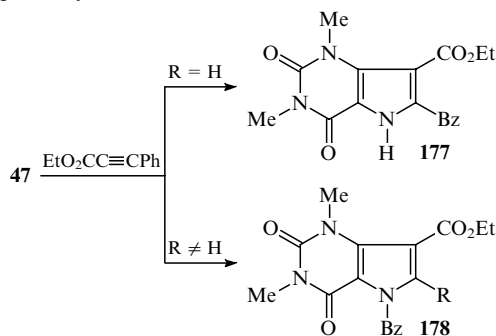


A similar reaction of 3-substituted fervenulin 4-oxides **47** (*R* = Me, Et, Ph) with alkyl acetylenedicarboxylates gives compounds **176**.



A — MeO₂CC≡CCO₂Me; B — MeO₂CC≡CH.

The reaction of fervenulin 4-oxides **47** with ethyl phenylpropionate also follows the pathway described above to give, depending on the presence of a substituent at position 3, 6-benzoyl- or 6-*R*-5-benzoyl-7-(ethoxycarbonyl)-1,3-dimethylpyrrolo[3,2-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **177** and **178**, respectively.^{106, 107}



V. Conclusion

A variety of methods for the synthesis and subsequent transformations of 1,2,4-triazine *N*-oxides makes these compounds very promising for the preparation of new 1,2,4-triazines with or without the *N*-oxide group. Methods of direct functionalisation of unsubstituted triazines (S_NH-processes) and their transformations under the action of nucleophilic agents and dienophiles resulting in azapyrines are of undisputable interest for the synthesis of new biologically active compounds.

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Complexes of natural carbohydrates with metal cations

Yu E Alekseev, A D Garnovskii, Yu A Zhdanov

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Abstract. Data on the interaction of natural carbohydrates (mono-, oligo-, and poly-saccharides, amino sugars, and natural organic acids of carbohydrate origin) with metal cations are surveyed and described systematically. The structural diversity of carbohydrate metal complexes, caused by some specific features of carbohydrates as ligands, is demonstrated. The influence of complex formation on the chemical properties of carbohydrates is discussed. It is shown that the formation of metal complexes plays an important role in the configurational and conformational analysis of carbohydrates. The practical significance of the coordination interaction in the series of carbohydrate ligands is demonstrated. The bibliography includes 571 references.

I. Introduction

Metal complexes of natural carbohydrates have been attracting interest for many years because these compounds participate in vitally important processes; they are used for configurational and conformational analysis, determination, and separation of sugars. According to our estimates, at least 1000 studies discussing various aspects of complex formation between metal ions and natural carbohydrates (mono-, oligo-, and polysaccharides, amino sugars, their polymers, carbohydrate carboxylic acids, natural organic acids of the carbohydrate origin, and cyclic and acyclic polyols) have been published.² However, even the most comprehensive monographs dealing with the chemistry of coordination compounds¹ or carbohydrates² do not consider carbohydrates to be ligands. Several reviews published to date^{3–16} cover only some aspects of this topic.

The purpose of this review is to survey as fully as possible the published data on the known complexes of natural carbohydrates

with metal cations; therefore it includes both recent studies and the most important of early studies. The formation of complexes by nucleosides and nucleotides is beyond the scope of the review, because the carbohydrate fragments of these molecules normally do not participate in the coordination of metals. Moreover, this aspect has been the subject of numerous reviews and monographs (see, for example, Refs 17, 18). The few known examples in which the carbohydrate fragments of nucleotides and nucleosides are involved in the formation of complexes with metals are presented in Section IV.

Data on the formation of metal complexes in the series of natural carbohydrates are mainly discussed in relation to reliably established structures. The information is classified according to the type of carbohydrates. Within each type, metal cations are arranged in accordance with their electronic configuration (*s*-, *p*-, *d*-, and *f*-metals) and their position in the Mendeleev Periodic Table.

II. Complexes of mono-, oligo-, and poly-saccharides and their derivatives

1. Ionic complexes with *s*-metal cations

The first review⁶ on the complexation of carbohydrates with *s*-metal compounds was published in 1966, and now it is only of historical interest. X-Ray diffraction data for metal complexes of this type can be found in a number of reviews (see, for example, Refs 19–23) including a review devoted to saccharose.²⁴ The data on the structures of solid ionic metal complexes obtained up to the middle of 1978 are surveyed most fully in the review by Poonia and Bajai.¹¹

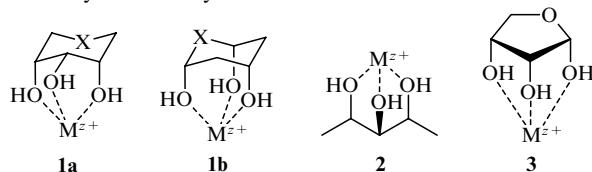
A systematic study of the structures of complexes of monosaccharides with *s*-metal cations in aqueous solutions carried out by Angyal^{7,8,12} has demonstrated that complexes of 1:1 composition predominate. In the case of cyclic forms of ligands, the most stable complexes are those with the axial–equatorial–axial orientation of three consecutively located hydroxyl groups in the ligand (complex **1a**, the first Angyal rule) or those with the energetically unfavourable triaxial orientation of these groups (complex **1b**, the second Angyal rule). Acyclic derivatives obey the first Angyal rule (complex **2**), while furanoses obey the second rule (complex **3** with a quasixial orientation of the hydroxyl groups). These rules were derived using ¹H NMR spectroscopy, *i.e.* they were first formulated for relatively con-

Yu E Alekseev, A D Garnovskii Research Institute of Physical and Organic Chemistry, Rostov State University, prosp. Stachki 194/2, 344104 Rostov-on-Don, Russian Federation. Fax (7-863) 228 56 67. Tel (7-863) 228 56 00 (Yu E Alekseev). Tel. (7-863) 228 56 00. E-mail: garn@ipoc.rnd.runnet.ru (A D Garnovskii)
Yu A Zhdanov Rostov State University, prosp. Stachki 194/2, 344104 Rostov-on-Don, Russian Federation. Fax (7-863) 228 56 67. Tel. (7-863) 265 04 77

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centrated solutions. Their validity for dilute solutions was confirmed later by calorimetry.²⁵



X = O, CHO; $z = 1, 2$.

Complex formation can shift the position of a tautomeric or conformational equilibrium for a ligand in an aqueous solution.^{7,8,12} The stability constants of the complexes are relatively low (0.1–6.0).^{7,8,12,16,26–30} The ability of *s*-metals to form complexes with disaccharides is less pronounced than that for monosaccharides.^{31,32} Evidently, this is due to the higher conformation rigidity of the former. The stability constants of *s*-metal complexes of monosaccharide carboxylic acids are only an order of magnitude larger.^{33–35} Thus, this complexation is very weak although fairly stereospecific. In solvents that are less polar than water (methanol, acetone, dioxane), these complexes are more stable because there are no water molecules to compete with the ligands for coordination to metal cations.³⁶

The formation of these ionic metal complexes is usually regarded^{7,11} as consecutive substitution of water molecules in the hydration shell of a metal ion by hydroxyl groups of the ligand, the optimum number of these groups (three) being determined by the Angyal rules. During the formation of solid complexes, this process is continued with participation of other ligand molecules, but does not go to completion. The data for a number of solid complexes of sugars with *s*-metal salts obtained by X-ray diffraction analysis^{10,15,37–45} and by IR spectroscopy^{46–53} permit the following general conclusions.

1. Carbohydrates act most often as bidentate ligands coordinated through vicinal diol fragments, which can be different in identical ligands. In some cases, the formation of a complex ends with incorporation of a monodentate ligand.^{38,54} Complexes of acyclic aldonic acids can contain only monodentate ligands.^{55,56}

2. Since there are only three known examples^{57–59} of tridentate coordination of cyclic ligands conforming to the first Angyal rule, one can conclude that this rule is not necessary for solid ionic metal complexes of sugars. At the same time, sugars containing no vicinal hydroxyl groups characterised by an axial–equatorial–axial arrangement (α -D-glucopyranose **4a**) do not form complexes of this type.¹¹

3. As a rule, these complexes are crystal hydrates in which all water molecules are coordinated to metal ions.

4. The complexes normally contain two or three ligands, although in some cases they contain only one ligand.^{60,61} In the case of acyclic carbohydrate derivatives, the number of ligands increases to four^{62,63} or even to six.^{55,56} The number of ligands in less studied disaccharide complexes is two^{44,64–67} or one.⁶⁸

5. After complexation, the coordination number of the metal remains approximately the same as that in the first coordination sphere of the initial hydration shell of the metal cation; most frequently it is equal to eight (square antiprism), six (octahedron), seven (pentagonal bipyramid), or nine (three-cap trigonal prism).¹³ The coordination polyhedra formed by calcium(II) ions are especially diverse.³⁹

6. In the majority of complexes of carbohydrate carboxylic acids, a metal ion is coordinated to an oxygen atom of the carboxyl group and to the hydroxyl group in the α -position (α -type coordination⁶⁹). Only in complexes with these ligands, can the ring oxygen atom be involved in coordination.⁷⁰

7. Conformational changes in the ligand following the complex formation are typical of neutral carbohydrates and normally reduce to the change in the conformation of the coordinated primary hydroxyl group⁴⁴ or in the dihedral angle between the coordinated vicinal hydroxyl groups.¹¹ In anionic ligands, coordination

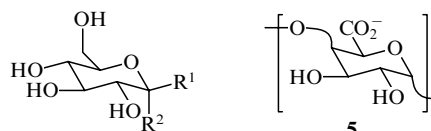
mostly involves the carboxyl group; this substantially decreases electrostatic interactions between the hydroxyl groups responsible for the conformational changes.^{11,64}

8. The cation and the anion of the metal salt are coordinated separately and, thus, they are relatively far removed from each other. There is only one known example⁴⁵ of formation of a complex in which a salt occurs as a contact ion pair.

9. The majority of the complexes studied are calcium compounds, while the smallest number is represented by magnesium compounds. The particular affinity for calcium is apparently a fundamental property of carbohydrates.^{11,39}

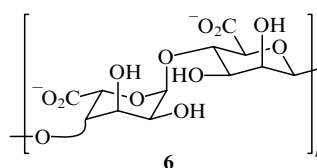
As regards polysaccharides, complexes of neutral polysaccharides with *s*-metal cations have been relatively little studied to date. Judging by X-ray diffraction data, the K^+ and Br^- ions in the complex of potassium bromide with amylose (a polymer of α -1,4-linked α -D-glucopyranose **4a**) are coordinated alternately in the cavity of the helix-like polymer chain.⁷¹ It has been noted⁷² that cellulose (a polymer of β -1,4-linked β -D-glucopyranose **4b**) only weakly binds Ca^{2+} ions. It was established unambiguously⁷³ that reaction of cellulose with alkali metal hydroxides gives inclusion compounds containing metal ions between the planes of the cellulose crystal lattice rather than the corresponding alkoxides.⁷⁴ The formation of alkoxides was denied even for monosaccharides⁷⁵ and disaccharides;^{75,76} in these cases, the formation of adducts of the type $RO^+H(M)OH^-$ stabilised by hydrogen bonds between the neighbouring hydroxyl groups was postulated.

A more detailed study⁷⁷ has been devoted to the formation of complexes of *s*-metal cations with a number of anionic polysaccharides, first of all, with pectate **5** (α -1,4-linked poly- α -D-galactopyranosurionate), alginate **6** (a polymer consisting of α -1,4-linked disaccharides formed by the α -L-gulopyranosuronic and β -D-mannopyranosuronic acid residues), and with carrageenans (polysaccharides containing 3-substituted residues of β -D-galactose and 4-substituted residues of α -D-galactose or 3,6-anhydro- α -D-galactose sulfated at different OH groups). Studies on this type of compounds have been stimulated by the fact that they form stable gels in the presence of *s*-metal salts.⁷⁷



4a: $R^1 = H, R^2 = OH$;

4b: $R^1 = OH, R^2 = H$



Study of the complex formation with metals in these polyelectrolytes is complicated by the presence of two types of binding: territorial (non-specific) binding involving hydrated counter-ions, and site (specific) binding involving non-hydrated counter-ions.⁷⁸ The latter type of binding corresponds apparently to the formation of a complex with a metal cation on the polyanion surface. At a definite concentration of counter-ions, a stereoregular anionic polysaccharide, for example, carrageenan, acquires a helical conformation.^{77,79} In the case of gel formation, *s*-metal cations are coordinated between the chains; this yields domains consisting of double or even triple helices.⁷⁹ Some researchers suggest that only single helices participate in intermolecular complex formation.⁸⁰ However, it is generally believed that cross-linking of two adjacent chains according to the 'egg box' pattern (Fig. 1a) is the primary process.

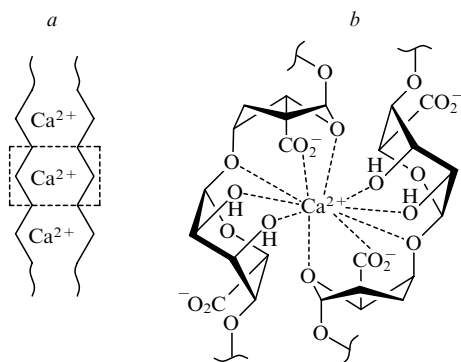
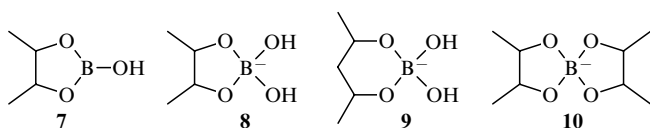


Figure 1. Formation of the intermolecular complex of a polysaccharide with calcium ions.

This model was proposed to interpret the gel formation by poly-L-gulonate in the presence of Ca^{2+} ions.^{81,82} Later it was confirmed for systems comprising Ca^{2+} and polygalacturonate **5**^{83,84} or Na^+ and alginate **6**.⁸⁵ Intramolecular complexation occurs upon the formation of a hydrophilic cavity between monomeric units of neighbouring chains (Fig. 1b).^{86,87} The formation of these cavities can account for the more efficient binding of Ca^{2+} cations by poly-L-gulonate **5**^{87,88} and also for the preferred binding of K^+ and Rb^+ cations by carrageenans.^{89,90}

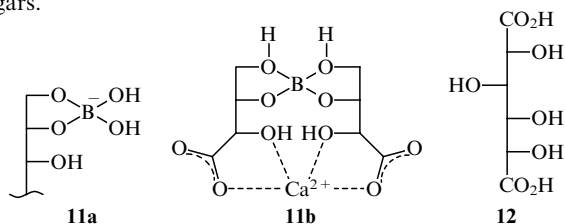
2. Complexes with *p*-metal cations

Borate complexes of carbohydrates are the most studied compounds in this series. They constituted the subject of early classical studies of Böeseken³ carried out by measuring the electrical conductivity of solutions. Later, the results of this study were supplemented by the data of ^1H (Ref. 91), ^{13}C (Ref. 92), and ^{11}B (Refs 93–95) NMR spectroscopy. This resulted in the detection of neutral complexes **7** (which predominate in acidic media),^{92,94} anionic monomeric complexes with five- (**8**)⁹⁴ and six-membered (**9**)^{94,95} rings, and anionic dimeric complexes **10**⁹⁴ of boric acid with polyhydroxyl compounds.



All these products are complexes formed by vicinal hydroxyl groups; nevertheless, complexes of the type **1b** are the most stable in conformity with the second Angyal rule.^{91,92,95,96} High stability constants (10^3 – 10^6 litre mol^{-1})^{97–99} imply a covalent character of these complexes; however, they have not been isolated in the crystalline state. Calorimetric,¹⁰⁰ titrimetric,¹⁰¹ and polarimetric¹⁰² studies have not provided evidence for the existence of the complexes of type **10**. However, they were detected in ^{11}B NMR studies.^{94,95}

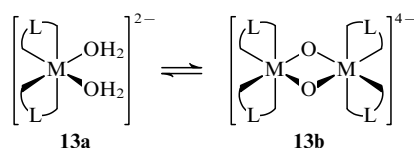
Borate complexes of acyclic polyols of type **11a** can be additionally stabilised owing to the formation of intramolecular hydrogen bonds. This accounts¹⁰³ for the higher stability of these complexes compared to the complexes formed by cyclic forms of sugars.



In aqueous solutions in the presence of borate ions, aldonic and aldaric acids² tend to form complexes with Ca^{2+} ions of the

composition CaBL_2 (L is the ligand). This synergism, which is relatively uncommon in the coordination chemistry of carbohydrates, has been explained¹⁰⁴ by assuming that the preliminary binding of borate ions makes carboxyl groups approach each other, which facilitates the formation of complexes **11b**.

The complexation of sugars with other Group IIIA cations has not received much study. Neutral non-hydrolysable complexes of Ga^{III} with monosaccharide carboxylic acids such as D-glucaric acid (LH_6 , **12**) of variable composition have been synthesised.¹⁰⁵ Complexes of In^{III} with D-glucaric acid **12** of the type $[\text{InLH}_{-2}]^+$, $[\text{InLH}_{-3}]^0$, and $[\text{InLH}_{-4}]^-$ were detected (the negative numerals in the subscripts denote the number of substituted hydrogen atoms).¹⁰⁶ The results of a study of complexation of the acid **12** with Al^{III} and Ga^{III} ions carried out by electrophoresis have been interpreted¹⁰⁷ in terms of an equilibrium between monomer **13a** and dimer **13b**, only carboxyl groups of the ligands being involved in the coordination.

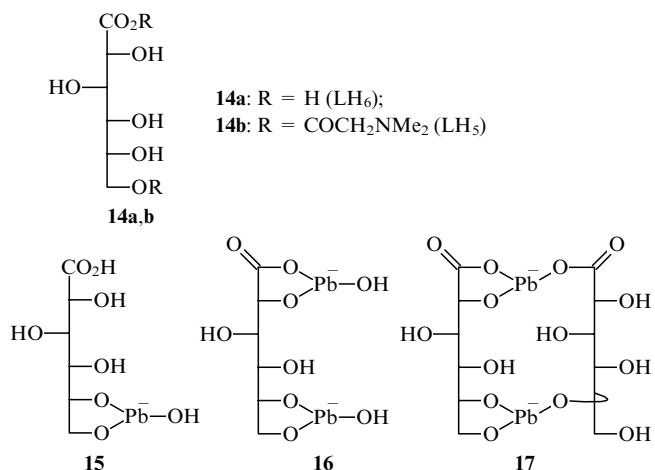


$\text{M} = \text{Al}, \text{Ga}$.

The complex formation of sugars with Group IVA cations is also little studied. It has been noted^{108,109} that germanic acid forms complexes of the composition $[\text{Ge}(\text{LH}_{-2})_2\text{OH}]^-$ and $[\text{Ge}(\text{LH}_{-3})_2]^{2-}$ with acyclic polyols and with α, β -D-glucopyranose **4a, b** and also 1 : 1 complexes with pentoses.⁹⁸ Note that in the latter case, the first Angyal rule holds. One publication¹¹⁰ describes the formation of 1 : 1 complexes of aldoses and ketoses with hexahydrostannate at high pH values.

The complexation of sugars with Pb^{II} has been studied somewhat more comprehensively. It has been shown¹¹¹ that pentoses and their glycosides form complexes of the composition PbL and PbL_2 . However, other researchers¹¹² claim that only the former type of complexes exists.

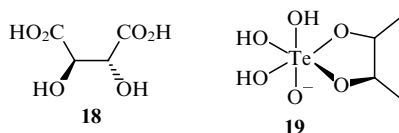
D-Xylaric acid reacts with Pb^{II} in an acidic medium to give the complex PbLH_{-2} as a result of deprotonation of the carboxyl groups.¹¹³ In alkaline media, this complex is hydrolysed giving a hydroxo complex.¹¹³ D-Gluconic acid **14a** in an acidic medium binds Pb^{II} only as a monodentate ligand by the carboxyl group; this gives the complexes $[\text{PbLH}_{-1}]^+$ and $[\text{Pb}(\text{LH}_{-1})_2]$.¹¹⁴ In an alkaline medium, $[\text{Pb}(\text{OH})_3]^-$ reacts with D-gluconic acid **14a** to afford complexes **15–17**.¹¹⁵ In solid lead D-gluconate, the metal coordinates two monodentate gluconate residues through the carboxyl groups and two bidentate gluconate residues through the carboxyl group and the hydroxyl group at C(2) (α -type coordination⁶⁹).¹¹⁶ Thus, the Pb^{2+} cation is surrounded by six oxygen atoms. Evidently, aldaric acids bind Pb^{II} more strongly than aldonic acids.¹¹⁷



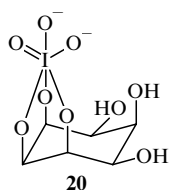
It has been noted^{118,119} that Pb^{II} complexes with oligomeric fragments of the pectate **5** are covalent compounds. In all probability, they contain two carboxyl groups per one Pb^{2+} cation; apparently, this accounts for the high selectivity of formation of Pb^{II} complexes with pectin.¹²⁰ The formation of Pb^{II} complexes with pectin can also occur with incorporation between polymer chains.¹²¹

The complexation of sugars with Group VA elements is little studied. The formation of complexes of monosaccharides and polyols with As^{III} and As^{V} of the composition $[\text{As}^{\text{V}}(\text{LH}_{-2})_3]^-$, $[\text{As}^{\text{III}}(\text{LH}_{-2})(\text{OH})_2]^-$, and $[\text{HAs}^{\text{III}}(\text{LH}_{-2})(\text{OH})_2]$ has been reported.^{109,122} Recently the Bi^{III} complex with L-tartaric acid **18** has been studied by X-ray diffraction analysis.¹²³ The composition of this complex was found to be $\text{Bi}[\text{O}_2\text{C}(\text{CHOH})_2\text{CO}_2][\text{O}_2\text{C}(\text{CHOH})_2\text{CO}_2\text{H}] \cdot 3\text{H}_2\text{O}$. In this complex, two dicarboxylate ligands are coordinated by the carboxyl and α -hydroxyl groups (α -type coordination⁶⁹) and one monocarboxylate ligand is coordinated by the two oxygen atoms of the carboxylate ion. The coordination number of Bi^{III} is equal to nine due to the additional coordination of three water molecules.

Complexes of monosaccharides with telluric acid (Te^{VI}) provide an example of complexes obtained for Group VIA elements. For these compounds, structure **19** was proposed.^{124,125} It was found¹²⁶ that in addition to the 1:1 complex, saccharose forms the complex $\text{L}(\text{TeO}_4)_4$.



Complex formation with Group VIIA elements has been studied only for iodine. Apparently, this is due to the fact that periodate oxidation is an important process in the chemistry of carbohydrates.² It was suggested² that this process starts with the formation of an unstable complex of the IO_4^- anion with a vicinal diol group; the structure of this complex is similar to that of the tellurate complex **19**, because the sizes of the corresponding ions are close. However, monosaccharides conforming to the first Angyal rule should form¹²⁷ stable complexes with periodate, for example, a complex of type **20**.



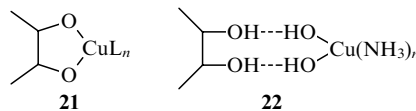
Later, both the fact of formation of the intermediate complexes and the observance of the first Angyal rule have been confirmed by NMR spectroscopy¹²⁷ and paper electrophoresis.¹²⁸

3. Complexes with *d*- and *f*-metal cations

This field of coordination chemistry of carbohydrates has been studied in the greatest detail, although quite irregularly. The vast majority of the data refer to complexes of carbohydrates with Cu, Fe, Co, Ni, Mo, and W.

Among complexes with Group IB metal cations, those with Cu^{2+} have received most study. The dissolution of freshly prepared copper hydroxide in ammonia-containing or alkaline aqueous solutions of polyhydroxyl compounds, including carbohydrates, which has long been used in analytical chemistry, was interpreted¹²⁹ as the formation of five-membered diolate complexes **21**. The stability constants of these complexes for $\text{L} = \text{NH}_3$ are of the order of 10^2 – 10^4 litre mol^{-1} . In

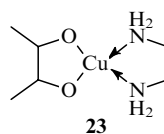
this case, complexes of the 1:1 composition are always formed.^{129–131} The assumption^{132–134} that cuprammonium complexes of vicinal diols are formed as structure **22** (which apparently involves hydrogen bonds) is hardly consistent with both the stability of these complexes and the maintenance of fixed dihedral angles between the coordinated oxygen atoms.⁶



$\text{L} = \text{NH}_3, \text{H}_2\text{O}, \text{OH}^-$.

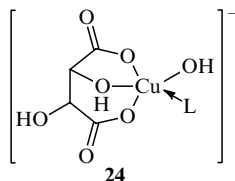
The structure **22** also does not agree with the observed induction of optical activity in the central atom (the appearance of optical activity in its electronic transitions);¹³⁵ in fact, in the complex **22**, this would be less likely than in the complexes **21**, because in the former case, the chiral centres (inducers) are further removed from the central atom.

Mannitol was found to form the complex $[\text{Cu}(\text{LH}_{-2})]$ when the ligand is present in a large excess¹³⁶ or Cu_2L when the reactants are present in equimolar amounts.¹³⁶ The latter complex is apparently anionic. This was confirmed¹³⁷ by isolation of a series of analogous anionic copper complexes of carbohydrates. An isomer of mannitol, sorbitol, forms the complex $[\text{Cu}_3(\text{LH}_{-6})]$ in strongly alkaline media¹³⁸ and a polymeric complex in less alkaline media. An NMR study with the use of a shift reagent has confirmed¹³⁹ that Cu^{II} is mostly coordinated to vicinal diol groups of the ligand, although the first Angyal rule can also be observed.¹⁴⁰ In neutral and acidic media, polyols do not coordinate Cu^{II} ions.¹⁴¹ This would require¹³⁰ deprotonation of at least one hydroxyl group. Structure **23** similar to **21** was ascribed¹⁴² to complexes containing ethylenediamine in place of ammonia.



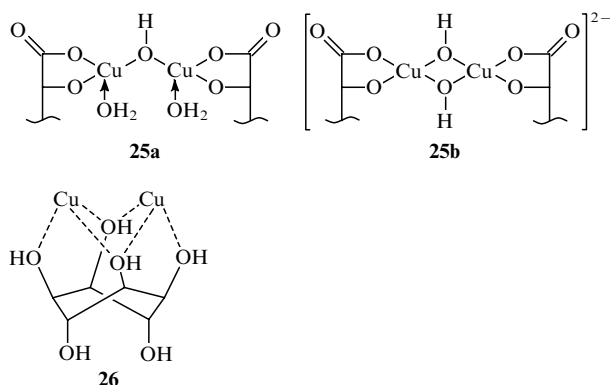
The complexation of Cu^{II} with carbohydrate carboxylic acids has also been studied fairly comprehensively, although, as in the previous cases, these complexes have not been isolated in the solid state. D-Galacturonic acid forms¹⁴³ the complexes $[\text{CuL}_2]^{2+}$, $[\text{CuL}_2\text{H}_{-1}]^+$, $[\text{Cu}(\text{LH}_{-1})_2]$, and $[\text{CuL}_2\text{H}_{-4}]^{2-}$, whereas D-glucuronic acid forms only the second type of complex.¹⁴³ In this case, coordination involves the ring oxygen atom,¹⁴⁴ as has also been observed for *s*-metal cations (Section II.1). D-Gluconic acid **14a** or its dimethylglycine ester (**14b**, pangamic acid, vitamin B₁₅) form mixed-ligand copper complexes in the presence of glycine;¹⁴⁵ the structure of these complexes is unknown.

Glucaric acids form complexes with Cu^{II} according to the α -type of coordination (Section II.1). The tartaric acids **18** give hydroxo complexes **24**^{146,147} containing a water, ammonia, or amine molecule as a ligand. In the case of D-glucaric acid **12**, formation of the complexes $[\text{Cu}(\text{LH}_{-3})]^-$ (at pH 3.65) and $[\text{Cu}(\text{LH}_{-2})_2]^{2-}$ (at pH 5–9, coordination only through the carboxyl groups) and formation of the polymer $[\text{Cu}(\text{LH}_{-3})_n]^{n-}$ (coordination through the carboxyl group of one ligand and the α -type coordination in another ligand) have been reported.¹⁴⁸



$\text{L} = \text{H}_2\text{O}, \text{NH}_3, \text{RNH}_2$.

Binuclear copper complexes of sugars are less frequently encountered. For example, D-gluconic acid **14a** can form ^{7,149} complexes of type **25a** or **25b**. In addition, one of the bridging hydroxyl groups in the complex **25b** can be deprotonated. At a favourable arrangement of four vicinal hydroxyl groups (which occurs, for example, in mucoinositol), sugars in cyclic and acyclic forms can react with Cu^{II} at pH 5 yielding binuclear complexes of type **26** in which the hydroxyl groups of the tetradentate ligand occupy bridging positions.¹⁵⁰

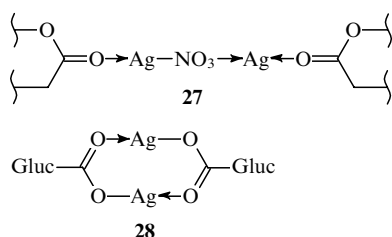


Considerable attention has been devoted to the study of complexation of Cu^{II} with polysaccharides. Thus dissolution of cellulose in a cuprammonium solution is an important technological process, which has been studied most vigorously.¹⁵¹ The formation of chelates of the type **21** with coordination through the hydroxyl groups at the C(2) and C(3) atoms of β-D-glucopyranose **4b** is considered to be the most likely. Polymers having a similar structure, dextrans, are also capable of binding Cu^{II} cations in alkaline media.^{152,153} This process might be accompanied by untwisting of the helical chains of the ligand.¹⁵² The formation of complexes of the type **23** is apparently responsible for the adsorption of the complex [Cu(en)₂]²⁺ (where en is ethylenediamine) on cellulose fibres.¹⁵⁴

Study of complexation of Cu^{II} with anionic polysaccharides has shown ¹⁵⁵ that D-galacturate itself binds Cu^{II} more strongly than its polymer, polygalacturonate **5**. The affinity for Cu^{II} decreases in the following sequence: pectate (polygalacturonate) **5** > alginate **6** > polymannuronate. A similar situation was observed for Ca^{II} ions.¹⁵⁶ The complex formation is a cooperative process.^{156,157} The ligand unit in the copper complexes of pectic acids has ¹⁵⁸ an octahedral configuration, the Cu^{II} cation being coordinated to four oxygen atoms in the symmetry plane.

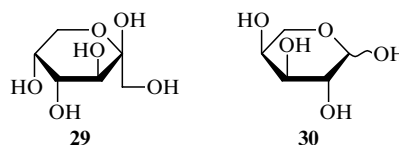
The formation of Cu^{II} complexes with anionic polysaccharides changes substantially the conformation of the polymer chains of the ligands. As in the case of Ca^{II}, the complex formation is a cooperative process.^{156,157} As this takes place, a sulfated polysaccharide, ι-carraginan, passes into a helical conformation.¹⁵⁹

The formation of complexes of carbohydrates with Ag^I has been studied only for the silver nitrate–D-glucurono-δ-lactone¹⁶⁰ and silver nitrate–D-glucurono-γ-lactone¹⁶¹ systems. It was concluded that in both cases, this affords two types of complexes: ‘lactone’ complex **27** and ‘carboxyl’ complex **28**.



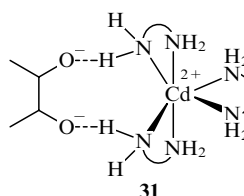
Among complexes with cations of Group IIB *d*-metals, compounds of Zn^{II} and Cd^{II} have been studied most thoroughly. β-D-Fructopyranose **29** and L-arabinopyranose **30** react with these

cations, as with Hg^{II} cations, to give solid complexes of the composition [MLX₂·4H₂O], where X = Cl, Br. In the complex of fructose, the coordination involves two ligand molecules; one of them binds the central ion through the O(2) and O(3) atoms and the other one binds this ion through O(4) and O(5).¹⁶² In the case of L-arabinopyranose **30**, the two ligands are also coordinated through different sites: the O(3) and O(4) atoms of one molecule and the O(1) and O(5) atoms of the other molecule.¹⁶³



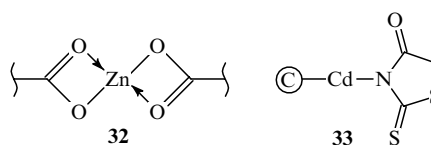
In the Zn^{II} and Cd^{II} complexes with both ligands (**29** and **30**), the metal ion coordinates additionally two water molecules, and thus its coordination number is equal to six. For the Hg^{II} cation, there is no coordination with water (the coordination number is four). The counter-ion of the initial salt is bound to the metal cation by electrostatic forces.

Sugars and their *O*-glycosides react with cadoxen (a solution of cadmium hydroxide in ethylenediamine) to give complexes incorporating two deprotonated equatorial hydroxyl groups of the pyranose ring. Presumably, they have the structure **31**.¹⁶⁴



This structure is additionally stabilised by hydrogen bonds. However, as in the copper complexes **22**, in this case, too, it is difficult to explain the observed induction of optical activity in the electronic transitions of Cd^{II}.¹⁶⁵

D-Gluconic acid **14a** and Cd^{II} form complexes with a Cd : L ratio of 1 : 2 (pH 5.8), 2 : 3, and 2 : 1 (pH 13–14).¹⁶⁶ D-Gluconic acid forms two types of solid complexes with Zn^{II}, Cd^{II}, and Hg^{II}: complexes produced *via* coordination through the carboxyl group and the ring oxygen atom of the first ligand molecule and the carboxyl group and the O(4) atom of the second molecule and those (**32**) in which coordination involves only the carboxyl groups.¹⁶⁷ In the *O*-methylglycoside of D-glucuronic acid, Zn^{II} is bound to the carboxyl group and to the ring oxygen atom.¹⁶ It has been noted ¹⁴⁸ that D-glucaric acid **12** forms a complex with Cd^{II}, but its structure has not been described.



© is a cellulose fragment.

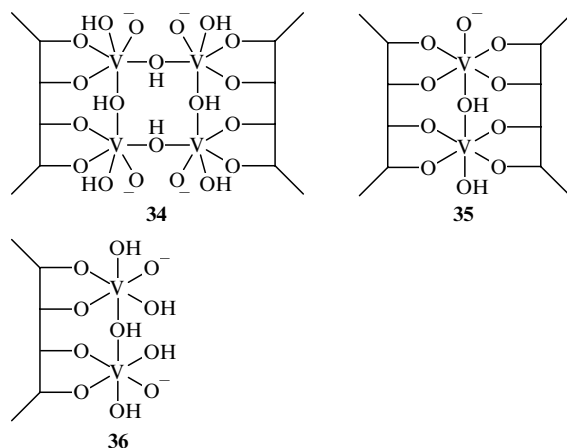
Complex formation of *O*-methylglucosides in aqueous solutions of zinc chloride has been reported.¹⁶⁸ Presumably, the metal ion is coordinated to the O(2) and O(3) atoms. The complex formation accounts ¹⁶⁸ for swelling of cellulose in these solutions.¹⁵¹ Cellulose is known ¹⁵¹ to dissolve in cadoxen. Apparently, this yields polymeric complexes like **31**. The reaction of rhodanine with cellulose in the presence of a cadmium salt gives rise to complex **33** with different ligands.¹⁶⁹ Substituted rhodanines afford similar complexes.¹⁷⁰

It was found that cadmium(II)¹⁷¹ and zinc(II)¹⁷² ions are bound to pectate **5** through the carboxyl groups, although the α-type coordination also cannot be ruled out. A similar situation is observed in the case of oligosaccharide fragments of pectic acids.¹⁷²

Complexes of carbohydrates with Group IIIB *d*-metals are represented by Y^{III} complexes of tartaric acid, the composition of which varies from 1 : 1 to 1 : 5 depending on the pH,¹⁷³ and by Y^{III} complexes of D-gluconic acid **14a**, the composition of which is 1 : 1 and the charge varies depending on the pH.^{174, 175} Complexes of La^{III} with tartaric, D-glucaric **12**, and D-galactaric acids have been obtained, their composition (1 : 1 or 1 : 2) being also dependent on the pH value.¹⁷⁶ No data on the structures of these complexes have been reported.

Several complexes formed by Group IVB elements are known. These are Ti^{IV} complexes¹⁷⁷ with tartaric (**18**) and D-gluconic (**14a**) acids and with mannitol (their composition is 1 : 1 or 1 : 2 depending on the pH), the Zr^{IV} complex with trihydroxyglutaric acid [Zr(OH)₃(LH₋₂)]²⁻,¹⁷⁸ and Zr^{IV} and Hf^{IV} complexes with tartaric, trihydroxyglutaric, and D-galactaric acids, which have similar structures.¹⁷⁹

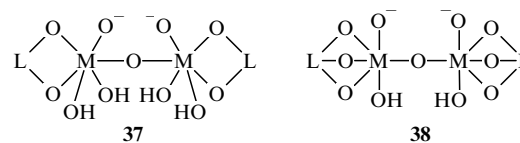
The known complexes of Group VB *d*-metals are mostly formed by vanadium. For example, metavanadate in aqueous solutions reacts with aldoses to give complexes incorporating the [VO₃L]⁻ and [(VO₃)₂L]²⁻ anions.¹⁸⁰ In the latter case, complex formation is observed only for D-glucitol (sorbitol) and maltose (which is a disaccharide). L-Tartaric acid **18**, its D-enantiomer, and the corresponding racemate form binuclear complexes with the vanadyl ion VO²⁺; the composition of the complexes is [(VO)₂L₂H_{-n}]⁽ⁿ⁻⁴⁾⁻ (*n* = 5, 6, or 8 depending on the pH).¹⁸¹ Mesotartaric acid forms a trinuclear complex, [(VO)₃L₃H₋₈]²⁻. For polynuclear complexes of acyclic polyols and aldonic acids in aqueous solutions, several types of structures containing tetradentate ligands have been proposed (structures **34–36**).^{181, 182}



Cyclic sugars and vanadate ions form mononuclear cyclic esters of 1 : 1 composition.¹⁸³ In the most stable complexes characterised by the *cis-cis* arrangement of three vicinal hydroxyl groups (for example, in the complex of β-D-mannopyranose), the ligand is coordinated in a tridentate manner, while in the other cases, in a bidentate manner. Polygalacturonates **5** are coordinated to V^{IV}O ions through the carboxyl groups.¹⁸⁴ At pH 3–7, Nb^V ions and D-gluconic acid form the complexes [Nb(OH)_n(LH₋₂)]⁽⁴⁻ⁿ⁾⁻, while at pH 7–9, the complexes [Nb(OH)_m(LH₋₂)]^{(3-m)-} are produced.¹⁸⁵

The complexation of sugars with cations of Group VIB *d*-metals has been studied fairly intensively. Primary attention has been devoted to complexes of molybdenum and tungsten. Chromium(III) cations do not form stable complexes with sugars in aqueous solutions,¹⁸⁶ whereas in dry methanol, aldoses form complexes with CrCl₃·Py (Py is pyridine); the composition of these complexes is 1 : 3 (aldose : CrCl₃·Py).¹⁸⁶ Conversely, D-glucaric acid **12** (and, perhaps, all the aldaric acids) and Cr^{III} in aqueous solutions form an equilibrium system, similar to the **13a** ⇌ **13b** system.¹⁰⁷ It has also been reported¹⁸⁷ that a stable complex of Cr^V of an unknown structure is formed during oxidation of D-galacturonic acid with Cr^{VI} cations.

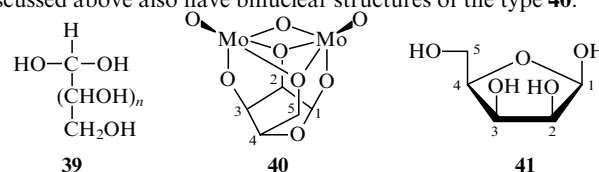
The complex formation of sugars and Mo^{VI} and W^{VI} oxo cations has been studied most comprehensively. Since the structures of carbohydrate complexes formed by these metals are similar,^{188–190} they will be discussed together. In most cases, binuclear complexes ML₂ with bidentate (complex **37**) and tridentate (complex **38**) types of ligand coordination are produced in aqueous solutions. The structure of **37** was unambiguously established only for the molybdenum complex of D-glucuronic acid *O*-methylglycoside. According to X-ray diffraction analysis,¹⁵ this complex is characterised by the α-type coordination. For carbohydrates existing in acyclic forms (alditols, aldonic acids), this type of coordination is accomplished in one tetradentate ligand in which the neighbouring hydroxyl groups occupy *cis*-positions.^{191–194} The complexes like **38** are formed in conformity with the first Angyal rule^{193, 194} even if the initial chair-like conformation of the pyranose ligand is distorted.^{195, 196}



M = Mo, W.

Since, due to their conformational mobility, acyclic forms of sugars are more prone to form complexes, it has been assumed and, to some extent, confirmed¹⁹⁷ that the hydrate of the aldehyde form **39** participates in the complex formation. It has been reported¹⁹⁸ that D-lyxose, D-mannose, and L-rhamnose are coordinated as tetradentate ligands only in the cyclic pyranose form, although D-lyxose in the furanose form can be also coordinated in this way (see structures **40** and **41**). However, other researchers¹⁹⁹ claim that these ligands are coordinated in a tridentate fashion. Upon the interaction of W^{VI} ions with an acyclic polyol (sorbitol), in addition to the tetradentate coordination (1 : 1 complexes as two regioisomers), a complex of the type **37** in which the ligand is coordinated bidentately has been detected.²⁰⁰ The carbohydrate complexes of W^{VI} are three orders of magnitude more stable than complexes of Mo^{VI}. This is due¹⁹⁸ to the fact that W^{VI} forms polyoxo anions more readily than Mo^{VI}.

Attempts to determine the structure of the carbohydrate complexes of Mo^{VI} and W^{VI} by X-ray diffraction analysis are not always successful. Thus, according to X-ray diffraction data,²⁰¹ the crystalline compound isolated upon the interaction of D-xylofuranose with ammonium molybdate proved unexpectedly to be a complex of D-lyxose **40**. The transformation of D-xylose into D-lyxose, which is the C(2) epimer of the initial ligand, was explained by the Lobry de Bruyn–Alberda van Ekenstein rearrangement occurring during the synthesis of the complex (Section VI.2). It was shown that the new ligand is coordinated in the furanose form **41**. Later, using X-ray diffraction analysis, a similar structure has been found for the molybdenum complex of an acyclic tetraol (erythritol).²⁰² Based on ¹³C and ⁹⁵Mo NMR spectra, it was shown that in solutions, molybdenum complexes of other acyclic polyols (mannitol, *etc.*) have similar structures.²⁰³ After these publications, there are grounds for believing that the other Mo^{VI} and W^{VI} oxo complexes discussed above also have binuclear structures of the type **40**.



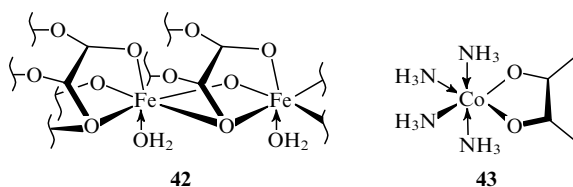
n = 1–4.

Among complexes of carbohydrates with Group VIIB *d*-metals, complexes of manganese in various (including low) oxidation states have been studied in most detail, because the low oxidation states of manganese, which are generally unstable,

can be stabilised by acyclic polyhydroxyl ligands in aqueous solutions.²⁰⁴ The greater the number of hydroxyl groups in the ligand, the more pronounced this stabilisation, because, according to the principle of hard and soft acids and bases,²⁰⁵ the Mn cations are more firmly bound to hydroxyl groups than to carboxyl groups.²⁰⁴ Judging by the results of electron–nuclear relaxation measurements, carbohydrates in the pyranose form coordinate only weakly Mn^{II} ions by the O(3), O(4), and O(6) atoms²⁰⁶ (see the structures **4a,b**). It should be noted that acyclic polyols also weakly coordinate Mn^{II}, but they form stable complexes with Mn^{III} and Mn^{IV} ions.²⁰⁴ However, it was stated²⁰⁷ that the complexes of sorbitol with Mn^{II} ions are also stable. The composition of complexes of acyclic polyols with Mn^{III} was found^{204,207} to be 1:2 or 1:3. In aqueous solutions, D-gluconic acid **14a** forms complexes [Mn^{II}(LH_{−2})₂]^{2−}, [Mn^{III}(LH_{−2})₂OH]^{2−}, and [Mn^{IV}(LH_{−2})₃OH]^{3−} (from data on electrochemical oxidation with variation of the electrode potential).²⁰⁸ The former complex is able to dimerise with successive deprotonation yielding a series of binuclear compounds. The complex of D-gluconic acid of the composition [Mn^{IV}(LH_{−2})₃OH]^{3−} is the first example of a stable carbohydrate derivative of Mn^{IV}. In the solid Mn^{II} gluconate, which is the only carbohydrate complex of manganese studied by X-ray diffraction analysis,²⁰⁹ the central ion was found to have an octahedral environment formed by two ligands and containing the carboxyl and hydroxyl oxygen atoms. These ligands exist in two conformations: a zigzag-like (similar to that of alkanes) and a bent conformation. The same conformation of the carbohydrate ligand was found in an aqueous solution of Mn^{II} gluconate.²¹⁰ Tartaric acid **18** forms a neutral Mn^{II} tartrate,²¹¹ which is deprotonated upon an increase in the pH, and in alkaline solution, it is oxidised by atmospheric oxygen to give hydroxytartrate complexes of Mn^{III}.²¹² Manganese(II) does not form complexes with D-glucaric acid **12**.¹⁴⁸ It has also been noted that Mn^{II} is bound by dextrans¹⁵³ and by polygalacturonate **5**.¹⁸⁴

Rhenium(VII) as perrhenate forms complexes with alditols (acyclic polyols), aldonic acids of the type **14a**, and their lactones. The complexation involves two hydroxyl groups having the *R*- and *S*-configuration, respectively.²¹³ It is believed that perrhenates form no complexes with these ligands.²¹³ However these data are disproved in another publication.²¹⁴

Among Group VIII elements, metals of the iron subgroup are represented most widely in the coordination chemistry of carbohydrates. Thus sugars and other polyhydroxyl compounds form stable complexes with Fe^{III} ions.²¹⁵ D-Glucopyranose **4a,b**²¹⁶ and D-fructopyranose **29**^{216–218} are the best complexones. Structural studies on the Fe^{III} complex of D-fructopyranose **29** confirm the polymeric polynuclear structure **42**.²¹⁶ In an aqueous solution, the polymer **42** occurs in equilibrium with monomeric and dimeric complexes.

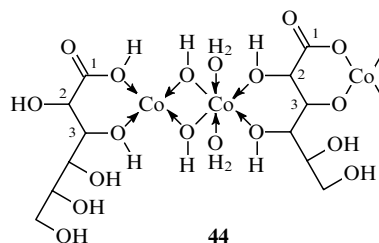


The complexation of Fe^{III} with tartaric acid **18** in an alkaline medium leads to the complex [Fe(LH_{−3})₃]^{6−} with coordination through both carboxyl groups and a hydroxyl group.²¹⁹ Apparently, a complex of the type **24** is formed. A ternary complex of the composition 1:1:1 was isolated from the Fe^{III}–sodium tartrate–saccharose system.²²⁰ This accounts for the dissolution of cellulose in iron–tartrate solutions.¹⁵¹ The following heteronuclear iron–vanadium tartrate complexes were prepared:²²¹ [FeVO(LH_{−2})₂]⁺, [FeVO(LH_{−3})(LH_{−4})]^{2−}, and [FeVO(LH_{−4})₂OH]^{4−}.

D-Gluconic acid **14a** forms^{7,222} chelates with Fe^{III} with bi- and tridentate coordination through only hydroxyl groups. Later,²²³ similar structures have been proposed for Fe^{III} complexes with trihydroxyglutaric acid. However, in this case, coordination can involve either one²²³ or two¹⁴⁸ carboxyl groups. The complexes of this type are fairly stable ($K_s = 10^4$ – 10^5 litre mol^{−1}).^{224,225} Preparation of polymeric Fe^{III} complexes of the type **42** with sorbitol or D-glucuronic acid has been reported.²²⁶

Cobalt(II) and nickel(II) cations form 1:1 coordination compounds with mannitol.¹³⁶ Ammonia complexes of Co^{III} react with D-ribose and L-sorbose to give chelates [Co(NH₃)₄L₂]³⁺ chiroptical properties of which point to a structure like **43**.²²⁷ In addition to these chelates, Co^{II} ions form a binuclear complex [Co₂(N-H₃)₃(OH)₂(H₂O)₂L]³⁺ with D-arabinose.²²⁸

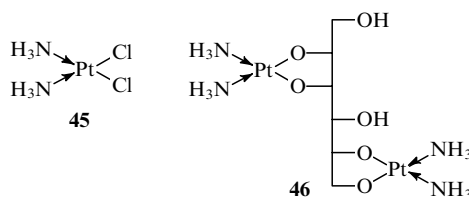
In the series of carbohydrate carboxylic acids, complex formation of Co^{II} and Ni^{II} with D-gluconic acid **14a** has been studied most extensively. It has been noted⁴ that this is not accompanied by substantial changes in the ligand conformation and that Ni^{II} chelates are more stable than Co^{II} chelates.²²⁹ It was found that in an acidic medium, unstable complexes [M(LH_{−1})]⁺ are formed.^{230–232} Polynuclear complexes [Co₂(OH)₃(LH_{−1})·H₂O and [Co₃(OH)₂(LH_{−2})₂·2H₂O] were detected in the pH range of 7.5–9.5.²³¹ The latter is a polymer of structure **44**. The complexes [Ni₂(OH)₃(LH_{−1})] and [Ni₂(OH)₄(LH_{−1})][−], which might have a similar structure, have been obtained.²³⁰ Tetraamminecobalt(II) reacts with D-gluconic (**14a**) and D-glucuronic acids to give the complexes [Co(NH₃)₄L]²⁺ (*n* = 4, 5) in which the ligands behave as monodentate ones.²³³ Study of solid nickel gluconates [Ni(LH_{−1})₂·2H₂O and [Ni₂(OH)₂(LH_{−2})₂·2H₂O] by spectroscopic and magnetic methods has shown that the chelate units in both complexes have a distorted octahedral configuration.²³⁴ The second complex has a polymeric structure with hydroxyl bridges, apparently, similar to the structure **44**.



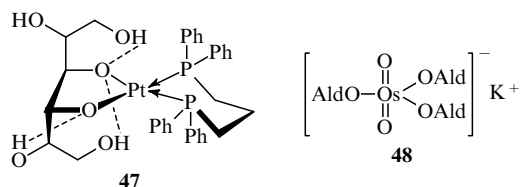
The diastereomeric Λ- and Δ-complexes [Co(LH_{−1})(en)₂]⁺ have been obtained by the reaction of racemic [Co(CO)₃(en)₂]²⁺ with aldonates and separated.¹³ Aldaric acids form¹⁴⁸ chelates of the type [M(LH_{−3})][−], the structure of which is apparently **24**, and a binary complex {[Ni(bipy)₃]₂(LH_{−2})} (bipy is bipyridine).²³⁵

Data on the complexation of Co^{II} and Ni^{II} with polysaccharides are scarce. Thus it is known that these cations are bound by dextrans¹⁵³ and polygalacturonate **5**¹⁸⁴ and that cellulose dissolves in solutions of the complexes [Co(en)₃(OH)₂], [Ni(N-H₃)₆(OH)₂], and [Ni(en)₃(OH)₂] yielding complexes of an unknown structure¹⁵¹ (supposedly of the type **31**).

Complexation of carbohydrates with cations of platinum group metals has been studied mostly in connection with their therapeutic effect (Section VI.1). When cisplatin **45** was made to react with D-mannitol, two complexes with identical structures (**46**) but with different colours and different chiroptical properties were isolated.²³⁶ The reasons for this result are unknown.



The reactions of acyclic polyols with the 1,3-bis(diphenylphosphino)propane platinum complex result in the formation of stable diolate chelate-type complexes **47**, which are additionally stabilised by intramolecular hydrogen bonds.²³⁷ The complexes have been structurally characterised. The reaction is regioselective and occurs most efficiently with vicinal diol groups. Peculiar anionic complexes, so called osmarines, are formed upon the reaction of osmium salt **48** with aldoses.^{238, 239}



Ald is the aldose residue.

These complexes are polymers the backbone of which consists of linked (possibly, *via* oxygen) Os atoms with 'grafted' monosaccharide residues. The molecular masses of these compounds are between 10^3 and 10^6 dalton. Some of the aldose fragments are oxidised to aldonic acids during complex formation; therefore, the complexes can be described by the general formula $K_m Os_n Y_x Z_y (H_2O)_z$, where Y is aldose, Z is aldionate (the therapeutic properties of these polymers are described in Section VI.5).

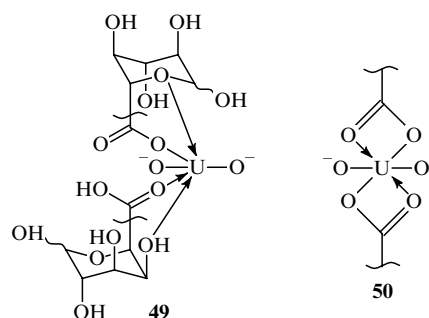
D-Gluconic acid **14a** forms two extremely stable complexes of the composition 1 : 1 with Pt^{II} cations; these products result from slow hydrolysis of the initial polymers of the composition 6 : 1.⁷ The Ru^{III} cation also forms a stable complex compound with D-gluconic acid in an alkaline medium.²⁴⁰ Similar stable complexes of D-gluconic acid have been obtained for Os^{III} , Os^{IV} , and Os^{VI} ions.²⁴¹ Mixed-ligand chelates $[PtL(1,3\text{-diamine})]$ have been obtained with D-gluconate and D-glucuronate in the presence of 1,3-diamines.²⁴²

Among the complexes formed from *f*-metals with sugars, those of lanthanides have been studied most thoroughly. The use of water-soluble lanthanide salts as shift reagents in NMR spectroscopy has demonstrated that the first Angyal rule holds for both cyclic²⁴³ and acyclic²⁴⁴ carbohydrate forms, while the second Angyal rule is obeyed for furanoses,²⁴⁵ *i.e.* there is a similarity between the behaviours of lanthanides and *s*-metals.

The complexation of lanthanide cations with carbohydrate carboxylic acids has been studied fairly comprehensively. The chiroptical properties of the complexes of lanthanides with tartaric acid **18** are discussed in a review.²⁴⁶ The α -type bidentate coordination and tridentate coordination through both hydroxyl groups and the carboxyl group have been assumed for the complexes resulting from the reaction of glyceric acid with Co^{III} .²⁴⁷ D-Galacturonic acid coordinates Eu^{III} ions through the oxygen atom of the carboxyl group, the hydroxyl group at the C(4) atom, and the ring oxygen atom (1 : 1 complex),²⁴⁸ while the *O*-methylglycoside of this acid binds Eu^{III} only by the carboxyl group and the ring oxygen atom {the $[Eu(LH_{-1})_3]$ complex}.²⁴⁹

D-Gluconic acid **14a** forms the most stable chelates with Ce^{III} ions.⁴ Structures with the α -type coordination and with tridentate coordination involving the carboxyl group have been proposed for 1 : 1 complexes of lanthanides.^{250, 251} The stability constants of these complexes at low²⁵² and high^{253, 254} pH values have been determined. An increase in the gluconate concentration leads to the formation of complexes $[M(LH_{-1})_n]^{(3-n)+}$, where $n = 2-4$.²⁵⁵

As regards actinides, only data on the complex formation of U^{VI} (as the uranyl cation, UO_2^{2+}) have been reported. This cation coordinates aldopyranoses and cyclic polyols at pH > 10 without observance of the first Angyal rule. Apparently, this is due to its large size.¹⁹⁹ D-Gluconic acid forms complexes **49** and **50** with these ions.²⁵⁹ Similar complexes are produced in the case of tartaric acid **18** and trihydroxylglutaric acid.²⁵⁷

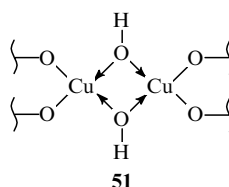


III. Complexes of cyclodextrins

Cyclodextrins (CD) are cyclic oligosaccharides consisting of six (α -CD), seven (β -CD), or eight (γ -CD) residues of α -D-glucopyranose **4a**. They are capable of incorporating various organic molecules into inner hydrophobic cavities.²⁵⁸⁻²⁶²

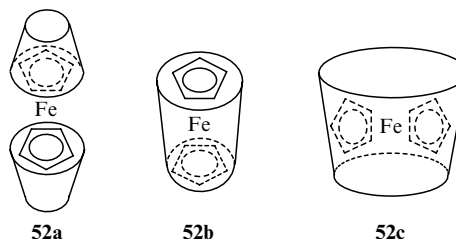
Less is known of the ability of cyclodextrins to form complexes with metal ions. Thus β -CD complexes alkali metal salts, although this mostly occurs due to binding of the anion.²⁶³ Complexes of α -CD with iodine of the type $(\alpha\text{-CD})_2 \cdot LiI_3 \cdot I_2 \cdot 8H_2O$ (a model of the blue iodine complex with amylose) and with cadmium ions have been described.²⁶⁴ In the β -CD complex with KOH, the K^+ ion is bound by six coordinate bonds with the hydroxyl groups of the glucopyranose residues thus forming a distorted trigonal prism.²⁶⁵ The lutetium ion can also be bound to β -CD.²⁶⁶ Metal complexes of coronands (crown ethers)^{267, 268} or their acyclic analogues, podands,²⁶⁸ can be incorporated into the cavities of cyclodextrins.

Some complex compounds of cyclodextrins with *d*-metal cations are also known. α -Cyclodextrin forms binuclear complexes **51** with Cu^{II} ; complexes of β -CD are formed similarly but contain deprotonated oxygen bridges.²⁶⁹⁻²⁷¹



Other *d*-metals are also prone to form polynuclear complexes with β -CD. For example, the complexes $[M_2(OH)_2(\beta\text{-CD}) \cdot 2H_2O]$ ($M = Mn^{III}, Cr^{III}$), $Na_2[M_2(OH)_2(\beta\text{-CD}) \cdot 2H_2O]$ ($M = Co^{II}, Ni^{II}, Cu^{II}$), and $[M_4(OH)_4(\beta\text{-CD}) \cdot 2H_2O]$ ($M = Fe^{III}$) have been described.^{272, 273}

However, the primary attention is paid to the inclusion of *d*-metal complexes into cyclodextrin cavities (second-sphere coordination).^{274, 275} Thus α -, β -, and γ -CD form host-guest complexes (inclusion compounds) **52a**, **52b**, and **52c**, respectively, with ferrocene.²⁷⁶⁻²⁷⁸

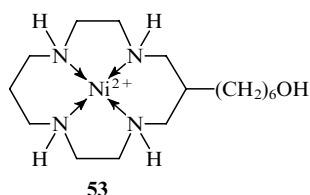


The 'guest' molecules in these complexes can rotate freely only at elevated temperatures.²⁷⁹ The axial incorporation of ferrocene in the complex **52b** was confirmed in a study of complexation of cyclodextrins with a model ferrocene derivative that can be arranged in the cavity only equatorially, as in the complex **52c**.²⁸⁰ Since the cavity of α -CD is small, it can incorporate only

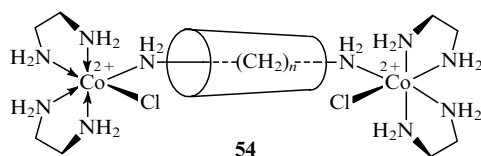
monosubstituted ferrocenes, whereas the other cyclodextrins form complexes with disubstituted ferrocenes as well.^{277, 278} In this type of cyclodextrin complex, a chiral 'host' molecule induces optical activity in a 'guest' molecule. This facilitates investigation of these compounds.^{281, 282} The complex $[(\eta^5\text{-C}_5\text{H}_5)\text{FeC}_6\text{H}_6\text{PF}_6 \cdot 2\alpha\text{-CD}]$ ^{283, 284} of the type **52a** and its analogues containing naphthalene, indan, tetralin, or thiophene instead of benzene²⁸⁴ have been prepared. Complexes of η^6 -arenetricarbonylchromium with β - and γ -CD of the composition 1 : 1 are known.²⁸⁵

Incorporation of organometallic π -complexes such as $[(\eta^3\text{-allyl})\text{Pd}]$,²⁸⁶ $[(\text{cod})\text{RhCl}_2]$ (cod is cyclooctadiene),²⁸⁷ $[(\text{cod})\text{PtX}_2]$ (X = Cl, Br, I),²⁸⁷ $[(\text{cod})\text{Rh}(\text{NH}_3)_2]$,^{288–290} and ordinary platinum complexes such as **45**^{290–293} into cyclodextrins has been studied.

Bulky metal complexes such as macrocyclic Ni^{II} complex **53**²⁹⁴ or the Fe^{III} complex with protoporphyrin IX (hemin)²⁹⁵ can also occupy the hydrophobic cavities of cyclodextrins.

**53**

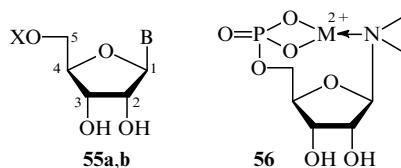
Rotaxane complexes of type **54** have been synthesised.^{296–299} Since the CD molecule is chiral, the synthesis involves asymmetric induction and yields predominantly stereoisomers with the (Δ, Δ)-configuration of the chelate units.^{298, 299}



$n = 8, 10, 12, 14$.

IV. Complexes of nitrogen-containing natural carbohydrates

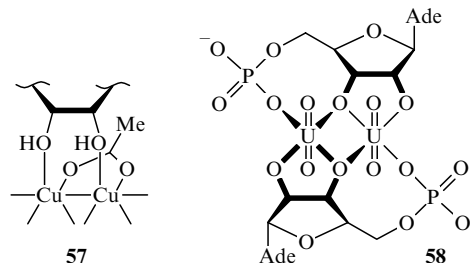
In the metal complexes of ribonucleosides **55a**, metal ions are normally coordinated to endocyclic nitrogen atoms in a base of the pyridine type (B).^{300–303} In the case of ribonucleotides **55b**, additional coordination to the phosphate group is possible; this gives cyclic complexes of the type **56**,¹⁸ in conformity with the principle of hard and soft acids and bases.²⁰⁵



X = H (a), PO_3H_2 (b); B is a heterocyclic base.

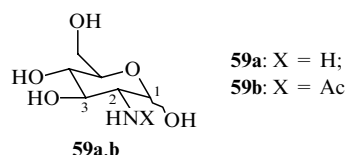
However, within the scope of this review we are interested in the exceptions to this rule, namely, complexes resulting from coordination of carbohydrate fragments. Thus in disodium uridine 3'-phosphate, the Na^+ cation is coordinated not only to the phosphate but also to the oxygen atoms at C(2') and C(5').³⁰⁴ Likewise, the ribose residue is one of the sites of coordination of the Li^+ ion to the nucleosides **55a**.³⁰⁵ In the sodium inosine phosphate, the Na^+ cation is coordinated to the hydroxyl groups at the C(2') and C(3') atoms of the ribose residue.³⁰⁶ The interaction of borate ions with pyrimidine nucleosides involves coordination at the vicinal diol group at C(2') and C(3') and results in a complex of the type **8**.³⁰⁷ Vanadate ions are coordinated in a similar way.^{183, 308} The same hydroxyl groups and Cu^{II} ions give binuclear complexes Cu_2L_2 of the type **51**.^{309, 310} It has

been suggested that Cu^{II} acetate forms three-dimensional binuclear complexes like **57**;³¹¹ however, other results^{312, 313} attest to the formation of ordinary coordination units of the type **21**. The uranyl complex of adenosine has the binuclear bridged structure **58**.^{314, 315} Desoxyribonucleosides and -nucleotides do not contain a vicinal diol group; therefore, their carbohydrate fragments do not participate in coordination.

**57****58**

Among natural aminosaccharides, D-glucosamine (2-amino-2-deoxy-D-glucopyranose, **59a**) has received most attention. Metal complexes of D-glucosamine have been studied by electronic spectroscopy, potentiometric titration, calorimetry, and EPR spectroscopy. No X-ray diffraction data for these complexes are available.

The complex formation of D-glucosamine **59a** with Cu^{II} has received the most study.^{141, 316–324} This interaction involves coordination not only to the amino group but also to the hydroxyl groups at the C(1) and C(3) atoms adjacent to the amino group.^{316, 321} In the complexes CuL and CuL_2 ,^{317, 320} the hydroxyl groups of the ligands can be either free³²¹ or deprotonated.³²³ Other researchers¹⁴¹ deny participation of free hydroxyl groups in the coordination and assume that deprotonation is typical first of all of the hydroxyl group at C(1), because it is the most acidic.³²⁵ In the case of the Cu^{II} complex of N-acetylglucosamine **59b**, the N-acetyl group is not coordinated to the Cu^{II} ion but stabilises the complex $[\text{Cu}(\text{LH}_{-1})_2(\text{OH})_2]^{2-}$.¹⁴¹

**59a,b**

The complexation of D-glucosamine **59a** with Ni^{II} ,^{141, 319–322} Co^{II} ,^{316, 319–324, 326, 327} and Fe^{III} ^{317–320} ions has been studied fairly comprehensively. For complexes of the composition ML , the following stability series was obtained: $\text{Cu}^{\text{II}} > \text{Pb}^{\text{II}} > \text{Zn}^{\text{II}} > \text{Ni}^{\text{II}} \equiv \text{Co}^{\text{II}}, \text{Cd}^{\text{II}}, \text{Mn}^{\text{II}} \gg \text{Ca}^{\text{II}}, \text{Mg}^{\text{II}}$,³²¹ and for complexes ML_2 , $\text{Fe}^{\text{III}} > \text{Cu}^{\text{II}} > \text{Co}^{\text{II}}$.³¹⁹

The formation of complexes of D-glucosamine **59a** of the composition ML_2 with the above cations is a multi-stage process,^{319, 323} which includes coordination of the cation to the amino group of the first ligand, to the amino group of the second ligand, coordination to the neighbouring hydroxyl groups followed by their stepwise deprotonation, and finally coordination to a hydroxide ion in a strongly alkaline medium.^{323, 326} However, other investigators^{141, 321} deny the possibility of coordination to a hydroxide ion. Solid hygroscopic complexes of D-glucosamine of the composition ML_2 with Ca^{II} , Ba^{II} , and Sr^{II} have been obtained.³²⁴

The cationic complexes $[\text{FeL}(\text{OH})_2]^+$ and $[\text{FeL}(\text{OH})]^{2+}$ are formed from Fe^{III} and D-glucosamine **59a** in a physiological salt solution.³²⁶ The crystalline complexes $[\text{NiL}_2]\text{X}$ (X = 2Cl^- , SO_4^{2-}) have been obtained.³²⁷ Synthesis of *cis*-dichlorobis(D-glucosamine)platinum(II) has been reported.³²⁸

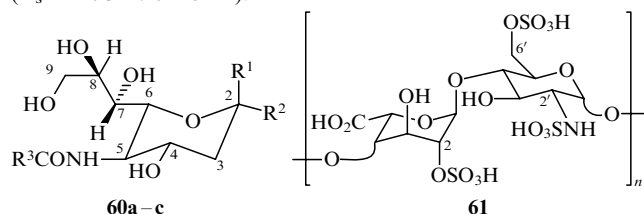
The interaction of D-glucosamine **59a** with tris(ethylenediamine)cobalt has led to contradictory results. First, it was reported³²⁹ that this gives an outer-sphere complex with a structure of the type **31**. Subsequently, it was shown³³⁰ that this affords four isomers with a $\Delta : \Lambda$ ratio of 7 : 3, which differ in the

anomeric configuration of the ligand and configuration of the chelate unit (complexes like **43** with an amino group instead of a hydroxyl group). Finally, recently³³¹ it was shown that the composition of the product mixture is even more complicated; eight(!) isomers were isolated from the mixture and characterised by X-ray diffraction analysis. In all of these compounds, the ligand had been converted preliminarily into a substituted *N*-glucoside, and after that, the reaction gave complexes of the type **43** [with an amino group instead of the hydroxyl group at the C(1) atom of the sugar]. The ligand in this complex was either transformed into the aldehyde form of the type **39** or into the furanose (keto) form as a result of the Amadori rearrangement,² or remained in the native pyranose form.

In order to model the chemical behaviour of natural polysaccharides containing residues of D-glucosamine **59a**, which might be able to form multi-ligand complexes, a ternary complex consisting of Cu^{II}, D-glucosamine, and prometone [2-methoxy-4,6-bis(isopropylamino)-*s*-triazine, PR] of the composition [CuPR(LH₂)₂] was synthesised.³³²

The complex formation of other natural 2-amino sugars has been much less studied. It has only been reported that Cu^{II} forms complexes with D-mannosamine,³³³ D-galactosamine, and D-talosamine.³³⁴ The latter complex is the most stable among copper complexes of natural 2-amino sugars. This was explained³³⁴ by the formation of a very strong hydrogen bond between the hydroxyl group at C(4) and the amino group at C(2), owing to their diaxial orientation.

An important constituent of natural glycolipids and glycoproteins is *N*-acetylneuraminic acid. The β -anomer of this acid **60a** forms^{335–337} a fairly stable complex with Ca^{II} of the composition 1 : 1 ($K_s = 121 \text{ litre mol}^{-1}$).³³⁵ The calcium complex with *N*-glycolylneuraminic acid **60b** is even more stable ($K_s = 193 \text{ litre mol}^{-1}$).³³⁶



R¹ = CO₂H, R² = OH; R³ = Me (**a**), CH₂OH (**b**);
R¹ = OH, R² = CO₂H, R³ = Me (**c**).

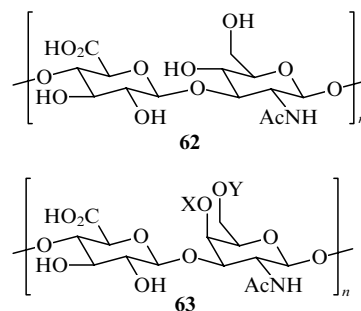
The complex formation of Ca^{II} with the ligand **60a** has been reported³³⁵ to involve the ring oxygen atom and the hydroxyl groups at the C(7), C(8), and C(9) atoms; however, according to another publication,³³⁷ coordination occurs through the ring oxygen atom and the hydroxyl groups at C(2) and C(8). The natural α -anomer of the *N*-acetylneuraminic acid **60c** weakly binds Ca^{II},³³⁷ binding of metal cations by the ligand **60c** becomes markedly stronger when Ca^{II} is replaced by Gd^{III} or Mn^{II},³³⁸ which coordinate **60c** in the region of the glycerol 'tail' and the carboxyl group. Natural gangliosides (oligosaccharides containing the acid **60c** and long hydrocarbon chains attached to them²) coordinate metal cations by the glycerol fragment of the natural α -anomer **60c**. In this case, Ca^{II} ions are bound much more strongly than Mg^{II}.³³⁹ However, since the *O*-methylglycoside of the α -anomer **60c** scarcely binds Ca^{II}, the coordination involves neighbouring monosaccharide fragments, in addition to the *N*-acetylneuraminic fragment.³⁴⁰ A similar enhancement of complexation is also observed³⁴¹ in the binding of Gd^{III} by glycoporphin A — a transmembrane glycoprotein with a high content of α -*N*-acetylneuraminic acid **60c**. In aqueous solutions, *N*-acetylneuraminic acids **60a,c** do not coordinate Na⁺ and K⁺ cations.³⁴²

Glycosaminoglycans are polymers containing 2-amino sugars and occurring in connective tissues (mucopolysaccharides²); therefore, study of their complexation presents considerable interest from biochemical and medical viewpoints. A typical representative of mucopolysaccharides is an anticoagulant hepa-

rin.^{343–345} The repeating disaccharide unit of this compound **61** consists (from left to right) of an L-iduronic acid residue sulfated at the hydroxyl group at C(2) and a D-glucosamine residue sulfated at the amino group and at the hydroxyl group at C(6'). On dissolution in water, sodium heparinate dissociates only by 34%.³⁴⁵ This corresponds to the normal behaviour of polyelectrolytes in which *s*-metal cations are bound non-specifically (territorial binding, Section II.1). In other words, they merely 'condense' on the negative charges in the polymeric chain,^{346, 347} according to the Manning theory.⁷⁸ However, in another study,³⁴⁸ specific binding of Na⁺ by two carboxyl groups of the neighbouring L-iduronic acid residues was suggested, based on the results obtained by ²³Na NMR spectroscopy. However, later the same results were explained³⁴⁹ in terms of the concept of condensation of counter-ions. On the other hand, in the case of Ca^{II}, ionic coordination with participation of the sulfo group of the L-iduronate and the sulfo group at the C(6') atom of the D-glucosamine residue³⁵¹ has been suggested.³⁵⁰ In the presence of excess Ca^{II}, neighbouring chains of the polymer are linked according to the 'egg box' pattern (Section II.1).³⁴⁵ The complexation hypothesis is supported by the series of the efficiency of binding of *s*-metals with heparin^{343, 352} (Na⁺ < K⁺ < Mg²⁺ < Sr²⁺ < Ba²⁺ < Ca²⁺), since, according to the condensation theory,⁷⁸ the most efficient binding would be observed for the Mg²⁺ cation characterised by the maximum charge density. The data of circular dichroism spectroscopy,³⁵³ which confirm this series, indicate simultaneously that there is no specificity in the binding of Ca^{II}. This contradiction might be explained by the fact that heparin is capable of both non-specific (condensation) and specific (complexation) binding of *s*-metal cations. This was discovered³⁵⁴ for electrostatic binding of heparin with Zn^{II}. It has been noted³⁵⁵ that this ability is peculiar only to heparin; however, according to another publication, heparin just possesses the highest affinity for Zn^{II} compared to other glycosaminoglycans.³⁵⁶

The interaction of heparin with Cu^{II} cations occurs as chelation involving the amidosulfate group.^{357, 358} At higher pH, the complex formation is enhanced. This was explained^{357–359} by straightening (despiralisation) of heparin molecules resulting in liberation of new coordination sites. It was suggested³⁵⁷ that Cu^{II} is coordinated inside the cavity of a helix, as in the case of Cu^{II} complexes with cyclodextrins (see Section III, the compound **51**). Among glycosaminoglycans, heparin possesses the highest affinity for [Co(NH₃)₆]³⁺ cations, apparently due to the high negative charge density in its macromolecule.³⁶⁰

Studies on the complexation of other glycosaminoglycans have also been concerned with hyaluronic acid (its dimeric unit **62** consists of the residues of D-glucuronic acid and *N*-acetylglucosamine **59b**) and chondroitinsulfates.³⁶¹ The latter compounds are built of dimeric units comprising a D-glucuronic acid residue and a residue of *N*-acetyl-D-galactosamine sulfated at the 4-position (chondroitin-4-sulfate, **63a**) or at the 6-position (chondroitin-6-sulfate, **63b**).



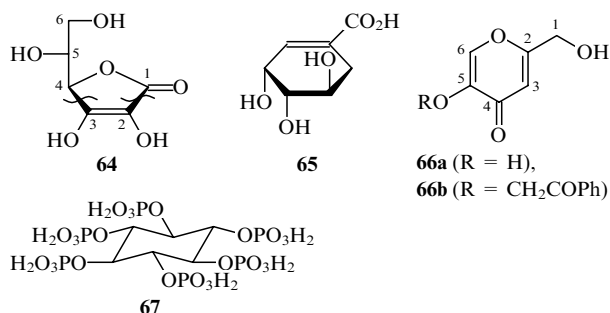
X = SO₃[−], Y = H (**a**); X = H, Y = SO₃[−] (**b**).

The presence of doubly charged *s*-metal cations ensures^{362,363} a helical conformation of hyaluronic acid **62**. In accordance with polarographic data, Cu^{II} forms complexes of the type CuL, CuL₂, and CuL_{*n*} (L is deprotonated hyaluronic acid).³⁶⁴ In the former case (an inner-chain complex), Cu^{II} is chelated by the carboxyl group and by the bridging oxygen atom,³⁶⁵ while at high pH values, the deprotonated *N*-acetyl group also participates in the coordination.³⁶⁶

Chondroitin-6-sulfate **63b** binds Na⁺ and Ca²⁺ ions non-specifically.³⁶⁷ In terms of the strength of their binding to chondroitin-4-sulfate, *s*-metal cations can be arranged in the same sequence³⁶¹ as in the case of heparin (see above). In the case of chondroitin-6-sulfate, there is no difference between the strengths of binding of doubly charged *s*-metal cations.³⁶¹ For a mixture of chondroitinsulfates **62a,b**, it has been shown³⁶⁸ that the efficiency of binding increases in the sequence Cu^{II} < Yb^{III} < La^{III}. In addition, chondroitin-4-sulfate **63a** binds Yb^{III} cations by the carboxyl group and the sulfo group of one chain and by two carboxyl groups of a parallel chain.³⁶⁹

V. Complexes of natural acids of the carbohydrate origin

In this Section, we describe a number of complexones such as ascorbic (**64**), shikimic (**65**), kojic (**66**), and phytic (phytin, myo-inositol hexaphosphate, **67**) acids. These particular subjects were chosen due to their biosynthetic origin from carbohydrates.^{2,370,371}

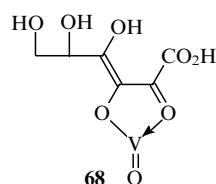


Numerous studies and a comprehensive review⁹ covering publications up to 1977 have been devoted to metal complexes with ascorbic acid (vitamin C) **64**. Being a dibasic acid [owing to the protic activity of the hydroxyl groups at C(2) and C(3)], ascorbic acid **64** can be converted into two anions, (LH₋₁)⁻ and (LH₋₂)²⁻. It forms complexes [M_xL_{*y*}]^z, [M_x(LH₋₁)_{*y*}]^z, [M_x(LH₋₂)_{*y*}]^z, and [M_x(LH₋₂)_{*y*}OH]^z virtually with all metal cations including oxo cations.⁹ Salts of ascorbic acid **64** [M_x(LH₋₁)^z] are formed upon coordination of a metal cation by the deprotonated hydroxyl group at C(3) (the strongest acidic site). The subsequent coordination involves the hydroxyl group at C(2) (either free or deprotonated) and the lactone carbonyl group at C(1). The vicinal hydroxyl groups in the 'tail' at the C(5) and C(6) atoms do not participate in the coordination in solutions,^{372,373} although in the condensed phase, this coordination is possible.^{374–377} Thus in solid Ti^{IV} ascorbate, the metal ion is additionally bound not only to the hydroxyl groups at C(5) and C(6) but also to the lactone carbonyl group. In solid ascorbates of divalent *s*-metals, a cation is coordinated to three anions, and only Mg^{II} binds two anions.³⁷⁹ In aqueous solutions, cations of univalent *s*-metals are bound by an ionic bond, except for Li⁺, which is bound by a covalent bond.³⁸⁰

In the case of In^{III} and Ga^{III}, polynuclear complexes predominate in acidic media,³⁸¹ while lanthanides form³⁸¹ complexes [M(LH₋₁)₂]⁺. The following stability series has been elucidated³⁸² for the complexes of divalent metals: Be > Pb > Mn > Fe > Co > Ni. These metals form complexes of the composition 1 : 1, and only Be^{II} forms stable 1 : 2 complexes.³⁸²

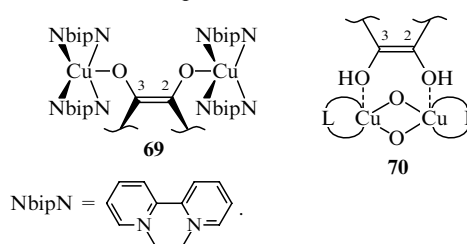
Complex formation of V^{IV}^{9,380,383} and V^V,³⁸⁴ which is accompanied by oxidation of the ligand yielding dehydroascorbic

acid, has been studied in detail. Upon the reaction with V^{IV}, dehydroascorbic acid undergoes the lactone ring opening being thus converted into diketogulonic acid. Chelate **68** is formed apparently from the enol form of this acid and the vanadyl ion.^{372,373,385–388}



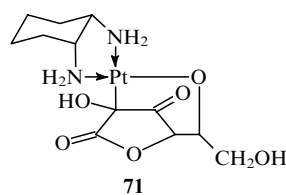
Complex formation of ascorbic acid with *d*- and *f*-metal cations has been studied.⁹ This ligand forms solid three-dimensional polymeric complexes with Zn^{II}, Co^{II}, and Hg^{II}.³⁸⁹ In solutions, monodentate [through the O(3) atom] or bidentate [through the O(2) and O(3) atoms] coordination is possible.³⁸⁹ The complexes of the acid **64** with Co^{II} in solutions have been studied in most detail.⁹ A study of spin–lattice relaxation in the ¹³C NMR spectra has confirmed³⁹⁰ the predominant chelation of Co^{II}, Fe^{II}, and Mn^{II} by the O(2) and O(3) atoms, while the lactone and ring oxygen atoms and the hydroxyl groups at C(5) and C(6) are weaker coordination sites.

The reaction of the acid **64** with [Co(NH₃)₄]²⁺ gives two complexes: a monodentate complex [with coordination through O(3)] and a bidentate one (with coordination to the lactone and ring oxygen atoms).³⁹¹ A stable ternary complex **69** formed by ascorbic acid and bis(2,2'-bipyridyl)copper(II) has been described.³⁹² Binuclear complexes of Cu^{II} **70** are readily reduced by ascorbic acid **64** if the sizes of the reactants are fitted in the intermediate complex **70**.³⁹³



An unusual organometallic complex of platinum with ascorbic acid (**71**) containing a C–Pt σ-bond has been synthesised within the framework of studies dealing with the development of new anticancer preparations.³⁹⁴ Complexes of the acid **64** with dicyclopentadienyltitanium [η-C₅H₅)₂TiL₂] and with dialkyltin [R₂SnL·H₂O] (R = Me, Et) have also been obtained.³⁹⁵ In the latter complex, the ligand L can be coordinated both in monodentate [by O(3)] and bidentate [by O(2) and O(3)] fashions.

Shikimic acid **65** forms³⁹⁶ a (1,2-diaminocyclohexane)platinum complex similar to the compound **71** prepared from ascorbic acid [the metal is coordinated to the carboxyl oxygen atom and to the alkene carbon atom C(2)].



Kojic acid **66a** containing an oxo-enol fragment forms numerous complexes with various cations^{371,397} including *s*-metal ions.^{13,371} The compounds of kojic acid with metal ions can be built³⁷¹ either as complex salts with coordination to the oxygen atom at C(6) or as chelates with an additional coordination to the oxo group. Synthetic 5-phenacylkojic acid **66b** also acts as a complexone.^{11,398–400} In its complexes, a metal ion is linked to

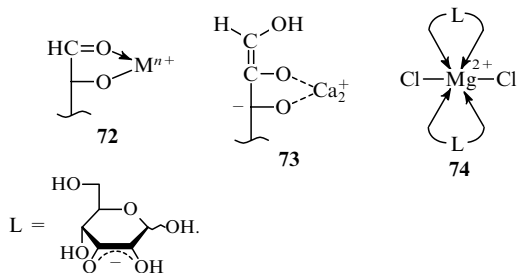
the carbonyl fragment of the phenacyl group, to the carbonyl group at C(4), and to the oxygen atom at C(6).

The formation of metal complexes with phytin has been intensely studied due to the dietary significance of this compound (Section VI.1). The thermodynamics of phytin complexation with Ca^{II} ,⁴⁰¹ Zn^{II} ,⁴⁰² Cu^{II} ,⁴⁰³ Mn^{II} ,⁴⁰⁴ Co^{II} , Ni^{II} ,⁴⁰⁵ Fe^{III} , and Cr^{III} ⁴⁰⁶ have been studied by calorimetry. Complex formation of incompletely substituted ester, myo-inositol 1,2,6-triphosphate, with alkali⁴⁰⁷ and transition⁴⁰⁸ metal cations has been investigated. For none of the complexes obtained, has the structure been determined.

VI. The significance and applications of metal coordination to carbohydrates

1. The influence of complex formation on the chemical properties of carbohydrates

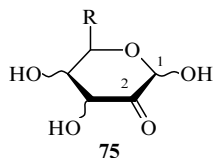
The catalytic role of metal cations in a key transformation of carbohydrates, namely, in the Lobry de Bruyn–Alberda van Ekenstein rearrangement^{2,409} [epimerisation of aldoses at the C(2) atom and their conversion into ketoses], has been explained by assuming the intermediate formation of complex **72**.⁴⁰⁹ In a discussion of the dehydration of carbohydrates, the special case of alkaline dehydration of D-mannose was interpreted using the suggestion⁴¹⁰ of formation of an enediol complex of type **73**. The formation of similar enediol metal complexes has been assumed⁴¹¹ to rationalise the mechanism of oxidation of monosaccharides by hydrogen peroxide. These complexes have been identified by electronic and NMR spectroscopy.⁴¹² The enediol complex **74** has been isolated and characterised.⁴¹³



Thus, the hypothesis of the formation of enediol forms of carbohydrates stable as metal complexes, put forward^{2,370} to account for the above transformations, can be considered to be experimentally proven. However, in view of the most recent results, participation of these species in epimerisation seems doubtful (see below).

Angyal *et al.*^{6,414–417} have shown that *O*-glycosylation according to Fischer (treatment of sugars with a methanolic solution of HCl)² carried out in the presence of calcium or strontium salts results in increased yields of *O*-methylfuranosides. This discovery made this type of compound readily accessible. Acyclic forms, aldose dimethyl acetals, can also be formed under these conditions.⁴¹⁸

The promotory effects of Ca^{2+} and Ba^{2+} ions on the alkaline oxidation of aldoses by 2-anthraquinonesulfate to aldonic acids of the type **14a** has been explained⁴¹⁹ by the fact that the stability of the intermediate aldoses-2-uloses **75** increases when these metal ions are coordinated to the hydroxyl group at the C(3) atom and to the oxo group. The angle between the two coordinate bonds must be $0–30^\circ$; otherwise, the influence of these cations is not manifested.



$\text{R} = \text{H}, \text{CH}_2\text{OH}.$

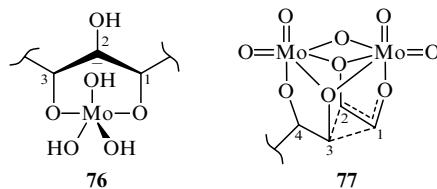
Complexation with boric and phenylboronic acid has been used⁴²⁰ to perform selective acetonation of monosaccharides; a similar approach used in the series of nucleosides and nucleotides is employed for their selective methylation at the base.⁴²¹ The use of a complexing polymer, polystyrylboronate, made it possible to prepare partially acetylated derivatives of *O*-methylglycosides, valuable from the synthetic viewpoint.⁴²² The addition of a borate during the aldol condensation of 2-acetamido-2-deoxy-D-glucose **59b** with oxaloacetate giving *N*-acetylneuraminic acid (a mixture of anomers **60a,b**) increases the yield of the product. Apparently, complexation suppresses side reactions.⁴²³ The presence of a borate shifts the aldose $\rightleftharpoons$ ketose equilibrium (the Lobry de Bruyn–Alberda van Ekenstein rearrangement^{2,409}) towards the latter.^{424,425} Cations of *d*-metals also catalyse this rearrangement.⁴²⁶ It was shown^{427,428} that the main event in the catalytic action of sodium aluminate on the isomerisation of D-glucose to D-fructose is stabilisation of the intermediate enediol *via* coordination giving a structure like **73**. The presence of an anion exchanger in the paramolybdate form also facilitates this transformation by suppressing side reactions.⁴²⁹

Complex formation has been successfully used to protect particular functional groups during selective *N*-acylation of aminoglycoside and aminocyclitol antibiotics in the presence of heavy metal salts.^{430–432} The direction of acetylation can be changed simply by changing the metal cation used.⁴³⁰

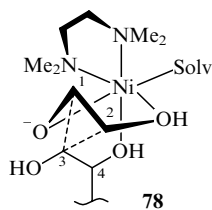
The numerous reactions of oxidation of aldoses in the presence of metal salts often yield initially intermediate metal complexes the stability of which varies over wide limits. Complex formation can occur in a transition state, or it can give highly unstable complexes.^{433,434} The intermediates can decompose either in a single-electron process giving free radicals, which act as the reactive species,^{435–438} or by a two-electron transfer mechanism giving reaction products.^{439–441}

In a number of studies,^{442–458} a preparative method has been developed, based on the ability of molybdate ions MoO_4^{2-} to catalyse epimerisation of aldoses and ketoses and their derivatives in relation to the carbon atom nearest to the carbonyl group. The most prominent example of this epimerisation,²⁰² the transformation of D-xylofuranose into D-lyxose, was discussed in Section II.3. When molybdate is replaced by tungstate, the complexation is not accompanied by epimerisation,⁴⁵⁹ because the carbohydrate complexes of tungstate are much more stable than the molybdate complexes¹⁹⁸ (see Section II.3). However, in the presence of a borate, D-arabinose incorporated in the tungstate complex readily epimerises to D-ribose, since the borate complex of the latter is more stable.⁴⁶⁰

Previously, the mechanism of epimerisation has been interpreted by assuming^{13,442} the intermediate formation of planar complex **76**, deprotonated at the C(2) atom, in which the metal is coordinated to the O(1) and O(3) atoms of the cyclic form of the substrate. The subsequent diastereofacial protonation of the complex **76** was assumed to give both the complex of the substrate and that of the product. However, later, using NMR spectroscopy of aldoses enriched in the ^{13}C and ^2H isotopes at the C(1) atom, it was shown⁴⁶¹ that in reality, this epimerisation includes a rearrangement of the substrate carbon skeleton. The C(1) and C(2) atoms exchange their positions in the hypothetical binuclear transition complex **77** containing the initial aldose in the acyclic aldehyde form. A similar complexation has been proposed⁴⁶² to explain epimerisation of D-glucose to D-mannose catalysed by $\text{Mo}_7\text{O}_{24}^{3-}$ ions.



It has been suggested^{13,463,464} that in the presence of Ni^{II} and N,N,N',N' -tetramethylethylenediamine, aldoses are wholly epimerised at the C(2) atom with a similar rearrangement of the carbon skeleton *via* transition complex **78** with the aldehyde form of the substrate. An analogous reaction occurs when Ca^{II} is used instead of Ni^{II} .⁴⁶⁵ Finally, it has been found⁴⁶⁶ that a rearrangement of the carbon skeleton of carbohydrates accompanied by epimerisation occurs even in such a simple system as methanol–calcium hydroxide. It is obvious that in view of these findings, the generally accepted mechanisms of the Lobry de Bruyn–Alberda van Ekenstein rearrangement⁴⁰⁹ should be revised. In the methanol– Ni^{II} – N,N' -diethylethylenediamine system, D-fructose **29** undergoes a more extensive rearrangement of the carbon skeleton resulting in a branched aldose, 2-C-hydroxymethyl-D-ribose.⁴⁶⁷ It is noteworthy that the side formation of ketoses in these processes is not accompanied by a rearrangement of the carbon skeleton of the initial aldoses.⁴⁶⁶ Apparently, ketoses are formed *via* the generally accepted mechanism of the Lobry de Bruyn–Alberda van Ekenstein rearrangement.^{2,409} The discovery of the change of the carbohydrate carbon skeleton upon the formation of metal complexes is undoubtedly an outstanding achievement in the coordination chemistry of carbohydrates.



Solv is solvent.

2. Reactions involving metal complexes of carbohydrates

Cyclodextrins react with RhCl_3 to give colloidal dispersions of rhodium, which efficiently catalyse hydrogenation of alkenes carried out at 30 °C under atmospheric pressure of hydrogen.⁴⁶⁸ Complexes of Cu^{II} with β -CD and its polyphosphate initiate vinylic polymerisation.⁴⁶⁹ Sugars are often used as donors of hydrogen in the catalytic hydrogenation of carbonyl compounds with hydrogen transfer.⁴⁷⁰ The mechanism proposed for this process⁴⁷⁰ assumes participation of metal complexes of carbohydrates formed intermediately. One example of the use of cyclodextrin as phase transfer catalyst, owing to its ability to coordinate s -metal cations, was reported.⁴⁷¹

The chirality of carbohydrates is employed in enantioselective catalysis. Well known^{472–475} catalysts for hydrogenation are L-tartaric acid **18** or its D-enantiomer adsorbed on the metal surface; in this case, chelation leading to the formation of a chiral environment on the metal surface is assumed. The optical yields in these reactions reach 55%–63%.^{476–478} This is a significant achievement, because these catalysts can be used repeatedly. Similar reactions catalysed by palladium supported on cellulose⁴⁷⁹ resulted in optical yields of only 0.10%–0.15%. Apparently, in the latter case, no metal binding on the surface of a chiral support is involved. The optical yields in the reduction of the complexes of ferrocenyl ketones with β -CD of the type **52b** vary from 5%⁴⁸⁰ to 32%–80%.^{481,482}

3. Modelling of enzymes by metal complexes of carbohydrates

This field of application of carbohydrate metal complexes is still limited to cyclodextrins. Thus alkaline hydrolysis of *p*-nitrophenyl acetate is suppressed almost entirely by the addition of the binuclear complex of Cu^{II} with α -CD **51**.⁴⁸³ When the corresponding complex with β -CD is used, the retardation of the reaction is less pronounced. This is due to the formation of a stable inclusion compound from the former complex and the substrate; this permits regarding this complex as an adequate model of a metal enzyme.⁴⁸³ A structurally related binuclear complex of Mn^{II} with

β -CD has been proposed⁴⁸⁴ as a model of a photosynthesis enzyme, which catalyses water oxidation to oxygen. It has been shown^{485,486} that complex formation of d -metals with cyclodextrins is a general way of stabilising hydroxo complexes of d -metals for the modelling of terminal enzyme systems for photosynthesis.

One aspect of enzyme activity, namely, the decrease in the number of degrees of freedom of the substrate upon its complexation with the enzyme, has been modelled by alkaline hydrolysis of esters of ferrocenecarboxylic acids.^{487–490} The molecular design was accomplished in such a way that the catalytic centre (a hydroxyl group of cyclodextrin) was located in the optimum vicinity of the reaction centre of the substrate when the latter had entered the cyclodextrin cavity.^{487–490}

4. Analytical methods based on the formation of metal complexes with carbohydrates

An important application of complex formation with metals is the solution of analytical and structural problems in the series of carbohydrates.

A large set of qualitative and quantitative electro(iono)-phoretic and chromatographic methods for the separation of sugar mixtures based on the complexation with metals have been developed. Early^{491,492} and more recent⁴⁹³ reviews survey the data on paper electrophoresis of sugar mixtures in aqueous solutions in the presence of various salts such as borates, germanates, stannates, arsenites, molybdates, and tungstates. It is significant that these modifications of the method supplement one another. Other efficient procedures are paper electrophoresis in the presence of Cu^{II} periodate, tellurate,⁴⁹⁴ acetate, and basic acetate^{150,495} and capillary electrophoretic separation of enantiomeric monosaccharides in the borate–dextrin (cyclodextrin) system, *i.e.* under conditions of double complexation.⁴⁹⁶ Electrodialysis through a polymeric membrane with grafted boric acid residues has been proposed as a method for separation of multicomponent product mixtures obtained upon the formose reaction.⁴⁹⁷

A broad range of methods consisting in paper and column chromatography of carbohydrates based on complex formation with metals have been surveyed in a review.⁴⁹³ The main column chromatography technique is ion exchange chromatography using Li^+ , K^+ , Ca^{2+} , and Ba^{2+} forms of cation exchangers and cellulose or silica gel impregnated with a borate. Column chromatography of aqueous solutions of sugars on alumina is also accompanied by complex formation.⁴⁹⁸ Closely related approaches are chromatography on anion exchangers in the aluminate form⁴⁹⁹ and chromatography on paper (cellulose) containing carboxylate groups grafted as La^{3+} , Ca^{2+} , and Ba^{2+} salts.⁵⁰⁰ Yet another efficient method is thin layer chromatography of sugars and their derivatives using the Ca^{2+} and La^{3+} forms of cation exchangers.⁵⁰¹ Racemic mixtures of ferrocene derivatives are readily separated on polyamide when an aqueous solution of β -CD is used as the eluent.⁵⁰²

Complex formation with metals has long been used for the determination of sugars. The most widely used procedures are the quantitative Bertrand method⁵⁰³ based on oxidation of copper complexes of aldoses to give Cu^{I} oxide and the related qualitative Fehling² and quantitative Somogyi⁵⁰⁴ methods. There are grounds for believing that oxidation occurs in enediol Cu^{II} complexes.⁵⁰⁵ Determination of sugars based on their oxidation by the Cu^{II} periodate complex⁵⁰⁶ or Ce^{IV} sulfate⁵⁰⁷ has also been described.

The formation of complexes of carbohydrates with metals proved to be useful for electrochemical, mainly polarographic, determination of metals. In the presence of acyclic or cyclic polyols, the half-wave potential of the metal cation being analysed substantially shifts, which enables its determination in the presence of other metal cations.^{508–510} The volumetric determination of Pt^{II} in an alkaline solution of D-mannitol in the presence of

cations of other platinum metals is another example of this approach.⁵¹¹

It is difficult to overestimate the role of complex formation in the configurational and conformational analysis of carbohydrates.^{512, 513} Thus, determination of the stability constants of the borate complexes of pyranoses permitted Angyal to propose a method for the calculation of the conformation energies of these ligands,^{512, 513} while the change of the specific rotation of aldoses following their complexation with borate made it possible to determine their anomeric configuration.^{2, 3}

Several methods of the conformational analysis of carbohydrates are based on the correlation between the complexing and rotational (chiroptical) properties of ligands [optical rotatory dispersion (ORD) and circular dichroism (CD) spectroscopy^{514–518}]. Thus CD spectroscopy of molybdate complexes has revealed⁴⁶⁹ a correlation between the orientation of the hydroxyl groups at the C(2) and C(3) atoms in the pyranose form (see the structures **4a,b**) and the signs of the Cotton effects in the CD spectrum of a colourless solution of the molybdate complex. Chiroptical methods are applied most often to solutions of coloured metal complexes containing Cotton-genic (manifested in the visible ORD and CD spectra) groups. This line of research was initiated by the classical studies of Reeves⁴ dealing with the rotational properties of copper complexes of *O*-methylglycopyranosides. As a result of these studies, a clear correlation between the sign of rotation of model compounds with a fixed arrangement of the hydroxyl groups and the sign of the dihedral angle between them was elucidated. Later, these results were confirmed by chiroptical methods^{135, 519–522} (ORD and CD spectroscopy). Similar correlations have been found for Ni^{II} complexes of carbohydrates,^{227, 228, 523, 524} Other Cotton-genic derivatives such as Mo^{II} acetate⁵²⁵ and other *d*-metal acetates,⁵²⁶ which form chiral complexes with vicinal diol groups of sugars, proved to be more convenient compounds from the viewpoint of methodology.

Complex formation of sugars with lanthanide cations used as shift reagents has also found a wide utility in the conformational analysis of carbohydrates by NMR spectroscopy.^{243–245, 527–537} Boric acid⁵³⁸ and Cu^{II} cations^{139, 539} have also been used as shift reagents.

The complex formation of sugars with metals has been employed^{540–542} for improvement of the mass spectrometry methods for their identification. The complexation of anthrylboronic acid with sugars is accompanied by quenching of its fluorescence; therefore, it has been used⁵⁴³ for the development of fluorescence chemical sensors for sugars.

5. The significance for biology and medicine

Previously the views on the biological functions of carbohydrates reduced to their food (glucose, fructose, starch) and structural (cellulose, chitin) properties. However, during the last decades, carbohydrates have been found to play a crucial role in a number of vitally important processes such as mutual recognition of molecules and cells (cell adhesion, agglutination, reception),⁵⁴⁴ tissue calcification as the initial stage of the formation of vertebrate bones and shells of molluscs and bird eggs.⁵⁴⁵ These discoveries substantially raised the biological status of carbohydrates. Since all the processes listed above are Ca²⁺-dependent, this has also stimulated studies dealing with the complex formation of carbohydrates with *s*-metal cations (Section II.1). The studies performed have demonstrated that carbohydrates are weak complexones for these cations and that complex formation with *s*-metals cannot play an important role in the above biological processes. For example, *N*-acetylneuraminic acid **60c**, which is an indispensable component of biologically significant oligo- and polysaccharides, forms Mg^{II} and Ca^{II} complexes in aqueous solutions the stability constants of which are 1.5 and 1.9 litre mol^{−1}, respectively.³⁴² Since in a living organism, carbohydrates are almost necessarily linked to proteins (glycoproteins and

proteoglycans²), a number of studies^{546–548} have been devoted to the complex formation of a model cation (Gd³⁺) with synthetic glycopeptides. It was found that coordination occurs both in the carbohydrate and peptide fragments, the latter being preferred. In general, there are no grounds to believe that complexation of carbohydrates themselves plays a significant role in biological processes. The examples given below confirm this point.

When sugars are specifically bound by protein compounds, lectins,^{549–552} in the presence of metal cations, the protein–sugar interaction is accomplished only by hydrogen bonds.⁵⁵² Apparently, metal cations ensure the appropriate conformation of the protein needed for sugar reception.⁵⁴⁹ At a certain stage of cell recognition, interaction of carbohydrate-containing proteins is due to the Ca²⁺ cation, but it is unknown to what particular fragment this ion is coordinated. By analogy with lectins, it can be assumed that in this case, too, the metal ion is coordinated to the protein fragment.^{553, 554} The complex formation of Ca²⁺ with sulfated polysaccharides is considered to play a certain role in its deposition in tissues.⁵⁴⁵

Metal complex formation with natural carboxylic acids of carbohydrate origin (see Section V) is important for medicine. Thus ascorbic acid decreases the level of mutations in workers in contact with heavy metals.⁵⁵⁵ Phytic acid is present in substantial amounts in vegetable oils, and its ability to form an insoluble complex with Ca²⁺ decreases the removal of calcium with urine.⁵⁵⁶ Binding with heavy metal cations can even inactivate metal-dependent enzymes, for example, α -amylase⁵⁵⁷ and carboxypeptidase A.⁵⁵⁸

The platinum complexes **46**²³⁶ and [PtL(1,3-diamine)]²⁴² (L is D-gluconate or D-glucuronate) exhibited a considerable antitumour activity. This activity was also found for the platinum complex **71**.³⁹⁴ Polymeric osmium carbohydrate complexes, osmarines,^{238, 239} (Section II.3) are used as antiarthritis preparations owing to their capability of binding superoxide ions, which are responsible for this disease.²³⁹ Copper(II) complexes with cyclodextrin of the type **51** can be used⁵⁵⁹ for treating the mildew blight of grapes, because these compounds are not toxic in wine. Water-soluble iron complexes of glucose and fructose **42** are used to treat anemia.⁵⁶⁰ Phytin **67** prevents foodstuffs from going bad under the action of atmospheric oxygen, because it binds Fe³⁺ and Cu²⁺ cations, which can act as efficient catalysts for undesirable oxidation processes.⁵⁶¹

The complex formation of metals with polysaccharides has also found use in medicine. Pectins (polymers of the type **5** with partly esterified carboxyl groups) isolated from fruits or vegetables efficiently bind toxic metal cations and thus they can be used for detoxification of an organism.⁵⁶² It has been proposed⁵⁶³ to use iron complexes of chondroitinsulfates **63a,b** for curing iron deficiency anemia. Metal complexes of dextran and inulin can be used as paramagnetic contrasting reagents⁵⁶⁴ in medical NMR spectroscopy. Treatment of cellulose with heavy metal salts and subsequent interaction with antibiotics imparts antibacterial properties to textiles.⁵⁶⁵

In nature, complex formation of metals with polysaccharides can be undesirable. Thus the formation of gels on the surface of plant roots may have negative consequences for plants, since their main components, acidic polysaccharides, bind metal cations, which come directly from soil particles and are needed for nutrition.⁵⁶⁶

s-Metal cations⁵⁶⁷ and *d*-metal cations⁵⁶⁸ are used to strengthen agaroid jellies. *d*-Metal hydroxides treated with sugars are employed for enzyme immobilisation.⁵⁶⁹ The natural polymer of *N*-acetyl-D-glucosamine — chitin — has been proposed⁵⁷⁰ as a reagent for extraction of heavy metals from waste water; the ferrite–alginate system is employed for the preparation of ferromagnetic particles used as a contrasting reagent⁵⁷¹ in NMR spectroscopy for medical purposes.

VII. Conclusion

The modern coordination chemistry of carbohydrates resembles an enormous picture painted with rough strokes in which only some sections are drawn thoroughly. This is due to the extreme complexity of the investigation subjects, caused by the specific character of carbohydrates as complexones. Carbohydrates can exist in both cyclic and acyclic forms; they can act as polydentate ligands and form regioisomeric complexes. In addition, chirality of carbohydrates results in the formation of unequal amounts of diastereoisomers in relation to the chelate unit. This diversity of compounds can be found in a single reaction mixture. Therefore, the overwhelming majority of conclusions concerning the structures of carbohydrate metal complexes have been drawn relying on more or less likely suggestions, except for those few cases where researchers were able to obtain a crystalline compound and study its structure by X-ray diffraction analysis. However, with the advent of NMR techniques using metal cations as shift reagents, it became possible to determine fairly reliably the structures of a number of metal complexes of carbohydrates in solution. It would hardly be an overstatement to say that nowadays the coordination chemistry of carbohydrates experiences a new stage of its development.

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

^g — *Organomet. Chem. (Engl. Transl.)*

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^j — *Kinet. Catal. (Engl. Transl.)*

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

Radiolysis of solutions of tetrazolium salts

A K Pikaev, Z K Kriminskaya

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Abstract. Published data on radiolysis of liquid (mainly aqueous, water–alcohol and alcoholic) and solid [mainly in poly(vinyl alcohol)] solutions of tetrazolium salts are generalised. The mechanism of radiolytic transformations of these compounds is discussed. Their application in dosimetry of ionising radiation is considered in detail. The bibliography includes 60 references.

I. Introduction

Reduction of colourless or weakly coloured tetrazolium salts yields formazans, which are intensely coloured. This property of formazans has found application in various fields of science and engineering. They have been used in botany as colouring compounds sensitive to ultraviolet radiation,¹ as substances suitable for estimating the productivity of seeds of agricultural plants^{2,3} and the viability of stem and leaf tissues,^{4,5} for distinguishing between normal and malignant tissues,⁶ and for studying the histochemistry of oxidative enzymes.^{7,8} The use of formazans as analytical reagents for detection of O_2^- radical ions has also been reported.^{9–11} In addition, it is known (see, for example, Ref. 12) that liquid and solid solutions of formazans can be employed in the dosimetry of ionising radiation.

The properties, methods for the synthesis, and the mechanism of chemical reduction of tetrazolium salts have been considered in numerous publications (see, for example, Refs 13–17). The present review is mainly devoted to radiolytic transformations of these salts in various solvents (alcohols, water, aqueous alcohols, *etc.*). Solutions of 2,3,5-triphenyltetrazolium chloride (TPTC) have been studied most often; solutions of 2-(*p*-nitrophenyl)-3,5-diphenyltetrazolium chloride (NPTC), 5-(*p*-nitrophenyl)-2,3-diphenyltetrazolium bromide (NPTB), 3-(1-naphthyl)-2,5-diphenyltetrazolium bromide (DPTB), 3,3'-bianisylene-4,4'-bis(2,5-diphenyl-2*H*-tetrazolium) chloride (Tetrazolium Blue, TB), 2,2'-di(*p*-nitrophenyl)-5,5'-diphenyl-3,3'-(dimethoxy-4,4'-diphenylene)-2*H*-tetrazolium chloride (Nitrotetrazolium Blue, NTB) and

some other derivatives have been studied more rarely. Considerable attention is paid to the use of these systems in the dosimetry of ionising radiation.

II. Alcoholic solutions

Detailed data on the radiation yields of reduction of tetrazolium salts in alcoholic solutions and on the mechanism and kinetics of this process can be found in the literature.

1. Radiation yields of reduction

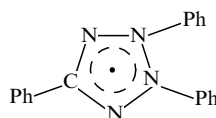
When colourless deaerated alcoholic solutions of tetrazolium (T^+) salts are exposed to radiation, the corresponding intensely coloured (pink, orange-red, or red) formazans are produced. For example, in the case of TPTC, this yields 1,3,5-triphenylformazan $PhNH-N=CPh-N=NPh$.

The radiation yields of formazans (F) in these solutions are listed in Table 1.

2. The mechanism of radiolytic reduction

Radiolytic reduction of tetrazolium salts is a two-electron process, *i.e.* the reduction of each tetrazolium salt molecule requires two reducing species. The yield of the formazan in this process is more than half the yield of solvated electrons (e_s^-) (for example, in isopropanol, the yield of e_s^- is 1.3²⁶). Based on this result, it was concluded that the salts are reduced by not only e_s^- but also by radicals of type $R\dot{C}HOH$ resulting from radiolysis of alcohols. When the doses are large enough, formazans undergo subsequent radiolytic transformations; the solutions become colourless, and hydrazidines are formed. The yields of decomposition of formazans have been determined for the radiolysis of solutions of 1,3,5-triphenylformazan,^{18,27} 3-(*p*-nitrophenyl)-1,5-diphenylformazan,²⁰ and 2,5-diphenyl-3-(1-naphthyl)formazan²⁰ in isopropanol (Table 2).

The conclusion about two-electron reduction of tetrazolium salts is confirmed by the data^{19,28,29} on pulse radiolysis of solutions of these compounds in ethanol and isopropanol. It was found that the interaction of the tetrazolium salt cation (T^+) with e_s^- or with an alcohol radical gives a short-lived species, namely tetrazolium radical ($T^\bullet$). In the case of TPTC, this radical has the following structure:



A K Pikaev Institute of Physical Chemistry, Russian Academy of Sciences, Leninskii prosp. 31, 117915 Moscow, Russian Federation.

Fax (7-095) 335 17 78. Tel. (7-095) 333 95 67

Z K Kriminskaya Russian Research Centre 'Research Institute of Organic Intermediates and Dyes', Bol'shaya Sadovaya ul. 1, 103787 Moscow, Russian Federation. Fax (7-095) 254 12 00

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Table 1. Yields of formazans [$G(F)$, molecule $(100 \text{ eV})^{-1}$] in various matrices upon γ -radiolysis in the absence of air.

Matrix	Tetrazo- lium salt	$10^3\ c/\$ mol litre^{-1}	$G(\text{F})$	Ref.	
Liquid isopropyl alcohol	TPTC	0.1	1.3	18	
	TPTC	0.5	1.5	18	
	TPTC	1.0	1.5	18	
	TPTC	5.0	1.7	18	
	TPTC	7.0	2.2	18	
	NPTC	0.1	1.5	19	
	NPTC	0.5	2.5	19	
	NPTC	1.0	2.5	19	
	NPTC	5.0	2.5	19	
	NPTB	0.1	2.2	19	
	NPTB	0.5	3.3	19	
DPTB	0.1–5	3.1	20		
Water, pH					
	6.9	TPTC	1.0	0.45	21
	7.5 ^a	TPTC	20	0.4	22
	10.3	TPTC	1.0	1.2	21, 23
	6.9	NPTC	1.0	0.6	21
	10.3	NPTC	1.0	1.4	21
	6.9	NPTB	0.5	1.2	21
	10.3	NPTB	0.5	1.2	21
	5.3	DPTB	1.0	0.6	20
	10.0	DPTB	1.0	0.7	20
	11.5	DPTB	1.0	0.8	20
Water–isopropanol (2.2 mol litre ⁻¹), pH 10.3	TPTC	1.0	3.5	21	
Water–isopropanol (20%), pH 11	TPTC	0.8	3.1	23	
Water–isopropanol (1 : 1 by volume), pH 11	TPTC	0.8	3.1	24	
Water–HCOONa (0.2 mol litre ⁻¹), pH 10.3	TPTC	1.0	3.0	21	
Water–EDTA (0.2 mol litre ⁻¹), pH 10.3	TPTC	1.0	3.1	21	
Poly(vinyl alcohol) film	TPTC	7.4	0.86	25	
	TPTC	11	2.6	25	
	TPTC	18	3.1	25	
	NPTC	3.2	2.8	25	
	NPTC	9.8	4.0	25	
	NPTC	13	4.8	25	
	NPTC	16	5.2	25	

^aFor radiolysis induced by X-rays (the highest energy 60 keV). The solution was buffered by triethanolamine and HCl.

Table 2. Yields of decomposition of formazans upon γ -radiolysis of deaerated isopropanol solutions.

Formazan	$10^4 c / \text{mol litre}^{-1}$	$G / \text{molecule } (100 \text{ eV})^{-1}$	Ref.
1,3,5-Triphenyl-formazan	1.4	3.5	18, 27
3-(<i>p</i> -Nitrophenyl)-1,5-diphenylformazan	5.8	3.1	20
2,5-Diphenyl-3-(1-naphthyl)formazan	0.27	1.3	20
	0.77	2.4	20

A similar species is formed as an intermediate during the chemical reduction of these compounds (see, for example, Refs 3 and 17).

The structure of the tetrazolium radical has been confirmed by the results of EPR studies of irradiated frozen solutions of TPTC and 2,3,5-triphenyltetrazolium tetrafluoroborate.^{30,31} It was found that irradiation of these solutions at 77 K affords solvated electrons and alcohol radicals. During the subsequent fast warming up to room temperature, these species react with the tetrazolium salt yielding tetrazolium radicals. The EPR spectra of the radicals recorded after cooling the samples to 77 K are identical for these two salts and consist of eight lines with a splitting of $\sim 1.4 \text{ mT}$.

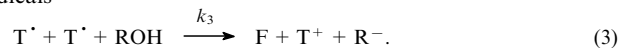
A similar EPR spectrum has been recorded at 77 K for the $T^{\bullet}$ radical resulting from reduction of TPTC with sodium ethoxide in isopropanol. The spectrum recorded at 300 K is somewhat different. Due to the anisotropy of the hyperfine coupling tensor, the spectrum of $T^{\bullet}$ in the liquid phase is characterised by smaller splitting ($\sim 0.7 \text{ mT}$).³¹

The data obtained in studies on pulse radiolysis of solutions of tetrazolium salts^{19,28,29} indicate that tetrazolium radicals arise in two processes, one of which is fast and the other is slow. For example, in the case of a triphenyltetrazolium salt (the TPT^+ cation) in isopropanol, this might occur as follows:



Table 3 contains the rate constants for reactions of this type for tetrazolium salts measured by the method of pulse radiolysis. Calculations using the Debye equation have shown that in the case of NPTC and NPTB, the rate of reaction (1) is controlled by diffusion, whereas for TPTC, the rate is lower than the diffusion limit.

The formazans are formed upon disproportionation of $T^{\bullet}$ radicals



Thus, the yield of the formazan (for example, in an isopropanol solution) should be equal to

$$G(F) = \frac{1}{2} \{ G(e_s^-) + G[(CH_3)_2\dot{C}OH] \}. \quad (4)$$

Since $G[(CH_3)_2\dot{C}OH]$ in isopropanol is ~ 5.5 molecule $(100 \text{ eV})^{-1}$,²⁶ the theoretical $G(F)$ value amounts to ~ 3.4 molecule $(100 \text{ eV})^{-1}$. Experimental yields are close to this value only for NPTB and DPTB (see Table 1). For TPTC and NPTC, the yields are substantially smaller. This is due to the fact that the tetrazolium radicals derived from these salts participate not only in reaction (3) but also in another reaction, which does not lead to formazan (for example, they can dimerise to give ditetrazolium salt TT).^{18,19}



According to our estimates,¹⁸ the k_3/k_4 ratio for a solution of TPTC in isopropanol is ~ 1.9 .

Tetrazolium salts dimerise relatively easily at the 4,4'-diphenyl bridge.³⁶ Nitrotetrazolium Blue is an example of this type of dimer. Ditetrazolium compounds have also been described in a review.¹⁷

Solutions of tetrazolium radicals in alcohols are characterised by intense optical absorption in the visible and ultraviolet spectral regions (Table 4). These radicals are relatively long-lived species, their lifetimes being of the order of milliseconds.

The reduction of formazan to hydrazidine (HH) is also a two-electron process.²⁶ It has been found by pulse radiolysis²⁷ that formazan reacts first with a solvated electron and an alcohol radical. The rate constants for these reactions in isopropanol are presented in Table 3. It was postulated²⁷ that the above reactions

Table 3. Rate constants [k / litre mol⁻¹ s⁻¹] for reactions of tetrazolium salts and formazans measured by pulse radiolysis.

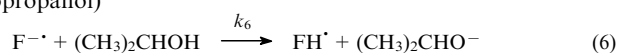
Matrix	Tetrazolium salt	Reaction	k	Ref.	Matrix	Tetrazolium salt	Reaction	k	Ref.
Ethanol	TPTC	$\text{TPT}^+ + \text{e}_s^-$	4.1×10^9	29	water, pH 7	TPTC	$\text{TPT}^+ + \text{O}_2$	3.7×10^7	23
Isopropyl alcohol	TPTC	$\text{TPT}^+ + \text{CH}_3\text{CHOH}$	2.5×10^8	29	7	NPTB	$\text{NPT}^+ + \text{O}_2$	4.5×10^7	23
	TPTC	$\text{TPT}^+ + \text{e}_s^-$	2.1×10^9	28	6.9	TPTC	$\text{TPT}^+ + \text{TPT}^+$	2.0×10^9	32
	TPTC	$\text{TPT}^+ + (\text{CH}_3)_2\text{COH}$	3.1×10^8	28				(see c)	
	NPTC	$\text{NPT}^+ + \text{e}_s^-$	1.5×10^{10}	19	water	TPTC	$\text{TPT}^+ + \text{TPT}^+$	1.0×10^9	35
	NPTC	$\text{NPT}^+ + (\text{CH}_3)_2\text{COH}$	1.9×10^9	19				(see c)	
	NPTB	$\text{NPT}^+ + \text{e}_s^-$	1.4×10^{10}	19	water, pH 6.9	NPTC	$\text{NPT}^+ + \text{NPT}^+$	1.8×10^9	32
	NPTB	$\text{NPT}^+ + (\text{CH}_3)_2\text{COH}$	1.7×10^9	19				(see c)	
	F ^a	$\text{F} + \text{e}_s^-$	3.3×10^{10}	27	2	TPTC	$\text{TPTH}^{++} + \text{TPTH}^{++}$	5.3×10^7	32
	F	$\text{F} + (\text{CH}_3)_2\text{COH}$	1.7×10^8	27				(see d)	
Water, pH 6.9	TPTC	$\text{TPT}^+ + \text{e}_{\text{aq}}^-$	1.1×10^{10}	32	2	NPTC	$\text{NPTH}^{++} + \text{NPTH}^{++}$	2.8×10^7	32
11.3	TPTC	$\text{TPT}^+ + \text{e}_{\text{aq}}^-$	6.7×10^9	32				(see d)	
6.9	NPTC	$\text{NPT}^+ + \text{e}_{\text{aq}}^-$	1.1×10^{10}	32	5.7	NTB	$\text{NTB}^{++} + \text{NTB}^{++}$	3.8×10^8	33
11.3	NPTC	$\text{NPT}^+ + \text{e}_{\text{aq}}^-$	9.2×10^9	32	10	NTB	$\text{NTB}^{++} + \text{OH}^-$	3.7×10^9	33
2	TPTC	$\text{TPT}^+ + \text{H}^+$	$\sim 1.4 \times 10^{10}$	32			$+ \text{NTB}^{++} + \text{OH}^-$		
2	NPTC	$\text{NPT}^+ + \text{H}^+$	5.7×10^9	32	water	NTB	$\text{NTB}^{++} +$	4.9×10^9	33
6.9	TPTC	$\text{TPT}^+ + \text{OH}^\bullet$	7.1×10^9	32			$+ \text{NTB}^{++} + \text{OH}^-$		
6.9	NPTC	$\text{NPT}^+ + \text{OH}^\bullet$	1.0×10^{10}	32	6.9	TPTC	$\text{TPTOH}^{++} \rightarrow$	1.2×10^4	32
7.07–11.1	NTB	$\text{NTB}^{2+} + \text{O}_2^-$	5.9×10^4	33			$\rightarrow \text{products}$	(see f)	
			(see b)	33	6.9	NPTC	$\text{NPTOH}^{++} \rightarrow$	2.3×10^3	32
10	TPTC	$\text{TPT}^+ + \text{COO}^{\bullet-}$	1.1×10^9	21, 34			$\rightarrow \text{products}$	(see f)	
10	NPTC	$\text{NPT}^+ + \text{COO}^{\bullet-}$	5.0×10^9	21				(see c)	
10	NPTC	$\text{NPT}^+ + \text{COO}^{\bullet-}$	1.9×10^9	21					
10	NTB	$\text{NTB}^{2+} + \text{COO}^{\bullet-}$	6.4×10^9	33					

^a F — 1,3,5-triphenylformazan. ^b The constant was determined by the stopped flow method. ^c The $2k$ value is given. ^d TPTH^{++} and NPTH^{++} are the H-adducts of the corresponding tetrazolium cations. ^e TPTOH^{++} and NPTOH^{++} are the OH-adducts of the corresponding tetrazolium cations. ^f Expressed in s⁻¹.

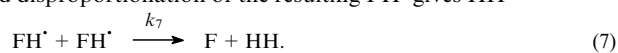
Table 4. Optical characteristics of the intermediate products of radiolysis of solutions of tetrazolium salts.

Matrix	Tetrazolium salt	Product	λ_{max} / nm	$10^{-2} \epsilon$ / m ² mol ⁻¹	Ref.
Ethanol	TPTC	TPT^+	< 375, 400 (shoulder)	—	29
Isopropyl alcohol	TPTC	TPT^+	365, 400 (shoulder)	10.7, 4.0	19, 28
	NPTC	NPT^+	405, 620	9.9, 2.5	19
	NPTB	NPT^+	370, 390 (shoulder)	6.3, 2.5	19
Water, pH 6.9, 11	TPTC	TPT^+	370	7.1	32
Water	TPTC	TPT^+	360	—	35
Water, pH 6.9, 11	NPTC	NPT^+	415	7.6	32
5.7–11	NTB	NTB^{++}	405	15	33
2, 6.9	TPTC	TPTH^{++}	380	4.6	32
2, 6.9	NPTC	NPTH^{++}	390	—	32
6.9	TPTC	TPTOH^{++}	365	4.0	32
Water	TPTC	TPTOH^{++}	345	—	35
Water, pH 6.9	NPTC	NPTOH^{++}	380	—	32

yield formazan radical anions $\text{F}^{\bullet-}$, which are responsible for an intense optical absorption band with a maximum at 700 nm (the molar extinction coefficient is 3.8×10^3 m² mol⁻¹). The lifetime of these species is relatively long (more than 1–2 ms). By analogy with the behaviour of other radical cations in alcoholic solutions (see, for example, Ref. 37), it was suggested that $\text{F}^{\bullet-}$ are protonated in the following way (the reaction is written for isopropanol)



and disproportionation of the resulting $\text{FH}^\bullet$ gives HH



It should be noted that similar reactions occur during two-electron reduction of quinones to hydroquinones.³⁸

Obviously, the yield of formazan reduction in isopropanol should be determined by the equation

$$G(-\text{F}) = \frac{1}{2} \{G(\bar{\text{e}}_s) + G[(\text{CH}_3)_2\dot{\text{C}}\text{OH}]\}. \quad (8)$$

The calculated value of $G(-\text{F})$ is ~ 3.4 molecule (100 eV)⁻¹, which coincides with experimental results for 1,3,5-triphenylformazan²⁷ and 3-(*p*-nitrophenyl)-1,5-diphenylformazan²⁰ (see Table 2). However, in the case of 3-(1-naphthyl)-2,5-diphenylformazan,²⁰ the experimental yield is much lower than the theoretical yield. This is apparently due to the fact that the rate constant for

the reaction of this formazan with the alcohol radical is relatively low.

It has been found¹⁸ that the yield of formazan in the radiolysis of alcoholic solutions of tetrazolium salts decreases when the radiation doses are high. This effect is least pronounced for solutions of DPTB in isopropanol.²⁰ Evidently, the yield decreases due to reactions of F with e_s^- and $(CH_3)_2C^*OH$. 2-Isobutylantraquinone added to an isopropanol solution of TPTC largely 'protects' the formazan from decomposition.¹⁸ The dependences of the concentration of the formazan formed in isopropanol solutions of TPTC on the radiation dose in the presence and in the absence of 2-isobutylantraquinone are shown in Fig. 1.

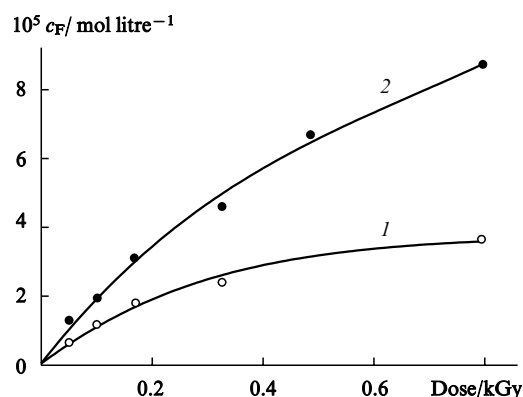
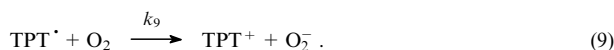


Figure 1. Concentration of the formazan formed *versus* the dose in a deaerated 3×10^{-3} M solution of TPTC in the absence (1) and in the presence (2) of 5×10^{-3} mol litre $^{-1}$ of 2-isobutylantraquinone.

3. Radiolysis of aerated solutions

The yield of formazans in aerated alcoholic solutions is appreciably lower than in deaerated solutions; in some cases, formazans are not formed at all. For example, they are not formed upon irradiation of air-saturated 1×10^{-3} M solutions of DPTB with a dose of 200–300 Gy.²⁰ According to another study,³⁹ the $G(F)$ values for aerated 5×10^{-3} and 4.5×10^{-2} M ethanolic solutions of TPTC are 0.048 and 0.135 molecule $(100 \text{ eV})^{-1}$, respectively (at a dose of ~ 10 kGy). It was found²² that in the case of X-ray radiolysis of an aerated solution of TPTC in ethylene glycol (maximum energy 60 keV), $G(F)$ increases with an increase in the concentration and reaches 1.03 molecule $(100 \text{ eV})^{-1}$ in a 0.1 M solution at a dose of 9.2 kGy.

This type of behaviour can be explained as follows. Since the concentration of TPTC is high, a large portion of tetrazolium radicals, generated, for example, according to reaction (1), are converted again into TPT^+ .



A similar effect is also observed in the case of aqueous solutions of tetrazolium salts (see below). Yet another possible reason (although it is less significant) is that the alcohol radical might react with oxygen to give the peroxy radical $RCH(OH)O_2^*$, and the latter reacts with TPTC slowly or not at all.

In an ethylene glycol solution, $G(F)$ is close to $0.5 G(e_s^-)$. Apparently, due to the high viscosity of this alcohol, reaction (9) in this system is relatively slow, and the TPT^* radicals generated mostly disproportionate. The alcoholic radicals do not reduce TPTC, but instead, they react with oxygen to give the peroxy radicals.

III. Aqueous and water–alcohol solutions

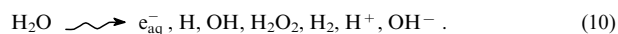
Radiolysis of aqueous and water–alcohol solutions of tetrazolium salts has been studied in several publications.^{20–24, 32, 35} It was found that as in the case of alcoholic solutions, reduction to formazans is the prevailing process.

1. Characteristic features of radiolytic reduction in deaerated aqueous solutions

Irradiation of a deaerated aqueous solution of any of the tetrazolium salts studied results in the formation of a precipitate. The solution obtained by filtering this precipitate off and dissolving it in an alcohol, or by adding a sufficient amount of an appropriate organic solvent to the irradiated solution, or by extracting the product with a solvent exhibits an optical absorption spectrum typical of formazan. Upon irradiation of solutions in aqueous alcohols, when the alcohol concentration is high enough (for example, in a 1:1 water–isopropanol mixture²⁴), the precipitate does not appear, but solution acquires an intense red colour caused by the formation of formazan. It should be noted that in aqueous solutions, the concentration of formazan arising upon radiolysis depends on the γ -radiation dose only at high doses, because the product precipitates. In aqueous alcohols, this dependence is sharper.

The measured $G(F)$ values for radiolysis of deaerated solutions of some tetrazolium salts are listed in Table 1. It can be seen that without additives $G(F)$ increases from 0.4 to 1.4 molecule $(100 \text{ eV})^{-1}$ with an increase in the pH of the solution from 5.3 to 11.5. However, in the case of NPTB, this dependence is not observed. Upon the addition of some organic compounds (formates, EDTA, isopropanol) or in water–isopropanol mixtures, the formazan yield increases to 3.5 molecule $(100 \text{ eV})^{-1}$.

The radiolysis of water is described by the following general scheme:²⁶



Obviously, the first four products can participate in the radiolytic transformations of tetrazolium cations. Hydrated electrons e_{aq}^- reduce the T^+ cations to tetrazolium radicals T^* ; the latter disproportionate to give formazan. Hydrogen atoms do not participate in the reduction,³² but they add to benzene rings giving rise to H-adducts. The OH radical reacts with T^+ to give an OH-adduct. Hydrogen peroxide can oxidise T^* .



Subsequent transformations of the H- and OH-adducts give no formazans. Therefore, we can write

$$G(F) = \frac{1}{2} [G(e_{aq}^-) - G(H_2O_2)] \quad (12)$$

Calculation using this equation affords $G(F) = 1.1$ molecule $(100 \text{ eV})^{-1}$. The experimental $G(F)$ values obtained for alkaline media (except for those for DPTB) are close to this predicted value. In the case of NPTB, the yields measured both in alkaline and neutral media coincide with those calculated from Eqn (12).

The experimental $G(F)$ values found for acidic, neutral, and weakly alkaline solutions of TPTC and NPTC are smaller than the theoretical values. As an example, Fig. 2 shows the dependence of $G(F)$ on the pH for a deaerated 1×10^{-3} M solution of TPTC.³⁴ At $pH < 4$, the formazan yield is close to zero, which is due to the fast reaction



The H atoms react with T^+ giving H-adducts.

Apparently, the T^* radicals derived from TPTC and NPTC not only disproportionate giving rise to formazan but also participate in some other processes, which do not lead to this

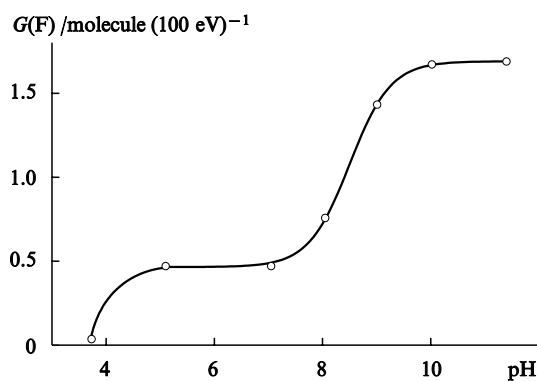
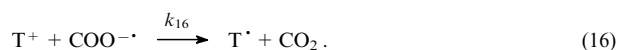
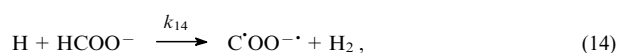


Figure 2. Dependence of $G(F)$ in a deaerated 1×10^{-3} M aqueous solution of TPTC on the pH.

compound (for example, they can dimerise).^{32, 34} The tetrazolium radicals generated from NPTB do not tend to dimerise (apparently, due to steric hindrance). In alkaline media dimerisation does not occur either, probably due to the fact that the product formed upon the reaction of $T^{\bullet}$ with OH^- only disproportionates.³² It was found by pulse radiolysis³² that in TPTC solutions at $pH > 9$, when $G(F)$ increases (see Fig. 2), a new short-lived species appears in place of the $T^{\bullet}$ radicals consumed.

2. Radiolysis in the presence of organic compounds

Radiolysis of deaerated alkaline aqueous solutions containing organic compounds (formate, EDTA, alcohols) or solutions in water–alcohol mixtures results in $G(F)$ values reaching 3.5 molecule $(100 \text{ eV})^{-1}$ (see Table 1). Evidently,²¹ when the concentration of an organic compound is relatively high, it reacts with hydrogen atoms and $OH^{\bullet}$ radicals (and $O^{\bullet -}$) to give reducing radicals able to reduce an additional amount of T^{+} to $T^{\bullet}$. The corresponding reactions for $HCOO^-$ taken as an example can be written as follows:



The occurrence of reaction (16) is confirmed by high k_{16} values determined by pulse radiolysis (see Table 3). However, these reactions are not controlled by diffusion; therefore, the k_{16} values correlate with the potentials of the first reduction wave for the corresponding tetrazolium salts measured by polarography.²¹

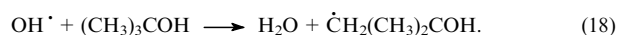
Hydrogen peroxide reacts with $T^{\bullet}$ [reaction (11)], and the $OH^{\bullet}$ radical formed in this process participates in reaction (16). This yields radical anions $COO^{\bullet -}$, which then reduce T^+ . Thus, the yield of formazan can be calculated as follows:

$$G(F) = \frac{1}{2} [G(e_{aq}^-) + G(H) + G(OH)]. \quad (17)$$

The calculation by this expression using the yields of the water radiolysis products reported in our monograph²⁶ affords $G(F) = 3.2$ molecule $(100 \text{ eV})^{-1}$. The corresponding experimental results are close to this value (see Table 1).

3. Mechanism of radiolytic reduction. Intermediate products

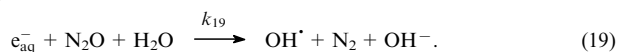
The properties of tetrazolium radicals $T^{\bullet}$ and the H- and OH-adducts formed by tetrazolium salts in aqueous solutions have been studied by pulse radiolysis.^{21, 23, 32, 35} The optical characteristics of $T^{\bullet}$ (see Table 4) were measured in deaerated neutral or alkaline aqueous solutions of TPTC and NPTC containing *tert*-butyl alcohol.³² In these solutions, $OH^{\bullet}$ radicals react with the alcohol



The *tert*-butanol radical formed is inert towards tetrazolium salts. *tert*-Butyl alcohol can also react with hydrogen; however, the rate constant for this reaction is relatively low (1.2×10^5 litre $\text{mol}^{-1} \text{ s}^{-1}$).⁴⁰ Under the conditions employed in the study cited,³² small amounts of the H-adduct could be formed. The reaction of T^+ with e_{aq}^- in these solutions gives mainly $T^{\bullet}$ radicals. The optical characteristics of the $T^{\bullet}$ radicals were obtained after applying a correction for the absorption of the H-adduct.

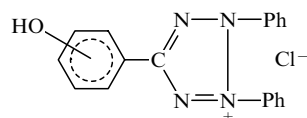
The optical characteristics of the H-adducts $TH^{+\bullet}$ (see Table 4) were determined using deaerated acidic ($pH \ 2$) solutions of TPTC and NPTC containing *tert*-butyl alcohol.³² In these solutions, hydrated electrons react with H^+ [reaction (13)] being thus converted into hydrogen atoms, and the $OH^{\bullet}$ radicals react with the alcohol [reaction (18)] to give $\dot{C}H_2(CH_3)_2COH$ radicals, which are inert with respect to tetrazolium salts. The subsequent transformations afford only the H-adducts in which hydrogen is attached to the benzene ring of the molecule. This conclusion is based on the following observation.³² Tetrazolium salt molecules contain two types of sites, which could be reactive towards H atoms, namely, the tetrazole heterocycle and the benzene rings. If hydrogen were attached to the tetrazolium ring, the tetrazolium salt would be simultaneously reduced; however, this is not observed experimentally. Formazans are not formed in relatively acidic media (see Fig. 2).

The spectra of the OH-adducts of tetrazolium salts were recorded for deaerated neutral aqueous solutions of TPTC and NPTC saturated with nitrogen hemioxide.^{32, 35} In these solutions, e_{aq}^- reacts with N_2O and water giving rise to $OH^{\bullet}$ radicals.



When this solution is exposed to radiation, OH-adducts and, to a much lesser extent, H-adducts are formed. The optical characteristics of the OH-adducts listed in Table 4 were determined after applying a correction for the absorption of the H-adducts. The rate constants for the reactions of $OH^{\bullet}$ radicals with tetrazolium salts are close in the order of magnitude to the rate constants for the reactions of $OH^{\bullet}$ with benzene derivatives;⁴⁰ this confirms the assumption that the $OH^{\bullet}$ groups are attached to a benzene ring in the tetrazolium salt molecule.

The structure of the OH-adduct formed by TPTC has been determined by quantum-chemical calculations.⁴¹ It was found that the $OH^{\bullet}$ radical in the TPTC molecule is bound most likely to the benzene ring that is attached to the carbon atom of the tetrazolium ring. This structure is described by the formula



No formazan is formed in solutions saturated with nitrogen hemioxide;³² this means that the H- and OH-adducts are not formazan precursors. Stable products formed in these solutions are soluble in water and absorb light in the ultraviolet region of the spectrum (the maxima of the absorption bands are at 300 and ~ 320 nm for solutions of TPTC and NPTC, respectively).³²

The tetrazolium radicals and the H-adducts are consumed in second-order reactions (see Table 3). It has been noted above that both in aqueous and in alcoholic solutions, the $T^{\bullet}$ radicals derived from TPTC and NPTC disappear not only through disproportionation but also through dimerisation.

The ratios of the rate constants for disproportionation and dimerisation in neutral aqueous solutions of TPTC or NPTC are equal to 0.5 and 1, respectively (*i.e.* they are much smaller than the corresponding ratio for isopropanol solutions of TPTC; as noted above, the latter is ~ 1.9).²¹ The ratio of these rate constants depends on the pH; it is greater in alkaline solutions than in

neutral ones. This dependence might be due to a change in the structure of the tetrazolium radicals in alkaline media, which decreases the probability of dimerisation because of steric hindrance. When the pH values are sufficiently high, dimerisation does not occur at all.

The OH-adducts disappear in first-order reactions³² (see Table 3). This might be an intramolecular rearrangement of the OH-adducts or their decomposition with abstraction of a water molecule. Similar processes have been observed for the OH-adducts formed by phenol, aniline and toluene.²⁶

4. Radiolysis of aerated solutions

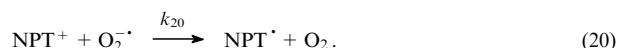
The $G(F)$ values for solutions of TPTC and NPTB saturated with air are substantially smaller than those for deaerated solutions (Table 5). A low yield of formazan [~ 0.16 molecule $(100 \text{ eV})^{-1}$] has also been found⁴² for X-ray radiolysis of an aerated 2% aqueous gel of agar-agar containing $0.09 \text{ mol litre}^{-1}$ of TPTC (the maximum energy of radiation was 60 keV).

Table 5. Formazan yields [$G(F)$ / molecule $(100 \text{ eV})^{-1}$] upon γ -radiolysis of deaerated and aerated aqueous and water–isopropyl alcohol (1 : 1 by volume) solutions of tetrazolium salts at various pH.^{23,24}

Tetra-zolium salts	Concentration/ mol litre^{-1}	Presence of alcohol	Gas saturating the solution	pH	$G(F)$
TPTC	8×10^{-4}	yes	argon	11.0	3.1
	8×10^{-4}	"	air	11.0	0.14
	1×10^{-3}	no	argon	6.9	0.45
	1×10^{-3}	"	air	10.3	1.2
	1×10^{-1} (see ^a)	"	"	7.0–7.5	0.22
NPTC	1×10^{-3}	"	argon	6.9	0.6
	1×10^{-3}	"	air	6.9	0.45
	1×10^{-3}	"	argon	11.3	1.3
	1×10^{-3}	"	air	11.3	1.5
	4×10^{-3}	yes	"	10.5	4.9
	1×10^{-2}	"	"	10.5	5.3
	5×10^{-4}	no	"	6.9	0.3
NPTB	5×10^{-4}	"	argon	6.9	1.2

^a Radiolysis under the action of X-rays (the maximum energy 60 keV). The solution contained the triethanolamine–HCl buffer.²²

However, in the case of aqueous solutions of NPTC, this difference in $G(F)$ is not manifested (see Table 5). This is due to the fact that the tetrazolium radical $\text{TPT}^{\bullet}$ generated from TPTC, as in alcoholic solutions, is able to react with oxygen to give the initial TPT^+ ion [see reaction (9)], whereas NPTC, on the contrary, can be reduced by the $\text{O}_2^{\bullet-}$ radical ions²⁴



Therefore, in aqueous and alcoholic solutions of NPTC, when the concentration of the tetrazolium salt is relatively high, atmospheric oxygen hardly influences the yield of formazan. In the case of solutions in aqueous alcohols, for the $\text{R}\dot{\text{C}}\text{HOH}$ radicals to be involved in the interaction with NPTC, the concentration of this salt needs to be high enough. Otherwise some of the alcohol radicals would react with oxygen to give peroxy radicals $\text{RCH(OH)O}_2^{\bullet}$, which are apparently unable to reduce NPTC.²⁴

The conclusions about the reasons for the low yields of formazan in aerated solutions of TPTC and NPTB have been confirmed by the results of a study carried out by the pulse radiolysis method.²³ It was found that the tetrazolium radicals $\text{T}^{\bullet}$ formed in these solutions in the presence of *tert*-butyl alcohol disappear much faster than in deaerated solutions. The constants

k_9 were determined by measuring the kinetics of consumption of $\text{T}^{\bullet}$ in the presence of oxygen (see Table 3).

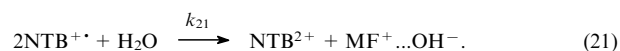
The direction of electron transfer in reactions the rates of which are not controlled by diffusion may be determined, for instance, by the electron affinity of the reactants. Evidently, the electron affinity of the oxygen molecule should be higher than that of the TPTC and NPTB molecules but lower than that of the NPTC molecule.²³ This is confirmed by the results of determination of the half-wave potentials for the polarographic reduction of tetrazolium salts.²¹ The potentials for the single-electron reduction of tetrazolium salts and two-electron reduction of oxygen are -0.40 , -0.30 , -0.17 , and -0.30 V for TPTC, NPTB, NPTC, and O_2 , respectively.^{21,23}

The $G(F)$ values attained at high concentrations of NPTC are larger than the theoretical value (see Table 5) calculated from Eqn (17) using the known yields of the products of water radiolysis. It cannot be ruled out that in this system, due to the relatively high concentrations of conjugated acceptors (the alcohol, on the one hand, and TPTC and oxygen, on the other hand), the reactions in spurs are largely suppressed, and this results in increased yields of the primary radiolysis products, responsible for the formation of formazan.

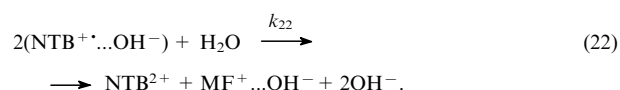
5. Radiolytic reduction of Nitrotetrazolium Blue

Interesting results have been obtained in a pulse radiolysis study of the mechanism of reduction of Nitrotetrazolium Blue in aqueous solutions.^{10,33} The reduction of the two-charged cation, NTB^{2+} , contained in this molecule to give the corresponding diformazan is a four-electron process, which gives consecutively the monotetrazolium radical $\text{NTB}^{\bullet+}$, monoformazan MF^+ , monoformazan radical $\text{MF}^{\bullet}$ and finally diformazan DF.

Conditions were selected³³ under which exposure of a formate-containing aqueous solution of NTB^{2+} to an electron pulse affords $\text{NTB}^{\bullet+}$. The rate constant for the reduction of NTB^{2+} with the $\text{COO}^{\bullet-}$ radical anion was measured (see Table 3). Study of the kinetics of consumption of $\text{NTB}^{\bullet+}$ showed that the rate constant for this process depends crucially on the pH. The following reaction was postulated for a neutral medium:

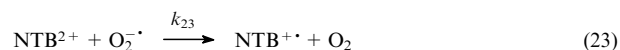


The reaction in an alkaline medium yields the hydroxy-derivative $\text{NTB}^{\bullet+} \dots \text{OH}^-$, which disappears more rapidly than $\text{NTB}^{\bullet+}$. The corresponding reaction can be written as follows:



The k_{21} and k_{22} values found for these reactions are listed in Table 3. The higher rate of reaction (22) is apparently due to the fact that the positive charge of $\text{NTB}^{\bullet+}$ is shielded by the hydroxyl ion. Dimerisation of $\text{NTB}^{\bullet+}$ does not occur, probably for steric reasons.

The kinetics of the reaction



were studied by the stopped flow method.³³

The constant k_{23} found in this study is presented in Table 3. It was noted that the back reaction does not occur under the conditions employed. It was concluded that Nitrotetrazolium Blue can be used for qualitative but not quantitative determination of the $\text{O}_2^{\bullet-}$ radical anions. It should also be emphasised that H_2O does not react with NTB^{2+} .

IV. Solid matrices

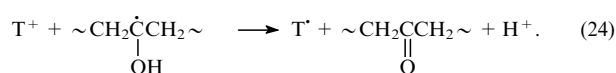
Polymeric films with tetrazolium salts (mainly TPTC) introduced into them have been mostly studied as applied to the dosimetry of ionising radiation (see above). Radiolytic transformations of

TPTC and NPTC in poly(vinyl alcohol) films have been studied in detail.²⁵

The paramagnetic species formed in poly(vinyl alcohol) films irradiated under various conditions have been investigated.^{25, 43, 49} The yield of these species is ~ 4 molecule $(100 \text{ eV})^{-1}$. The EPR spectrum of an irradiated film recorded at 77 K points to the presence of three paramagnetic species: a captured electron and the $\sim \text{CH}_2\text{CH}[\text{OC}^+(\text{CH}_3)\text{O}^-\text{H}^+]\text{CH}_2\sim$ and $\sim \text{CH}_2\text{C}^+(\text{OH})\text{CH}_2\sim$ radicals. At room temperature, only the former radical is detected.

All the paramagnetic species mentioned above possess reducing properties. At relatively high temperatures, the species become mobile, and their interaction with TPTC and NPTC resulting in the formation of formazans becomes possible. This conclusion is confirmed experimentally. Table 1 presents the $G(\text{F})$ values obtained at room temperature for films containing various amounts of these salts.²⁵ It is noteworthy that the formazan concentration obeys a linear dependence on the radiation dose up to a dose of 25 kGy.

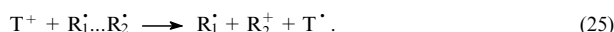
Evidently, the formation of formazan in films is also a two-electron process, T^+ ions being reduced in reactions with mobile electrons and with the radicals mentioned above. For example, the following reaction is possible²⁵



Thus, $G(\text{F})$ should be $0.5 G(\text{radical})$,[†] i.e. it should be equal to ~ 2 molecule $(100 \text{ eV})^{-1}$. However, only in a film containing $7.1 \times 10^{-3} \text{ mol litre}^{-1}$ of TPTC, $G(\text{F}) < 0.5 G(\text{radical})$; in all other cases, $G(\text{F})$ is greater than $0.5 G(\text{radical})$ (see Table 1), and for large concentrations of NPTC it is more than twice as great. It can be concluded that $G(\text{F})$ is determined both by the distance between tetrazolium salt molecules and by the electron-acceptor properties of these molecules.²⁵

A similar situation has been observed for poly(vinyl alcohol) films containing methylviologen MV^{2+} .^{47, 48} When these films are exposed to radiation, the colourless MV^{2+} dication is reduced via a single-electron process to give $\text{MV}^{+\cdot}$, which has an intense blue colour. According to several measurements,^{44, 45} the $G(\text{MV}^{+\cdot})$ values vary from 8.1 to 9.8 molecule $(100 \text{ eV})^{-1}$. This is much larger than the $G(\text{radical})$ value.

It was postulated²⁵ that the high $G(\text{F})$ values observed are due to the reactions of T^+ with radical pairs $\text{R}_1\cdots\text{R}_2$, which are formed in some polymers including poly(vinyl alcohol) films (see, for example, Ref. 50)



In the absence of tetrazolium salts, the radical pair undergoes recombination. The EPR spectrum of a poly(vinyl alcohol) film contains an unresolved signal with a g -factor of 4 corresponding to this radical pair;²⁵ the intensity of this signal is four orders of magnitude lower than that of the signal characterised by a g -factor of 2. Another possible reason is the transfer of the excitation energy along the chain of polymer bonds to a tetrazolium salt molecule.

Thus, in a solid matrix of a polymeric alcohol, tetrazolium salts are also reduced to formazans by electrons and 'alcohol' radicals.

V. The use of tetrazolium salts in dosimetry

The property of colourless or yellowish liquid or solid solutions of tetrazolium salts to turn pink, orange, or orange-red upon radiolytic reduction to formazans has been recommended for use in the dosimetry of ionising radiations.

1. Alcoholic, aqueous and water-alcohol solutions

Back in the late 1940s,¹² it was found that aqueous solutions and gelatine emulsions of TPTC change to a red colour on exposure to

UV light ($\lambda < 365 \text{ nm}$), α -particles, or X-rays. It was also found that the colour intensity did not depend on the pH in the range 5.5–6.6

In a number of publications (see, for example, Refs 22, 42, 51–53), it has been suggested to use TPTC in radiology and radiobiology in order to obtain three-dimensional images of dose distribution upon X-ray treatment. For example, a 2% aqueous gel of agar-agar containing TPTC (0.05%) has been used⁵² to model the three-dimensional dose distribution in fish and meat foodstuffs treated with X-rays (maximum energy 60 keV, dose $\sim 15 \text{ kGy}$). It has been reported⁴² that gels of this type are suitable for measurement of three-dimensional dose distribution for X-ray and electron radiations. It was also shown that the concentration of the formazan produced depends linearly on the radiation dose up to a dose of 12 MGy.

The influence of various parameters (the nature of the buffer solution, TPTC concentration, the presence of oxygen in the solution, and the dose rate) on the yield of formazan has been studied in detail.²² The precipitate of formazan formed upon irradiation with X-rays with a maximum energy of 60 keV was dissolved in an organic solvent (for example, in tetrahydrofuran) added to the solution. It was found that in aerated solutions, $G(\text{F})$ does not depend on the pH of the solution over the range 5–8. At higher pH values the yield increases, while at lower pH it decreases, and becomes equal to zero at pH 1.5. If the concentration of TPTC increases, the yield first increases and then remains constant in the concentration range from 3×10^{-3} to $1 \times 10^{-1} \text{ mol litre}^{-1}$. The $G(\text{F})$ values in deaerated solutions are approximately twice as large as those in aerated solutions. In systems saturated with oxygen, the $G(\text{F})$ values are 2.7 times lower than in aerated solutions. The addition of hydrogen peroxide decreases $G(\text{F})$. It was proposed to use aerated 2×10^{-2} – $1 \times 10^{-1} \text{ M}$ aqueous solutions of TPTC containing a triethanolamine–HCl buffer for the measurement of absorbed X-ray radiation doses ranging from 0.18 kGy to 0.18 MGy. Note that the dosimetric solution should be stored in the dark.

The possibility of using aerated ethanolic solutions of TPTC for determination of the absorbed doses of γ -radiation has been studied.³⁷ Solutions in ethanol containing 5% of methanol and 5% of isopropanol were used. It was found that a $4.5 \times 10^{-2} \text{ M}$ solution of TPTC can be used to measure radiation doses in the range 1–16 kGy. For lower concentrations of TPTC, the upper limit of the measurable doses decreases (at higher doses, the dependence of the formazan concentration on the dose becomes nonlinear, because the formazan starts to decompose).

Figure 3 presents the dependence of the optical absorption of aerated solutions of TPTC on the dose. It can be seen that the yield of formazan diminishes with a decrease in the TPTC concentration; the yield obtained in a $5 \times 10^{-3} \text{ M}$ solution is ~ 2.3 times

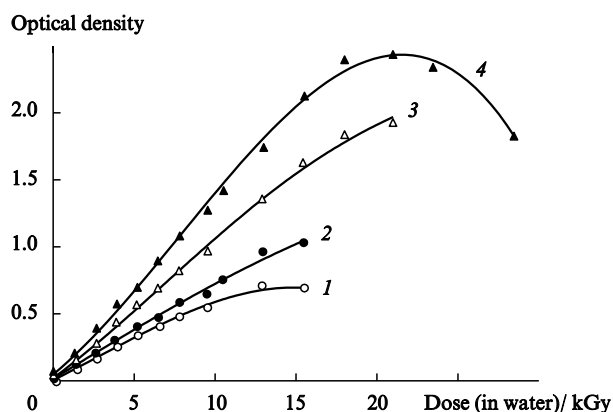


Figure 3. Optical density ($\lambda = 480 \text{ nm}$) of aerated 5×10^{-3} (1), 1×10^{-2} (2), 1.8×10^{-2} (3), and $4.5 \times 10^{-2} \text{ M}$ (4) ethanolic solutions of TPTC versus the radiation dose (optical path length 0.1 cm).

[†] $G(\text{radical})$ implies the yields of both radicals and electrons.

lower than that in a 4.5×10^{-2} M solution. The yields also depend on the temperature. The temperature coefficient in the range 0–30 °C is approximately +0.8% per 1 °C, but in the temperature range between 30 and 60 °C, it is substantially larger. Non-irradiated and radiated solutions are stable during storage in the dark in sealed tubes for at least 5 days. However, exposure to daylight and especially to bright sunlight leads to slow formation of formazan upon photolysis. If the solution is saturated with oxygen, the upper limit of determination of the dose increases to 36 kGy. Deaerated solutions are more 'sensitive' but the upper limit decreases to ~ 3 kGy. The optical characteristics of 1,3,5-triphenylformazan and other formazans are listed in Table 6.

Table 6. Optical characteristics of formazans.

Formazan	Matrix	$\lambda_{\max}/\text{nm}$	$10^{-3} \epsilon_{\max} / \text{m}^2 \text{mol}^{-1}$	Ref.
1,3,5-Triphenylformazan	ethanol ^a	480	1.5	39
	isopropanol	485	1.6	18
	acetone	480	—	42
	water–isopropanol mixture (1 : 1 by volume)	485	1.6	21, 24
	2% aqueous	515,	—	42
	agar-agar gel	565	—	
	poly(vinyl alcohol)	500	0.92	25
	the same	493, 540 (shoulder) ^b	—	35
	"	490	—	55
1-(<i>p</i> -Nitrophenyl)-3,5-diphenylformazan	polyvinylpyrrolidone	550 ^c	—	56
	water–isopropanol mixture (1 : 1 by volume)	475–480	1.9	21, 24
	polyvinylpyrrolidone	500	0.80	25
1,5-Diphenyl-3-(<i>p</i> -nitrophenyl)formazan	water–isopropanol mixture (1 : 1 by volume)	480	1.2	21
Monoformazan from NTB	water, pH 5.7–6.7	530	1.28	33
	water, pH 9.5–11.0	530	2.54	33
Monoformazan from TB	aqueous	560	—	54
	ethanol	—	—	—
	poly(vinyl alcohol)	540	—	54

^a Ethanol contained 5% of methanol and 5% of isopropyl alcohol. ^b The shoulder at 540 nm belongs apparently to ditetrazolium salt. ^c The band at 550 nm might belong to ditetrazolium salt.

The formation of formazan in solutions of TPTC is inhibited by oxygen. Figure 4 shows the concentrations of the formazan formed in aerated 1×10^{-3} M aqueous solutions of TPTC versus the γ -radiation dose for two different pH values.²⁴ It can be seen that at low doses almost no formazan is formed. When the doses are larger than 0.8 kGy and oxygen in the solution is consumed almost entirely, the yield of formazan increases substantially.

A similar type of behaviour has been observed in the case of aerated solutions of Tetrazolium Blue in aqueous alcohols. These properties have been used to develop a threshold chemical dosimeter.⁵⁴ The threshold dose is detected by a sharp increase in the optical absorption of the solution in the maximum of the formazan band. This dose changes upon variation of the concentration of ethanol (the solubility of air in ethanol is approximately an order of magnitude higher than that in water) or tetrazolium

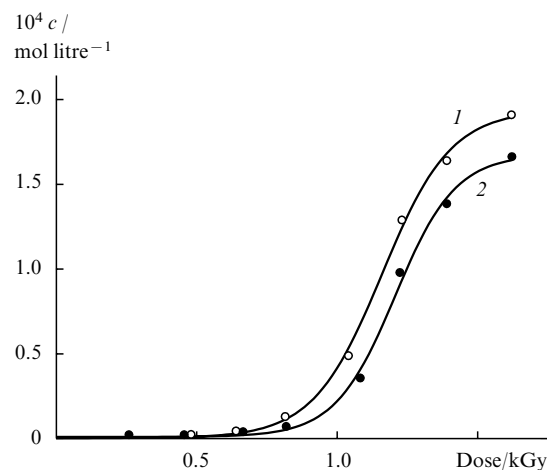


Figure 4. Dependence of the formazan concentration in an aerated 1×10^{-3} M aqueous solution of TPTC at pH 10.3 (1) and 8.5 (2) on the absorbed dose.

salt in the solution. The threshold doses measured by means of aerated solutions of TPTC or TB in aqueous ethanol amount to 1.6–3.4 kGy.

It follows from the foregoing that, due to the 'inhibiting' effect of oxygen, aerated aqueous and alcoholic solutions of TPTC can be used only for determination of relatively large radiation doses. It has been found²⁴ that this effect is not manifested in aqueous solutions of NPTC (see Table 5). An aerated $(0.4–1) \times 10^{-2}$ M solution of NPTC in a water–isopropyl alcohol mixture (1 : 1 by volume) containing $0.2 \text{ mol litre}^{-1}$ of formate (pH 9.5–11) can be used to determine absorbed γ -radiation doses in the range between 5 and 50 Gy (Fig. 5). Formate is needed to eliminate the short 'induction period'. The sensitivity of the spectrophotometric method for formazan analysis based on the use of a system with a 5×10^{-3} M solution of NPTC amounts to $6 \times 10^{-3} \text{ Gy}^{-1} \text{ cm}^{-1}$. When the NPTC concentration is equal to $1 \times 10^{-2} \text{ mol litre}^{-1}$, the sensitivity of the method increases to $1 \times 10^{-2} \text{ Gy}^{-1} \text{ cm}^{-1}$, and the threshold of the dose determination decreases to 1 Gy.

The optical absorption of irradiated solutions changes by not more than 3% over a period of 24 h. The solutions are sensitive to

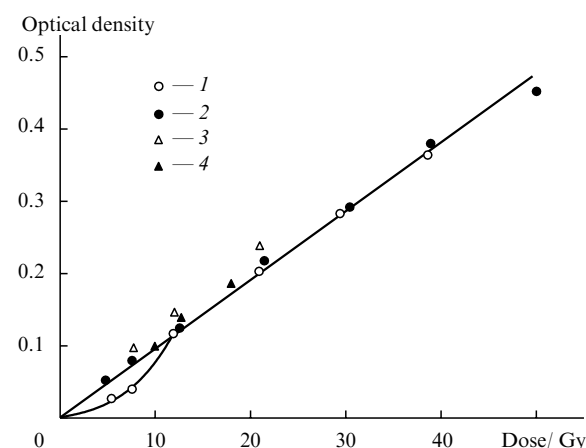


Figure 5. Dependence of the optical density ($\lambda = 475 \text{ nm}$) of aerated water–alcohol (1 : 1 by volume) solutions of NPTC on the γ -radiation dose; (1) a 4×10^{-3} M water–isopropanol solution, pH 10.5; (2) the same solution containing $0.2 \text{ mol litre}^{-1}$ of formate; (3) a 1×10^{-3} M water–isopropanol solution containing $0.2 \text{ mol litre}^{-1}$ of formate, pH 10.5; (4) a 4×10^{-3} M water–ethanol solution containing $0.2 \text{ mol litre}^{-1}$ of formate, pH 9.5 (optical path length 1 cm).

light; therefore, they should be stored in the dark. The results are liable to a positive temperature effect, but if the measurements are carried out at $20 \pm 5^\circ\text{C}$, this effect can be neglected.

Similar results have been obtained with aerated weakly alkaline (pH 8.5–9) solutions of NTB (concentration 1.5×10^{-4} – 4.5×10^{-3} mol litre $^{-1}$) in aqueous alcohols (1 : 1 by volume).⁵⁴ Aqueous solutions of ethanol and isopropanol were used. This method permits determination of doses from 5 to 150 kGy.

2. Polymer films

Dosimetric systems based on tetrazolium salts in polymeric films have been described in the literature. The Kodak Pathe company (France) have developed a dosimetric gelatine film containing TPTC, suitable for measuring doses of about tens of kilogray.⁵⁷ Practical details of the application of these films in the dosimetry of ionising radiation can be found in the literature.^{55, 58, 59}

Other TPTC-containing polymeric films, for example, poly(vinyl acetate),³⁷ polyvinylpyrrolidone,⁵⁶ and poly(vinyl alcohol) films^{25, 35, 54, 60} have also been proposed for dosimetry.

Poly(vinyl alcohol) films have been studied most comprehensively. These films can be used to measure absorbed doses in the range from 0.5 to several tens of kilogray.²⁵ Another publication³⁵ presents a somewhat different range of measurable doses, from 1 to 100 kGy. For NPTC-containing films, the lower limit of determination of absorbed doses is 0.1 kGy.²⁵ In the case of films with TPTC, the readings do not depend on the dose rate, at least in the range from 0.96 to 3.2×10^7 Gy s $^{-1}$.^{35, 64} The optical absorption of irradiated films containing TPTC or NPTC changes by not more than 14% over a period of 27 days.⁵⁴ However, the readings are somewhat dependent on the temperature. The temperature coefficient for the readings for TPTC-containing poly(vinyl alcohol) films is about +0.46% per 1°C . This can be neglected if the measurements are performed at $20 \pm 5^\circ\text{C}$. The main drawback of films containing monotetrazolium salts is that they are sensitive to light. Therefore, they should be stored in the dark. This drawback can be largely eliminated if TB is used as the radiochromic additive.⁵⁴ During storage under ordinary conditions, the optical absorption of these films remains almost invariable over a period of 14 days. Transparent and matt films containing TB have been used for a long period as dose indicators for radiation sterilisation of medical wares.⁶⁰ The use of matt films is due to the need to distinguish more clearly the colours of nonirradiated and irradiated films.

It has been proposed³⁵ that TPTC-containing poly(vinyl acetate) films can serve for determination of doses between 5 and 50 kGy. In addition, they can be used to obtain radiographic images. It has been suggested⁵⁶ that polyvinylpyrrolidone films with TPTC may find application for determination of doses of up to 40 kGy, while NTB can be used as a radiochromic additive to polymeric matrices.

VI. Conclusion

The above discussion leads to the following conclusions.

1. The use of radiation-chemical methods (first of all, pulse radiolysis) made it possible to study the kinetics of reduction of tetrazolium salts to formazans in aqueous and alcoholic solutions and in solid matrices and to elucidate the nature of the intermediate species.

2. The investigation of radiolytic transformations of tetrazolium salts provided more precise data about some aspects of the action of ionising radiation on liquid alcohols and poly(vinyl alcohol) films. In particular, the nature of the free radicals formed in irradiated poly(vinyl alcohol) was determined, and the hypothesis of participation of radical pairs in radiation-induced chemical reactions with admixtures present in the polymer was confirmed.

3. Studies of the radiolytic transformations of tetrazolium salts led to new applications of these compounds in chemistry and biochemistry.

4. The development of dosimetric systems based on tetrazolium salts suitable for the measurement of different ranges of absorbed doses and their three-dimensional distribution in irradiated objects is fairly significant from the practical viewpoint.

The main drawback of these systems (their low resistance to light), which holds up their wide use, can be largely eliminated by using poly(vinyl alcohol) films containing Tetrazolium Blue as a radiochromic additive.

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Peculiarities of the structure and properties of highly cross-linked polymer networks

A A Askadskii

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Abstract. Data on the structure and properties of highly cross-linked polymer networks in which the distance between cross-link points is several repeating units or even less than one unit, up to the networks consisting of nothing but cross-link points containing no linear fragments, are generalised. The dependences of a number of physical properties (the glass transition temperature, the modulus of elasticity, *etc.*) on the degree of cross-linking and the influence of various defects (branchings, dangled chains, *etc.*) on the properties of highly cross-linked networks are analysed. It is shown that the passage from sparse networks to highly cross-linked networks is accompanied by fundamental changes in their properties and that these properties can be described quantitatively taking into account the chemical structure of the network. The influence of the chemical structure of a cross-link point of the network on the properties is analysed; it is shown that the distances between the cross-link points in such networks can be estimated by nontraditional methods. Particular attention is paid to the cross-linked systems that are the basis for gradient-modulus materials in which the modulus of elasticity, the refractive index, and other properties vary over a wide range. The bibliography includes 93 references.

I. Introduction

The aim of this review is to analyse the influence of the structure of highly cross-linked polymer networks on their physical properties. The concept of the network structure includes the chemical structure of cross-link points and linear fragments between them, branchings, isolated loops, and other defects always present in the network. We will solve the above problem on the basis of an approach that is being developed by the author (in collaboration with Yu I Matveev) over many years and that makes it possible to take into account the influence of the energies of intermolecular interaction and chemical bonds on the properties of polymers. According to this approach, the repeating unit of a polymer or the

repeating fragment of a network is represented as a set of anharmonic oscillators interconnected by different types of intermolecular interactions (*e.g.*, dispersion, dipole-dipole, and hydrogen interaction) and chemical interactions. The temperature at which the set of oscillators loses its stability characterises the onset of such processes as glass transition or melting (energy changes on the level of intermolecular interaction), or the onset of intense thermal degradation (energy changes on the level of chemical bonds). Only the chemical structure of polymers needs to be known for calculating their properties. Any change in the topology of the network is related to changes in its chemical structure, which in turn affect its properties.^{1–4}

A purely empirical approach developed by Van Krevelen based on group contributions to a particular property is often used for calculating properties of polymers. Compared to the approach used in this study, it has a number of limitations and certain advantage. The limitations are the following: (1) if a group makes no contribution, then the properties of a polymer containing this group cannot be calculated; (2) the applicability of the approach only to linear polymers; there is no mention of polymer networks even in the third edition of the book by D W Van Krevelen *Properties of Polymers* Third Ed. (Amsterdam: Elsevier, 1990); and (3) group contributions to properties have no physical sense. The simplicity of calculations is an advantage of Van Krevelen's approach.

In this review, we have analysed the results obtained to date of studies of the influence of the above-mentioned structural network peculiarities on the properties of polymers. In the preparation of the review, the author not only compiled the published data, but also carried out numerous additional calculations of the properties of highly cross-linked polymer networks. This was associated with an attempt to answer the most frequently asked questions of specialists concerning the influence of the degree of cross-linking, the topology of the network, the chemical structure of the cross-linking agent (*i.e.*, the chemical structure of cross-link points), 'dangled' chains, branchings, loops, and other structural features on the properties.

Before considering peculiarities of the structure and properties of highly cross-linked polymer networks, it is necessary to define the concepts of a cross-link point, of a highly cross-linked network, and of a sparse network. *A cross-link point of the network is a group of atoms comprising an atom from which the chain branching occurs, neighbouring atoms chemically bonded to this*

A A Askadskii A N Nesmeyanov Institute of Organoelement Compounds of the Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 83. Tel. (7-095) 135 93 98. E-mail: andrey@ineos.ac.ru

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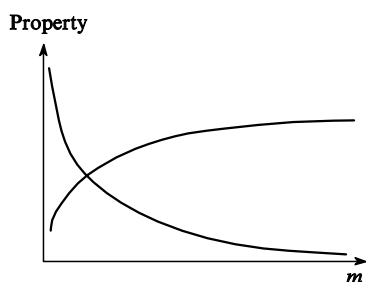


Figure 1. Examples of dependences illustrating sharp changes in properties on the number of repeating units (m) between the neighbouring cross-link points of a network.

atom, and their nearest substituents.^{5, 6} A decrease in the number of repeating units between cross-link points (if it amounts to several tens) affects insignificantly the glass transition temperature, the molar volume, the refractive index, and some other characteristics. However, when the number of the repeating units between cross-link points is very small (several units), its decrease results in abrupt changes in the properties (Fig. 1). This is particularly noticeable when none of 'normal' polymer units remains between the cross-link points. Such systems are the most highly cross-linked polymer networks; cured epoxy resins, phenol-formaldehyde resins, graphite, diamond, and a number of other compounds can serve as examples.

A detailed study of the properties of highly cross-linked polymer networks was carried out for hypothetical tri- and tetrafunctional polyethylene-based networks, networks based on styrene-divinylbenzene copolymers, *etc.*¹ Abrupt changes in the properties of all polymers considered occurred when the number of repeating units in the linear fragments between cross-link points decreased down to 4–5. It is these networks that will be classified as highly cross-linked networks. Principal changes in both the structure and properties of highly cross-linked networks occur if the network virtually consists of nothing but cross-link points.

II. Density and the molar volume

The concept of 'a repeating fragment of a network' is illustrated in Fig. 2 in which tri- and tetrafunctional networks are represented schematically. The functionality of a network is characterised by the number of chains issuing out of one cross-link point. The molecular weight M_f of a repeating fragment of a trifunctional network (Fig. 2a) is calculated using the following formula

$$M_f = M_{c-1} + 1.5M_0m, \quad (1)$$

where M_{c-1} is the molecular weight of the cross-link point, M_0 is the molecular weight of the repeating unit of linear fragments connecting the cross-link points, and m is the average number of the repeating units in the linear fragments between the cross-link points.

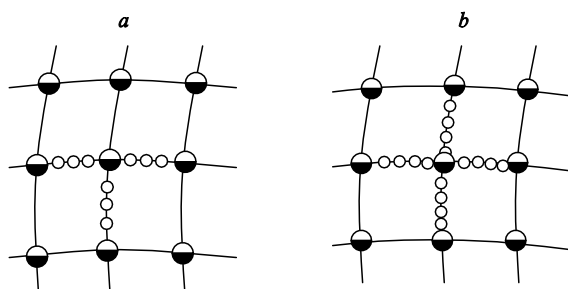


Figure 2. Trifunctional (a) and tetrafunctional (b) networks with the same chemical structure of linear fragments.

The van der Waals volume of the repeating fragment of the network can be found from the relationship

$$\left(\sum_i \Delta V_i\right)_f = \left(\sum_i \Delta V_i\right)_{c-1} + 1.5\left(\sum_i \Delta V_i\right)_0 m, \quad (2)$$

where $\left(\sum_i \Delta V_i\right)_{c-1}$ and $\left(\sum_i \Delta V_i\right)_0$ are the van der Waals volumes of the cross-link point and of the repeating unit of the linear fragments between the cross-link points, respectively.

The formulae for calculating density (ρ_c) and molar volume (V_c) of a polymer network have the form

$$\rho_c = \frac{M_f k}{N_A \left(\sum_i \Delta V_i\right)_f} \quad \text{and} \quad V_c = \frac{N_A \left(\sum_i \Delta V_i\right)_f}{k},$$

where N_A is the Avogadro constant and k is the average value of the molecular packing coefficient.[†]

The van der Waals volumes of carbon, oxygen, sulfur, nitrogen, and other atoms chemically bonded to other atoms have been reported.^{3, 7} Using these data, the van der Waals volumes of repeating fragments of networks of different chemical nature (Table 1) can be calculated easily.

Studies of the bulk properties of polymer networks have shown that the average molecular packing coefficient at room temperature k_{25} is equal to ~ 0.7 , which is somewhat larger than that of linear polymers (0.681).

The relationships (1) and (2) are valid for rather sparse polymer networks in which the number of repeating units in the linear fragments between the cross-link points exceeds 10. The following relationships are valid for highly cross-linked polymer networks

$$M_f = M_{c-1} + 3M_0^* + 1.5(m-2)M_0$$

and

$$\left(\sum_i \Delta V_i\right)_f = \left(\sum_i \Delta V_i\right)_{c-1} + 3\left(\sum_i \Delta V_i\right)_0^* + 1.5(m-2)\left(\sum_i \Delta V_i\right)_0, \quad (3)$$

where M_0^* and $\left(\sum_i \Delta V_i\right)_0^*$ are respectively the molecular weight

and the van der Waals volume of the repeating units of linear chains immediately adjacent to the cross-link point (these units are of different chemical structure as compared to the 'normal' units).

For tetrafunctional sparse networks (see Fig. 2b) we have

$$M_f = M_{c-1} + 2M_0m \quad \text{and}$$

$$\left(\sum_i \Delta V_i\right)_f = \left(\sum_i \Delta V_i\right)_{c-1} + 2\left(\sum_i \Delta V_i\right)_0 m.$$

For highly cross-linked networks we get

$$M_f = M_{c-1} + 4M_0^* + 2(m-2)M_0$$

and

$$\left(\sum_i \Delta V_i\right)_f = \left(\sum_i \Delta V_i\right)_{c-1} + 4\left(\sum_i \Delta V_i\right)_0^* + 2(m-2)\left(\sum_i \Delta V_i\right)_0. \quad (4)$$

[†] It will be recalled that the molecular packing coefficient is the ratio of the van der Waals molar volume of a body to the molar volume of the body.²

Table 1. Parameters of networks of different structure.

Network structure	$\left(\sum_i \Delta V_i\right)_{c-1} / \text{\AA}^3$	$\left(\sum_i \Delta V_i\right)_l / \text{\AA}^3$	$\left(\sum_i \Delta V_i\right)_f / \text{\AA}^3$	$\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_l / \text{\AA}^3 \text{ K}^{-1}$	$\left(\sum_i K_i \Delta V_i\right)_{c-1} / \text{\AA}^3 \text{ K}^{-1}$
1	73.4	17.1 <i>m</i> – 34.2	5.0 + 34.2 <i>m</i>	160.4 <i>m</i> – 320.8	102.9
2	39.2	0	39.2	0	54.3
3	5.0	0	5.0	0	5.7
4	62.3	17.1 <i>m</i> – 34.2	11.0 + 25.6 <i>m</i>	119.9 <i>m</i> – 239.8	87.9
5	34.6	0	34.6	0	46.8
6	11.0	0	11.0	0	14.96
7	48.3	152.3 <i>m</i> + 252.3	300.6 + 152.3 <i>m</i>	519.3 + 490.6 <i>m</i> + 175.6	66.1
8	53.3	109.7 <i>m</i> – 17.1 + 29.4	109.7 <i>m</i> + 64.6	294.0 <i>m</i> – 80.2 + 67.6	72.9
9	36.2	29.4	65.6	67.6	48.6
10	35.2	29.4	65.6	67.6	47.4
11	17.1	92.6	109.7	213.8	24.3
12	0	109.7	109.7	294	0
13	198.0	41.8 + 108.1 <i>n</i>	239.8 + 108.1 <i>n</i>	176.0 + 721.5 <i>n</i>	252.3
15	73.4	17.1 <i>m</i> – 34.2	11.1 + 34.2 <i>m</i>	160.4 <i>m</i> – 336.2	102.9
16	0	96.8	96.8	255.8	0
17	62.7	208.8	146.1	401.0	69.9
18a	92.2	0	92.2	0	136.9
18b	111.1	0	111.1	0	172.8
18c	92.2	18.9 <i>n</i> – 18.9	73.3 + 18.9 <i>n</i>	141.7 <i>n</i> – 283.5	172.8
18d	0	81.5	81.5	400.7	0
19	35.0	339.7 + 72.1 <i>m</i>	714.4 + 144.2 <i>m</i>	2120.6 + 481 <i>m</i>	47.6
20a	47.1	54.0	101.1	71.6	21.5
20b	0	123.05	123.05	505.5 – 263.2	0
20c	0	99.05	99.05	331.9 – 123.6	0
20d	47.15	44.1	91.25	120.7	56.5
20e	0	123.05	123.05	505.4 – 94.8	0

Notes. All the components of the parameters are listed. For the structures of networks **1** – **13** and **15** – **20**, see text. The subscripts c-1, l, and f correspond to the cross-link point of the network, the linear fragment, and the repeating fragment, respectively.

It has been found^{7,8} that for all polymers irrespective of their chemical structure the molecular packing coefficient near absolute zero k_0 is nearly the same and is equal to ~ 0.731 .

At a glass transition temperature T_g , which is specific to each polymer, the molecular packing coefficient is also almost constant and is assessed as $k_g \approx 0.667$. For highly cross-linked polymer networks, $k_g \approx 0.681$ (see Ref. 4).

Since the molar volume of a polymer at the glass transition temperature is

$$V_g = V_0(1 + \alpha T_g),$$

where V_0 is the molar volume at absolute zero, α is the thermal coefficient of volume expansion, and

$$V_g = \frac{N_A \left(\sum_i \Delta V_i \right)}{k_g} \quad \text{and} \quad V_0 = \frac{N_A \left(\sum_i \Delta V_i \right)}{k_0},$$

then

$$\frac{k_0}{k_g} = 1 + \alpha T_g \quad \text{and} \quad \alpha = \frac{k_0/k_g - 1}{T_g}.$$

The coefficient of volume expansion in the rubbery state α_L can be approximately calculated using the φ_f constant from the Simkha–Boyer equation; the experimental constant for cured resins is equal to 0.106, i.e.,

$$\varphi_f = (\alpha_L - \alpha) T_g = 0.106.$$

Hence

$$\alpha_L = \frac{0.106 + \alpha T_g}{T_g}.$$

The molecular packing coefficient at 293 K and the density at the same temperature can be calculated using the following formulae

$$k_{293} = \frac{k_0}{1 + \alpha_{293}} \quad \text{and} \quad \rho_{293} = \frac{k_{293} M_f}{N_A \left(\sum_i \Delta V_i \right)_f} = \frac{1}{V_{u293}},$$

where $k_0 = 0.731$ and V_{u293} is the specific volume of the network at 293 K.

The calculated and experimental dependences of ρ_{293} on M_f for a number of epoxy resins based on bisphenol A and dicarbox-

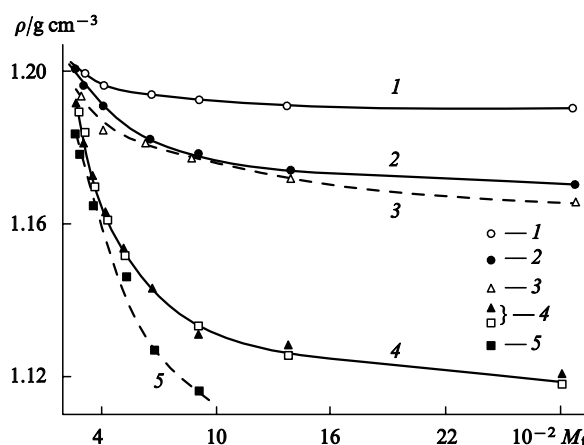


Figure 3. Dependences of the density on the molecular weight of the repeating fragment obtained by the hydrostatic weighing method (1, 4), calculations (2, 4), and according to thermal dilatometric data (3, 5) for cured epoxy resins containing azelaic acid (1–3) and oleic acid (4, 5).

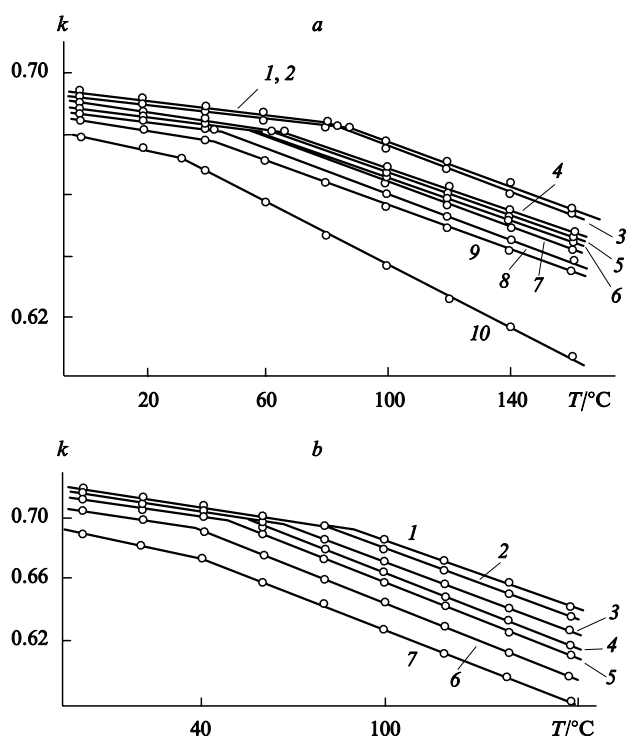


Figure 4. Temperature dependences of the molecular packing coefficient for epoxy resins containing azelaic acid (a) and oleic acid (b) cured with methyltetrahydrophthalic anhydride.

The content of azelaic acid, mole fraction: (1) 0.1; (2) 0.2; (3) 0.3; (4) 0.4; (5) 0.5; (6) 0.6; (7) 0.7; (8) 0.8; (9) 0.9; and (10) 1.0; the content of oleic acid, mole fraction: (1) 0.1; (2) 0.2; (3) 0.3; (4) 0.4; (5) 0.5; (6) 0.6; (7) 0.7; (8) 0.8; and (9) 0.9.

ylic azelaic acid (or monocarboxylic oleic acid) added to the compositions to lengthen the linear fragments or to introduce 'dangled' chains are shown in Fig. 3.

Temperature dependences of the molecular packing coefficient k for these networks are of interest (Fig. 4). These dependences were calculated using the specific volume measured at different temperatures

$$k(T) = \frac{N_A \left(\sum_i \Delta V_i \right)_f}{V_u(T) M_f}.$$

The empty volume ΔV_{ev} , which is the difference between the volume of the body at a given temperature and its van der Waals volume, is calculated as follows:

$$\Delta V_{ev}(T) = V(T) - N_A \left(\sum_i \Delta V_i \right)_f,$$

where $V(T)$ is the molar volume at temperature T .

At the glass transition temperature T_g , we have

$$\Delta V_{ev}(T_g) = V(T_g) - N_A \left(\sum_i \Delta V_i \right)_f,$$

and the fraction of the empty volume is

$$\frac{V_{ev}(T_g)}{V(T_g)} = 1 - k_g,$$

where k_g is the molecular packing coefficient at the glass transition temperature T_g . For highly cross-linked polymer networks, this parameter is constant in the first approximation and is equal to 0.322.

III. Analysis of the structure of highly cross-linked polymer networks

Analysis of the structure of highly cross-linked polymer networks is hampered by the fact that the initial oligomers (*e.g.*, epoxy oligomers) are, as a rule, polydisperse and contain various impurities. In addition, chemical processes occurring in the course of curing are complicated by side reactions. Therefore preference should be given to direct spectroscopic investigation techniques; however, indirect methods also can be useful.

The structure of polymer networks is analysed by both chemical and physical methods. Among purely chemical methods, mention may be made of a method based on a polymer chain fragmentation by unambiguous reactions.⁹ The network structure can be judged from the composition of the products formed. Another method consists in introducing stable nitroxyl radicals into the polymer matrix and estimating their molecular mobility from EPR spectra.¹⁰ IR spectroscopy is also used for analysing the structure of highly cross-linked networks.

The last method was used to study curing of bisphenol A diglycidyl ether with *m*-phenylenediamine.¹¹ The degree of curing with respect to epoxy groups was estimated from the decrease in the absorption band at 914 cm^{-1} . If the epoxy groups are in excess compared to the amino groups, they react mainly with hydroxyl groups at deep stages of curing. The network structure is also established by NMR spectroscopy and elemental analysis. These methods were used, *e.g.*, by Yu and Bell¹² who studied the reaction of bisphenol A diglycidyl ether with diphenyl carbonate in the presence of various catalysts. The epoxy resin reacts with polycarbonate to form polymer networks with a maximum glass transition temperature $T_g \approx 120^\circ \text{C}$. In studies of reactions of epoxy resins with aromatic polyesters,^{13–15} it has been found that the epoxy groups react with the ester groups to form networks possessing increased heat resistance.

NMR spectroscopy is used not only for analysing the chemical structure, but also for assessing the topology of the network structure. Using nuclear magnetic cross-relaxation data, a study was carried out of a number of epoxyamine polymers obtained with different ratios of the epoxy and the amino groups (diepoxide was partially replaced by monoepoxide so that the stoichiometric ratio was retained).¹⁶ The two-component spectrum of the cross-relaxation times and the values and the nature of temperature and concentration changes in the populations of selected groups of protons are due to the topology of the network structure.

Pulse NMR was used to study the relaxation properties of a number of model epoxy polymers based on resorcinol diglycidyl ether with different concentrations of cross-links, degrees of branching, and the nature of the cross-link point. On glass transition, the molecular motion in polymer networks occurs by at least two types of segments, *viz.*, by cross-link points with adjacent chain fragments and by linear fragments.

New results were obtained in pulse NMR studies of epoxy oligomers and networks based on them.^{17–20} This method was used to study the relaxation properties of epoxy oligomers.¹⁷ The kinetic inhomogeneity of these substances is associated either with phase separation or with a broad fractional composition. A comparison of the results obtained by pulse NMR with those of viscosimetric and dielectric studies has shown that the free volume of the system mainly affects the nature of the temperature dependence of relaxation parameters. NMR cross-relaxation, differential microcalorimetry, and IR spectroscopic studies of the process of structure formation of a polymer based on bisphenol A diglycidyl ether and 1,3-bis(aminomethyl)adamantane have shown¹⁸ that native specimens possess an ensemble of slowly relaxing protons with a glass transition temperature 20 K higher than that of a fully cured polymer. The temperature of freeing the mobility of the structural elements of native and fully cured polymers decreases as the temperature of isothermal curing increases. A model of large-scale motion in highly cross-linked polymer networks was pro-

posed,²⁰ which allowed one to rationalise the experimental results obtained in a pulse NMR study of epoxy networks.

Physical methods for the analysis of the structure of highly cross-linked networks are most widely used.^{21–23} They include swelling, mechanical measurements, osmometry, cryoscopy, measurements of ultrasound velocity, dielectric measurements, *etc.* Methods of determining hardness and penetration have been used widely to judge the degree of curing of thermosetting resins; the apparatus for such measurements was described by Ciecierski and Kohman.²⁴ Dynamic mechanical analysis is most widely used.^{25,26} The degree of conversion is judged from changes in the modulus of elasticity and in the loss factor $\tan \delta$.

A method for assessing the linear network fragment M_c based on measuring the depression of the solvent freezing temperature in the swollen network has been described.²⁷ The degree of curing can also be estimated from changes in the refractive index;²⁸ however, this method is only suitable at the initial curing stage. Another method consists in measuring linear expansion of a specimen and comparing this parameter with that of a standard specimen.²⁹ These studies are closely related to investigations of the kinetics of network curing.^{30–37} However, mechanical measurements (the equilibrium rubbery modulus) and sorption methods (the equilibrium degree of swelling or measurements of mechanical properties of swollen networks) remain most widely used methods for assessing the M_c value in polymer networks. Another method for assessing the structure of highly cross-linked polymer networks based on comparison of the calculated and experimental values of the glass transition temperature is also possible. As to the equilibrium rubbery modulus, the classical theory of rubber elasticity is, as a rule, inapplicable to highly cross-linked systems and another approach described in detail below is required in this case.

IV. Calculations of glass transition temperatures of polymer networks

Like many other properties of cross-linked systems, the glass transition temperature depends on the number (m) of repeating units between cross-link points (see Fig. 1). The glass transition temperature of a sparse network depends slightly on m ; however, a sharp increase in the glass transition temperature occurs to reach very high values as the number of repeating units of linear chains between adjacent cross-link points decreases substantially. The results of experiments and calculations show that the onset of sharp increase in the glass transition temperature is observed as the number of units in the linear fragments connecting cross-link points becomes less than 4 or 5. As was mentioned above, it is just the value m that suggests the passage from sparse networks to highly cross-linked networks.

Let us consider two limiting cases.

1. The network is too sparse, and $m \rightarrow \infty$. In this case, the network properties are virtually the same as those of a linear polymer of the same chemical structure. The glass transition temperature can be calculated using the following equation^{7,8}

$$T_g = \frac{\left(\sum_i \Delta V_i\right)_0}{\sum_i a_i \Delta V_i + \sum_j b_j}, \quad (5)$$

where a_i and b_j are parameters characterising the energy of a weak dispersion interaction averaged for each atom and the energy of strong intermolecular interaction (different kinds of the dipole-dipole interaction and hydrogen bonds), respectively.

2. The network is extremely highly cross-linked and consists of nothing but cross-link points. In this case, softening of the network upon heating can occur only because of its thermal degradation due to the cleavage of chemical bonds in the cross-link points. The softening temperature (more rigorously, the

temperature of the onset of intense thermal degradation) of this network can be calculated using the following equation³⁸

$$T_d = \frac{\left(\sum_i \Delta V_i\right)_{c-1}}{\sum_i K_i \Delta V_i}, \quad (5a)$$

where K_i is a parameter dependent on the energy of chemical bonds

$$K_i = \frac{63}{2} \frac{R}{(ad_0E)_i},$$

R is the universal gas constant, and a , d_0 , and E are parameters of the Morse potential

$$\phi(d) = E \{(\exp[-a(d-d_0)]-1)^2-1\},$$

where d is the distance between the chemically bonded atoms, d_0 is the equilibrium distance, and E is the bond dissociation energy.

Detailed calculations of glass transition temperatures of linear polymers and softening temperatures of highly cross-linked polymer networks can be found in the literature.^{3,7,8}

For the most part, actual networks correspond to an intermediate case since they contain rather long but finite-length linear fragments between cross-link points. Generalisation of Eqns (5) and (5a) taking into account the effects of both linear fragments and cross-link points of the network on the glass transition temperature resulted in the following relationship:^{5,6}

$$T_g = \frac{\left(\sum_i \Delta V_i\right)_f}{\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_l + \left(\sum_i K_i \Delta V_i\right)_{c-1}}, \quad (6)$$

where the denominator is the sum of the sets of the increments of the linear chains constituting the repeating fragment (the 'l' subscript) and of the cross-link point (the 'c-l' subscript).

This equation can be applied both to extremely sparse and to most highly cross-linked networks as well as to the networks of intermediate structure. In fact, if the network consists virtually of nothing but linear fragments, the effect of cross-link points can be neglected and Eqn (6) becomes Eqn (5). On the contrary, if the network consists of nothing but cross-link points, then Eqn (6) becomes Eqn (5a). For intermediate cases both terms in the denominator of Eqn (6) are taken into account.

Let us consider two important methodological problems. The first problem is associated with the assessment of the van der Waals volume of the repeating fragment of the network. For networks with tri- and tetrafunctional cross-link points considered above (see Fig. 2), the van der Waals volumes of repeating fragments are calculated using Eqns (3) and (4), respectively.

Yet another type of network is shown in Fig. 5. In such a network, linear chains and cross-linking bridges are of different chemical nature. The formula for calculating the van der Waals volume of the repeating network fragment has the form

$$\begin{aligned} \left(\sum_i \Delta V_i\right)_f = & \left(\sum_i \Delta V_i\right)_{l,1} (m_1 - 2) + 2 \left(\sum_i \Delta V_i\right)_{l,1}^* + \\ & + \left(\sum_i \Delta V_i\right)_{l,2} \frac{m_2 - 2}{2} + \left(\sum_i \Delta V_i\right)_{l,2}^* + \left(\sum_i \Delta V_i\right)_{c-1}, \end{aligned}$$

where $\left(\sum_i \Delta V_i\right)_{l,1}$ is the van der Waals volume of the repeating unit of linear fragments of chains that are being cross-linked, m_1 is

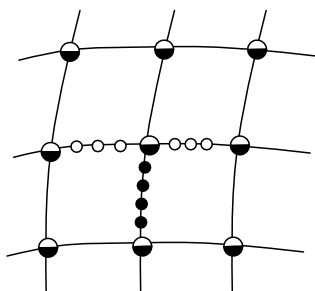


Figure 5. A network built of linear chains of the same chemical nature and cross-linking bridges of other chemical nature (a trifunctional cross-link point is shown).

the average number of such units between the cross-link points;

$\left(\sum_i \Delta V_i\right)_{1,1}^*$ is the van der Waals volume of the unit immediately adjacent to the cross-link point (this unit differs in its chemical structure from 'normal' units); $\left(\sum_i \Delta V_i\right)_{1,2}$ is the van der Waals volume of the repeating unit of linear fragment of cross-linking bridges, m_2 is the number of such units; and $\left(\sum_i \Delta V_i\right)_{1,2}^*$ is the van der Waals volume of the unit immediately adjacent to the cross-link point.

Let us dwell once again on the concept of 'a cross-link point of the network'. To formulate this concept, Eqn (6) was 'calibrated' using experimental glass transition temperatures of numerous well-characterised cross-linked systems.⁵ It turned out that the best agreement between the calculated and experimental results is achieved with the definition of the cross-link point given in the Introduction.

The molecular weight of averaged linear fragment can be estimated based on the chemical structure of the network and the experimental glass transition temperature. To this end, one must substitute the experimental T_g value into Eqn (6) and solve it with respect to m . Let us perform such an analysis in a general form for different types of networks.

First, we consider the network shown in Fig. 2b; four chains issue out of each cross-link point of this network and all the linear fragments have the repeating units of the same chemical structure. Using relationship (3) and Eqn (6), we can write for the repeating network fragment

$$T_g = \frac{2(m-2)\left(\sum_i \Delta V_i\right)_1 + 4\left(\sum_i \Delta V_i\right)_1^* + \left(\sum_i \Delta V_i\right)_{c-1}}{\left[2(m-2)\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1 + 4\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1^* + \left(\sum_i K_i \Delta V_i\right)_{c-1}\right]}, \quad (7)$$

where the first term in the denominator is the set of increments for the repeating unit of linear chains, the second term is the set of the increments for the outer units immediately adjacent to the cross-link points, and the third term is the set of increments for the cross-link point of the network.

The molecular weight M_c of linear chains between the cross-link points can be determined using the following formula

$$M_c = (m-2)M_0 + 2M_0^* + \frac{1}{2}M_{c-1}, \quad (8)$$

where M_0 is the molecular weight of a 'normal' unit, M_0^* is the molecular weight of the unit immediately adjacent to the cross-link point, and M_{c-1} is the molecular weight of the cross-link point.

Let us introduce the following designations:

$$\left(\sum_i \Delta V_i\right)_1 = A, \quad 2\left(\sum_i \Delta V_i\right)_1 + \frac{1}{2}\left(\sum_i \Delta V_i\right)_{c-1} = B,$$

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1 = C,$$

$$2\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1^* + \frac{1}{2}\left(\sum_i K_i \Delta V_i\right)_{c-1} = D.$$

Then, after some transformations relationships (7) and (8) respectively take the form

$$m-2 = \frac{B - T_g D}{T_g C - A}, \quad M_c = \frac{B - T_g D}{T_g C - A} M_0 + 2M_0^* + \frac{1}{2}M_{c-1}.$$

Let us analyse a network with trifunctional cross-link points and chain fragments of the same chemical structure issuing out from the cross-link point (see Fig. 2a). We can write for the repeating fragment of such a network

$$T_g = \frac{\left[(m-2)\frac{3}{2}\left(\sum_i \Delta V_i\right)_1 + 3\left(\sum_i \Delta V_i\right)_1^* + \left(\sum_i \Delta V_i\right)_{c-1}\right]}{\left[(m-2)\frac{3}{2}\left(\sum_i a_i \Delta V_i + \sum_j b_j\right) + 3\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1^* + \left(\sum_i K_i \Delta V_i\right)_{c-1}\right]}. \quad (9)$$

Taking into account the designations introduced we have

$$m-2 = \frac{2}{3} \frac{B_1 - T_g D_1}{T_g C - A},$$

where

$$B_1 = 3\left(\sum_i \Delta V_i\right)_1^* + \left(\sum_i \Delta V_i\right)_{c-1},$$

$$D_1 = 3\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_1^* + \left(\sum_i K_i \Delta V_i\right)_{c-1}.$$

Hence

$$M_c = (m-2)M_0 + 2M_0^* + \frac{2}{3}M_{c-1} = \frac{2}{3} \frac{B_1 - T_g D_1}{T_g C - A} M_0 + 2M_0^* + \frac{2}{3}M_{c-1}.$$

For the network shown in Fig. 5, the dependence of T_g on the composition has the form

$$T_g = \frac{\left\{(m-2)\left(\sum_i \Delta V_i\right)_{1,1} + 2\left(\sum_i \Delta V_i\right)_{1,1}^* + \frac{2}{3}\left(\sum_i \Delta V_i\right)_{c-1} + \frac{m_2-2}{2}\left(\sum_i \Delta V_i\right)_{1,2} + \left(\sum_i \Delta V_i\right)_{1,2}^* + \frac{1}{3}\left(\sum_i \Delta V_i\right)_{c-1}\right\}}{\left\{(m_1-2)\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{1,1} + 2\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{1,1}^* + \left(\sum_i K_i \Delta V_i\right)_{c-1} + \frac{m_2-2}{2}\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{1,2} + \left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{1,2}^*\right\}}, \quad (10)$$

where m_1 and m_2 are the numbers of 'normal' units in the linear chains and in the cross-linking bridges between adjacent cross-link points, respectively, and the asterisked parameters correspond to the units immediately adjacent to the cross-link points. The m_1/m_2 ratio is equal to the mole ratio of the components 1 and 2

$$\frac{m_1}{m_2} = \frac{q_1}{q_2},$$

where q_1 and q_2 are the numbers of moles of the components 1 and 2, respectively. Substituting this relationship into formula (10), we get

$$m_1 - 2 = \left[B_2 - 2A_1 - A_2 - T_g(D_2 - 2C_1 - C_2) - 2T_g \left(C_1 - \frac{q_1}{2q_2} C_2 \right) + 2 \left(A_1 - \frac{q_1}{2q_2} A_2 \right) \right] / \left[T_g \left(C_1 + \frac{q_1}{2q_2} C_2 \right) - \left(A_1 + \frac{q_1}{2q_2} A_2 \right) \right],$$

where

$$\begin{aligned} B_2 &= 2 \left(\sum_i \Delta V_i \right)_{1,1} + \frac{2}{3} \left(\sum_i \Delta V_i \right)_{c-1} + \left(\sum_i \Delta V_i \right)_{1,2} + \frac{1}{3} \left(\sum_i \Delta V_i \right)_{c-1}; \\ A_1 &= \left(\sum_i \Delta V_i \right)_{1,1}; \quad A_2 = \left(\sum_i \Delta V_i \right)_{1,2}, \\ D_2 &= 2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{1,1}^* + \left(\sum_i K_i \Delta V_i \right)_{c-1} + \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{1,2}^*; \\ C_1 &= \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{1,1}; \quad C_2 = \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{1,2}. \end{aligned}$$

Let us introduce the following designations:

$$B^* = B_2 - 2A_1 - A_2 + 2 \left(A_1 + \frac{q_1}{q_2} A_2 \right),$$

$$D^* = D_2 - C_2 + \frac{q_1}{q_2} C_2, \quad C^* = C_1 + \frac{q_1}{q_2} C_2; \quad A^* = C_1 + \frac{q_1}{q_2} A_2.$$

Taking into account these designations, we obtain

$$m_1 - 2 = \frac{B^* - T_g D^*}{T_g C^* - A^*}. \quad (11)$$

For a network consisting of the fragments of different nature, it is expedient to calculate two values of the molecular weight of the linear chains between cross-link points, viz., $M_{c,1}$, which is the molecular weight of the linear chain fragment between cross-link points for the chains that are being cross-linked, and $M_{c,2}$, which is the molecular weight of the linear chain fragment between cross-link points for the cross-linking bridges

$$M_{c,1} = (m_1 - 2)M_1 + 2M_1^* + M_{c-1,1}, \quad (12)$$

$$\begin{aligned} M_{c,2} &= (m_2 - 2)M_2 + 2M_2^* + M_{c-1,2} = \\ &= \left(\frac{q_1}{q_2} m_1 - 2 \right) + 2M_2^* + M_{c-1,2}, \end{aligned} \quad (13)$$

where $M_{c-1,1}$ is the molecular weight of a part of the cross-link point shared by the chains that are being cross-linked (see Fig. 5, filled segments of the circles) and $M_{c-1,2}$ is the molecular weight of

a part of the cross-link point shared by cross-linking bridges (see Fig. 5, open segments of the circles). The sum $M_{c-1,1} + M_{c-1,2}$ is equal to the molecular weight of the entire cross-link point M_{c-1} .

Taking into account formula (11), expressions (12) and (13) take the form

$$M_{c,1} = \frac{B^* - T_g D^*}{T_g C^* - A^*} M_1 + 2M_1^* + M_{c-1,1},$$

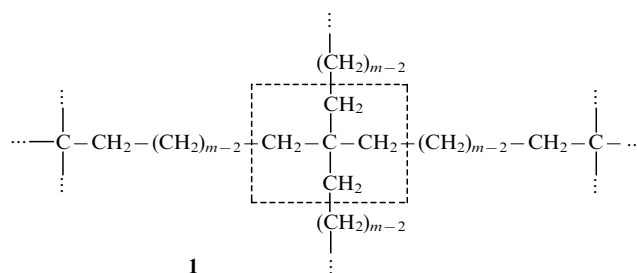
$$M_{c,2} = \frac{q_1}{q_2} M_2 \left(\frac{B^* - T_g D^*}{T_g C^* - A^*} + 1 \right) + 2(M_2^* - M_2) + M_{c-1,2}.$$

The average molecular weight M_a of the chain between cross-link points of the network can be calculated using the following formula

$$M_a = \alpha M_{c,1} + (1 - \alpha) M_{c,2},$$

where $\alpha = q_1/(q_1 + q_2)$.

Networks with tetrafunctional cross-link points. Let us consider calculations of T_g and M_c for three types of networks in more detail. We will analyse a hypothetical polyethylene-based network (structure 1) as the simplest example of a network with a tetrafunctional cross-link point and linear chains of the same chemical structure issuing out of the cross-link point.



For such a network, the van der Waals volume of the repeating fragment can be determined using the following relationship

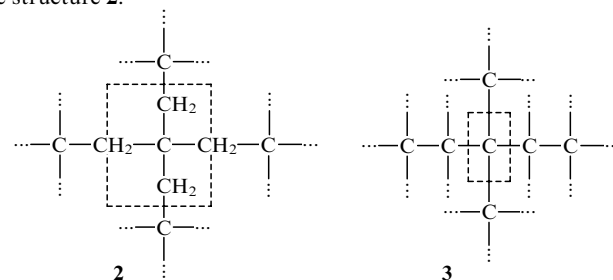
$$\left(\sum_i \Delta V_i \right)_f = \left(\sum_i \Delta V_i \right)_{c-1} + 2 \left(\sum_i \Delta V_i \right)_0 (m - 2),$$

where the first term is the van der Waals volume of the cross-link point (enclosed by dashes), and the second term is the van der Waals volume of the CH₂ group. The values of all the parameters of the network are given in Table 1. By substituting them into Eqn (7), it is possible to calculate the glass transition temperature

$$T_g = \frac{34.2m + 5}{160.4m - 217.86} \times 10^3. \quad (14)$$

Relationship (14) is valid if $m \geq 2$. The dependence of T_g on m calculated using this formula is shown in Fig. 6a.

If $m = 1$, then the situation changes so that the network has the structure 2.



Such a network consists of nothing but cross-link points, each CH₂ group being shared by two adjacent cross-link points. For the calculated values of the above mentioned parameters of the network, see Table 1.

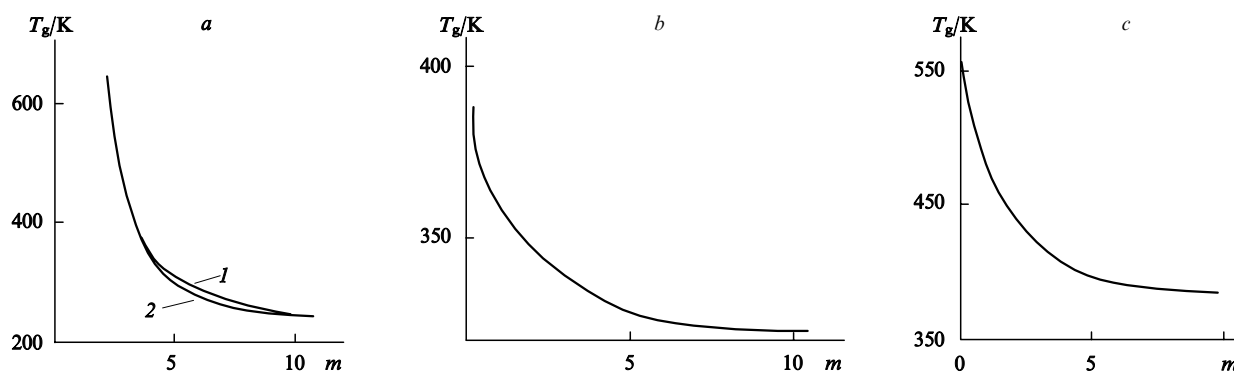


Figure 6. Dependences of T_g on m for a model polyethylene-based network with a trifunctional (1) and tetrafunctional (2) cross-link points (a), for cured epoxy resin (b), and for a network based on polystyrene and divinylbenzene (c).

This network contains no linear fragments; hence $\left(\sum_i a_i \Delta V_i + \sum_j b_j\right) = 0$ and softening of such a network occurs only because of thermal degradation (*i.e.*, decomposition through cleavage of chemical bonds). Substitution of all the parameters into Eqn (7) gives

$$T_g = T_d = \frac{39.2}{54.3} \times 10^3 = 721 \text{ K}.$$

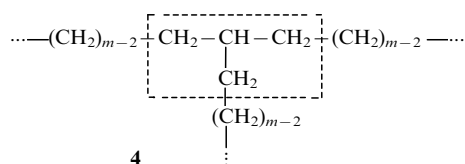
The network with $m = 0$ has structure **3** (the ideal diamond structure). The parameters of such a network are also listed in Table 1.

After substituting the numerical values into Eqn (7) we obtain

$$T_g = T_d = \frac{5.0}{5.7} \times 10^3 = 870 \text{ K}.$$

Thus, the calculated temperature of the onset of thermal degradation of diamond is equal to $\sim 873 \text{ K}$; it is known that the complete combustion of diamond occurs on heating to 1273 K.

Networks with trifunctional cross-link points. Let us consider the behaviour of a network with a trifunctional cross-link point (marked by dashes).

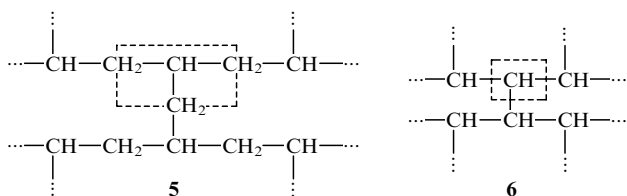


Substitution of all parameters of the network (see Table 1) into Eqn (9) gives

$$T_g = \frac{11 + 25.65m}{119.9m - 151.9} \times 10^3. \quad (15)$$

The dependence of T_g on m is shown in Fig. 6a. It can be seen that T_g decreases sharply as m increases, *i.e.*, with increase in the size of linear fragments between cross-link points.

Formula (15) is valid if $m \geq 2$. If $m = 1$, we have the structure **5**.



Network **5** consists of nothing but cross-link points, which are the repeating network fragments (indicated by dashed lines in the scheme).

Substituting the parameters of this network (see Table 1) into Eqn (9), we get

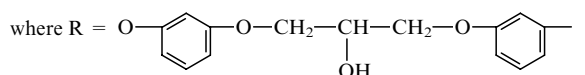
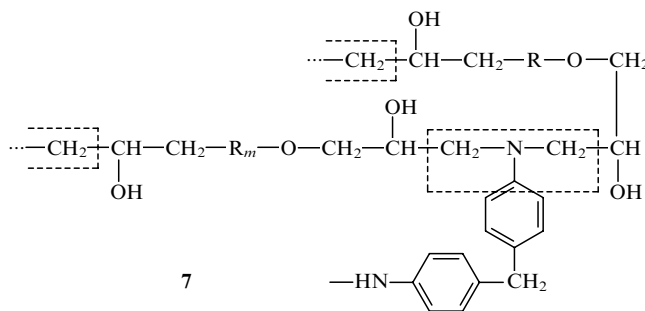
$$T_g = T_d = \frac{34.65}{46.88} \times 10^3 = 740 \text{ K}.$$

If $m = 0$, we have the structure **6**, in which each carbon atom is a branching point.

Substitution of the network parameters (see Table 1) into Eqn (9) gives

$$T_g = T_d = \frac{11.0}{14.96} \times 10^3 = 735 \text{ K}.$$

Let us consider a network in which linear chains and cross-linking bridges are of different chemical structure. We will analyse an actual epoxy resin-based network **7** as an example.



The stoichiometric composition of the network was 2 moles of an epoxy oligomer per 1 mole of a curing agent (diamine). The cross-link point of the network is indicated by dashed lines.

Substituting the values of the network parameters (see Table 1) into Eqn (10), we get

$$T_g = \frac{300.6 + 152.3m}{519.3 + 490.6m + 175.6 + 66.1} \times 10^3. \quad (16)$$

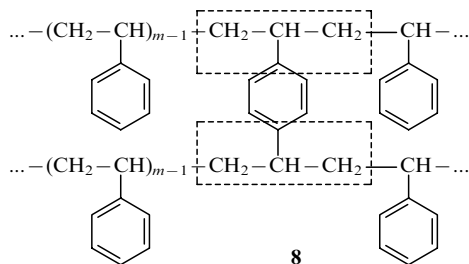
If $m = 0$, we have the structure of cured epoxy resin based on diglycidyl ether of the corresponding bisphenol. For such a resin the calculated $T_g = 395 \text{ K}$, while the experimental $T_g = 396 \text{ K}$.

The dependence of T_g on m calculated using formula (16) is shown in Fig. 6b. The glass transition temperature increases as the

linear network fragment between cross-link points decreases, which is particularly noticeable if $m \rightarrow 0$.

1. The effect of the cross-link distribution in the network on the glass transition temperature

Let us analyse the effect of the cross-link distribution along the chains on the glass transition temperature of the network taking a well-studied network **8** based on polystyrene cross-linked with divinylbenzene as an example. This is a trifunctional network, *i.e.*, three chains issue out of each cross-link point (marked by dashed lines).



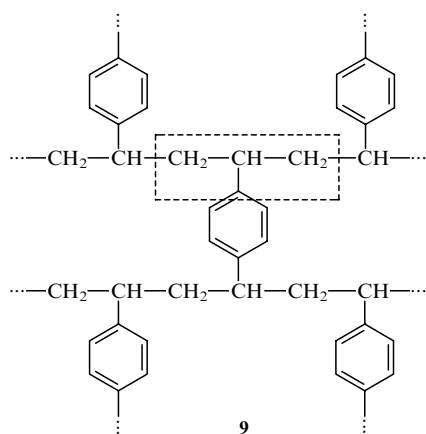
Substituting the values of the network parameters (see Table 1) into Eqn (10), we get

$$T_g = \frac{53.3 + 109.7m - 17.1 + 29.4}{72.9 + 294.0m - 80.2 + 67.6} \times 10^3 = \frac{64.6 + 109.7m}{60.3 + 294.0m} \times 10^3. \quad (17)$$

Formula (17) is valid if $m \geq 1$.[‡] The dependence of T_g on m calculated using formula (17) is presented in Fig. 6 *c*.

It can be seen that the glass transition temperature increases sharply as the number of polystyrene units between adjacent cross-link points decreases, particularly when the number of these units ($m - 1$) $\rightarrow 0$.

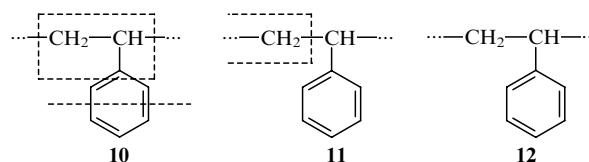
If $m = 0$, then the degree of cross-linking of the network is equal to 100%. In structure **9**, the cross-link point of such a network is outlined by dashes.



Substituting the values of the network parameters (see Table 1) into Eqn (10), we obtain

$$T_g = \frac{36.2 + 29.4}{48.6 + 67.6} \times 10^3 = 656 \text{ K}.$$

Let us consider the effect of the cross-link distribution along linear chains on the glass transition temperature using the concept of the degree of cross-linking α .



Let us calculate the values of all parameters of Eqn (10) for a fragment of network **10** (see Table 1).

Account must be taken of the fact that the CH₂ group in the polystyrene repeating unit immediately adjacent to the cross-link point of the network (marked by dashes) is a constituent of the cross-link point. The parameters for this unit are listed in Table 1. The parameters for the 'normal' polystyrene unit (**12**) are also given in Table 1. Having calculated all parameters of Eqn (10), let us consider three cases.

a. Uniform cross-link distribution

In the case of uniform cross-link distribution Eqn (10) takes the form

$$T_g = \left[\alpha \left(\sum_i \Delta V_i \right)_1 + (1 - \alpha) \left(\sum_i \Delta V_i \right)_{12} \right] / \left[\alpha \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_1 + \alpha \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_2^* + (1 - 2\alpha) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{12} \right], \quad (18)$$

where α is the degree of cross-linking, which characterises the portion of phenyl groups involved in cross-links and is equal to $1/m$. Substituting the values of all the network parameters into Eqn (18), we get

$$T_g = \frac{\alpha 65.6 + (1 - \alpha) 109.7}{\alpha 116.2 + \alpha 238.1 + (1 - 2\alpha) 294.0} \times 10^3. \quad (19)$$

Formula (19) is valid only if $0 < \alpha \leq 0.5$. If $\alpha \geq 0.5$, the network is free of polystyrene units and formula (19) takes the form

$$T_g = \frac{\alpha 65.6 + (1 - \alpha) 109.7}{\alpha 116.2 + (1 - \alpha) 238.1} \times 10^3. \quad (20)$$

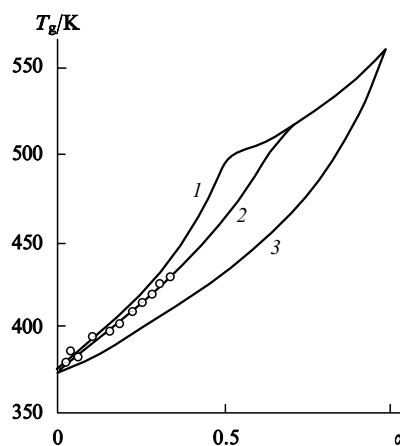


Figure 7. Dependence of T_g on the degree of cross-linking α for the network based on polystyrene and divinylbenzene. The distribution of cross-link points: (1) uniform; (2) random; and (3) the most non-uniform. The points represent the experimental values.

[‡] It should be noted that if $m \rightarrow \infty$, we obtain the calculated T_g of linear polystyrene (373 K).

If $\alpha = 0$, we get the calculated glass transition temperature of linear polystyrene.

The dependence of T_g on the degree of cross-linking α calculated using Eqns (19) and (20) is shown in Fig. 7 (curve 1). Two portions, in which fast and slow increase in T_g are observed can be distinguished in the curve of this dependence. From the analysis performed above, it follows that this is due to a specific effect of cross-link points of the network on T_g .

b. Random cross-link distribution

The function of distribution in distances for a random field of points distributed along a straight line takes the form

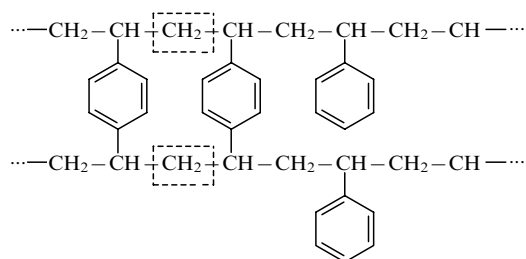
$$\bar{f}(l) = 1 - e^{-l/l_a},$$

where l is the distance between neighbouring points (in our case it is the distance between cross-link points), and l_a is the average distance.

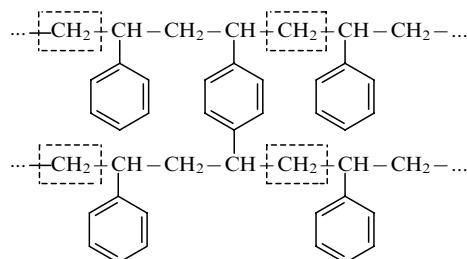
Going to the degree of polymerisation m , we get

$$\bar{f}(m) = 1 - e^{-m/m_a}.$$

In the case of neighbouring cross-link points, the number of the CH_2 groups belonging both to styrene units and to cross-link points (marked by dashed lines)



will be less than in the case when cross-link points are separated by linear fragments.



As a result, the $\alpha \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_2^*$ value decreases by an amount proportional to the number of adjacent cross-links. Simultaneously, the $(1 - \alpha) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{12}$ value increases by the same amount.

Since our interest is focused on neighbouring cross-link points, at $m = 1$ the function $\bar{f}(m)$ has the form $\bar{f}(m) = 1 - e^{-1/m}$, and taking into account that $m_1 = 1/\alpha$, we obtain

$$\bar{f}(1) = 1 - e^{-\alpha}.$$

Then we should substitute $\alpha - \alpha(1 - e^{-\alpha}) = \alpha/e^\alpha$ for α in the second term and $1 - 2\alpha + \alpha(1 - e^{-\alpha}) = 1 - \alpha - \alpha/e^\alpha$ for $(1 - 2\alpha)$ in the third term in the denominator of relationship (19).

On substitution, we obtain

$$T_g = \left[\alpha \left(\sum_i \Delta V_i \right)_1 + (1 - \alpha) \left(\sum_i \Delta V_i \right)_{12} \right] / \left[\alpha \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_1 + \right. \quad (21)$$

$$\left. + \frac{\alpha}{e^\alpha} \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_2^* + \left(1 - \alpha - \frac{\alpha}{e^\alpha} \right) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{12} \right].$$

Substituting the parameters of networks 8, 10–12 (see Table 1) into Eqn (21), we get

$$T_g = \frac{\alpha 65.6 + (1 - \alpha) 109.7}{\alpha 116.2 + (\alpha/e^\alpha) 238.1 + (1 - \alpha - \alpha/e^\alpha) 294.0} \times 10^3. \quad (22)$$

Formula (22) is valid if $(\alpha + \alpha/e^\alpha) \leq 1$, which corresponds to $\alpha \leq 0.66$.

If $(\alpha + \alpha/e^\alpha) \geq 1$, there are no uncross-linked polystyrene units and formula (22) goes over into relationship (20). The dependence of T_g on α obtained using Eqns (22) and (20) is shown in Fig. 7 (curve 2).

c. The most non-uniform cross-link distribution

The most non-uniform distribution corresponds to the case where a large number of cross-link points are adjacent and form long sequences connected by linear fragments of polystyrene chains (Fig. 8). For such a distribution of cross-link points, the number

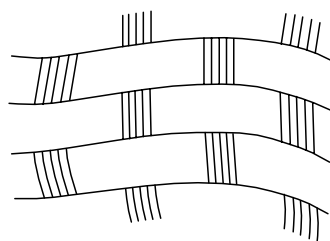


Figure 8. The most non-uniform distribution of cross-link points.

of polystyrene units immediately adjacent to the point can be neglected and we can write

$$T_g = \left[\alpha \left(\sum_i \Delta V_i \right)_1 + (1 - \alpha) \left(\sum_i \Delta V_i \right)_{12} \right] / \left[\alpha \left(\sum_i a_i \Delta V_i + \sum_j b_j + \sum_i K_i \Delta V_i \right)_1 + \right. \quad (23)$$

$$\left. + (1 - \alpha) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{12} \right].$$

Substituting all values of the network parameters (see Table 1) into formula (23), we obtain

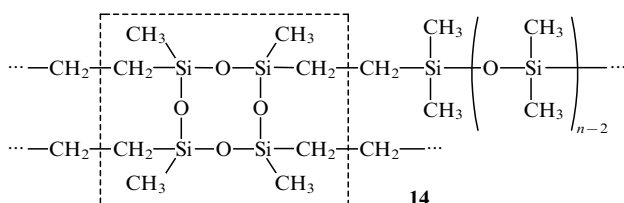
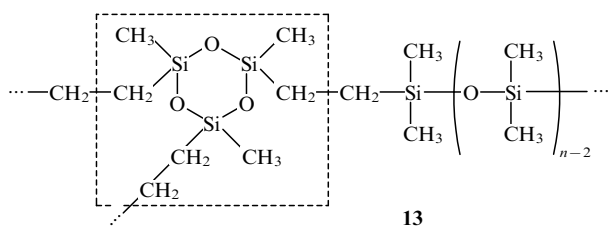
$$T_g = \frac{\alpha 65.6 + (1 - \alpha) 109.7}{\alpha 116.2 + (1 - \alpha) 294.0} \times 10^3. \quad (24)$$

The dependence of T_g on α calculated using relationship (24) is shown in Fig. 7 (curve 3). The experimental data obtained by Shefer and Gottlieb³⁹ are also shown in this figure. Curve 2 fits well the experimental points; this indicates a random distribution of cross-link points in the actual network.

2. The influence of the structure of the cross-link point on the glass transition temperature of the network

Let us consider the problem of the influence of the chemical structure of the network on its glass transition temperature taking networks with linear fragments between cross-link points of the same chemical structure and cross-link points of different chemical

structure as an example. Polydimethylsiloxane networks with the following chemical structure⁴⁰



are suitable for such an analysis.

The synthesis of highly cross-linked polymer networks with small n values is based on the use of individual compounds with a precisely set value of n ; therefore, if the degree of conversion is close to 100%, then the M_c value of such networks is given with sufficient accuracy.

The values of all increments entering into Eqn (6) are given in Table 1. Substituting them in Eqn (6), we get the following dependence of the glass transition temperature T_g of the network on the degree of polymerisation

$$T_g = \frac{239.8 + 108.1n}{428.3 + 721.5n} \times 10^3. \quad (25)$$

This dependence fits well the experimental points corresponding to glass transition temperatures; the plot is shown in Fig. 9. It can easily be shown for the networks with tetrafunctional cross-link points (**14**) that the calculated $T_g(n)$ dependence is described by the same formula (25), since each value in the numerator and in the denominator of this formula is multiplied by the same number (4/3). The experimental $T_g(n)$ dependence for network **13** is the same as that for network **14**.

Let us consider the influence of the structure of the cross-link point of polydimethylsiloxane networks on their glass transition temperature.

To calculate T_g values of the networks containing cross-link points of different structure, it is expedient to determine first the

$\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{lf}}$ and $\left(\sum_i \Delta V_i\right)_{\text{lf}}$ values for one linear network fragment between two neighbouring cross-link points. The calculations lead to the following values of these parameters:

$$\left(\sum_i \Delta V_i\right)_{\text{lf}} = 72.1n - 0.5 \text{ \AA}^3,$$

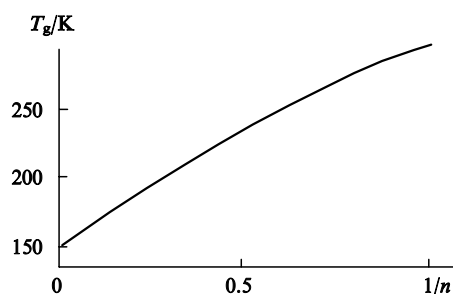
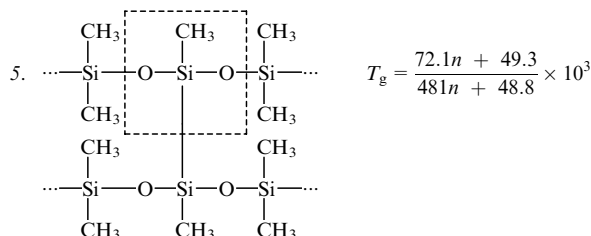
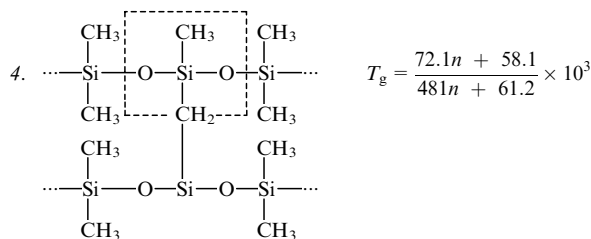
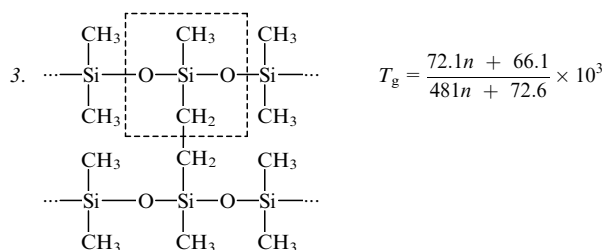
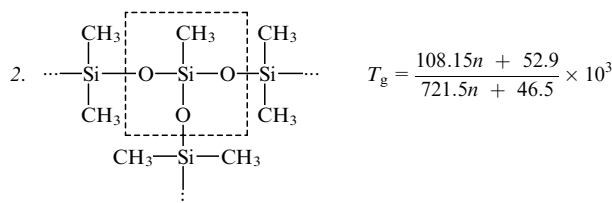
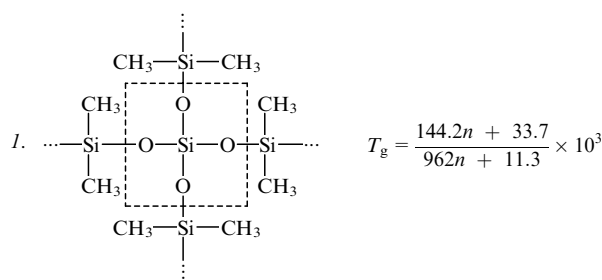


Figure 9. Dependence of T_g on n for the structures **13** and **14**.

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{lf}} = (481n - 11.5) \times 10^{-3} \text{ \AA}^3 \text{ K}^{-1}.$$

The $\left(\sum_i \Delta V_i\right)_{\text{lf}}$ and $\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{lf}}$ values found are the same for all the networks under consideration.

Using Eqn (21), the relationships were obtained that make it possible to calculate the T_g value depending on the number of repeating units n in the linear fragments connecting cross-link points of polydimethylsiloxane networks.



The $T_g(n)$ dependences for polydimethylsiloxane networks calculated using these relationships are shown in Fig. 10. It can be seen that the structure of the cross-link point affects considerably the T_g value only if n varies from 1 to 4 ($\alpha = 1 - 0.25$). The effect of cross-link points rapidly decreases as the distance between them increases, and glass transition temperatures of all networks approach that of polydimethylsiloxane (150 K) already at $n = 10$.

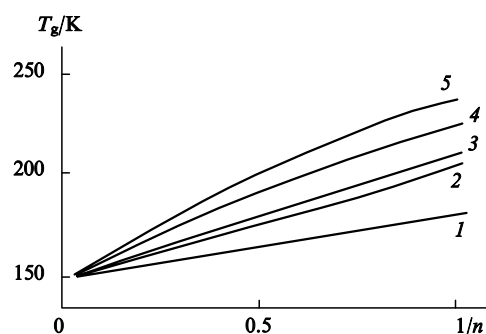
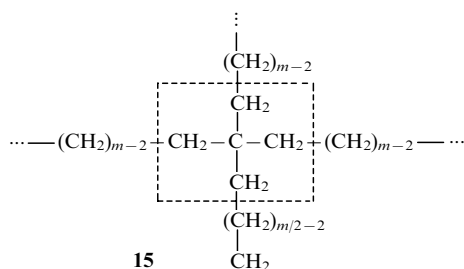


Figure 10. Dependences of T_g of polydimethylsiloxane networks on n for different types of cross-link points. For the designations of fragments (1–5), see text.

3. The influence of dangled chains and other defects of the network on the glass transition temperature of polymer networks

Among a wide variety of types of dangled chains we will dwell only on two types. The first type is a modification of network **1** with a portion of cross-linking bridges 'cut' in two.



In this case the cross-link point of the network is retained; however, it becomes trifunctional (as can be seen in the scheme, the chemical structure of the cross-link point is also retained).

The repeating fragment of this structure consists of the repeating fragment of a trifunctional network and a dangled chain. Then, we can write for the van der Waals volume

$$\left(\sum_i \Delta V_i\right)_f = \left(\sum_i \Delta V_i\right)_{c-1} + 1.5 \left(\sum_i \Delta V_i\right)_0 (m-2) + \left(\sum_i \Delta V_i\right)_{dc},$$

where the first, the second, and the third terms are the van der Waals volumes of the cross-link point of the network (outlined by dashes in the scheme), of the CH_2 group, and of the dangled chain, respectively. In this case

$$\left(\sum_i \Delta V_i\right)_{dc} = \left(\sum_i \Delta V_i\right)_0 \left(\frac{m}{2} - 2\right) + \left(\sum_i \Delta V_i\right)_{\text{CH}_3},$$

where the last term is the van der Waals volume of the end CH_3 group.

It should be noted that, in principle, it is impossible for a network free of dangled chains and for a network containing them to be of the same chemical structure. In other words, the appearance of dangled chains always leads to changes in the chemical structure of the network, which affects the glass transition temperature and other properties.

Substituting the values of the parameters of structure **15** (see Table 1) in Eqn (6), we obtain

$$T_g = \frac{\alpha(11.1 + 34.2m) + (1 - \alpha)(5.0 + 34.2)}{\alpha(160.4m - 336.2 + 102.9) + (1 - \alpha)(160.4m - 217.86)} \times 10^3$$

or

$$T_g = \frac{5.0 + 34.2m + 6.1\alpha}{160.4m - 15.44\alpha - 217.86} \times 10^3. \quad (26)$$

Relationship (26) is valid if $\alpha \leq 0.5$ since if $m \geq 2$, then two cross-link points, out of which dangled chains issue, appear as a result of 'breaking' each linear chain.

The $T_g(\alpha)$ dependence calculated using formula (26) is shown in Fig. 11a. It can be seen that T_g increases slightly as α increases and that the slope of this dependence decreases as the number of units (m) between cross-link points increases. At first glance, it may seem that the appearance of network defects such as dangled chains must result in a decrease in the glass transition temperature rather than in its increase. However, it should be kept in mind that in this case the appearance of dangled chains does not reduce the number of cross-link points; even their chemical structure is retained. In addition, the appearance of each branching requires introducing a b_f increment, which favours the increase in T_g .

If upon 'breaking' of the chains the cross-link point ceases to fulfil its initial function (*i.e.*, it is no longer a cross-link point of the network), it is natural that the glass transition temperature will decrease. An example of such a network is shown below.

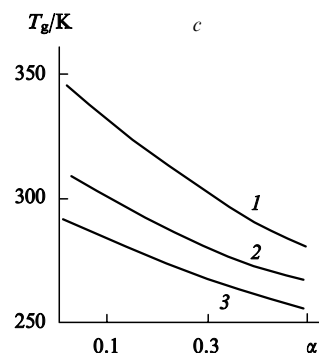
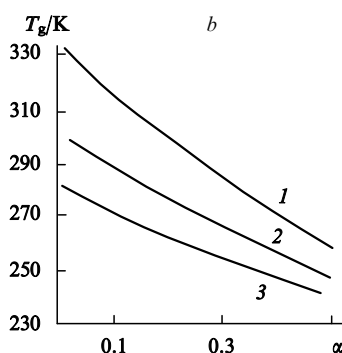
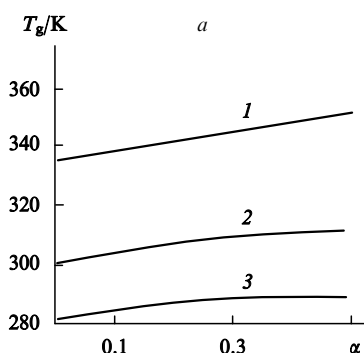
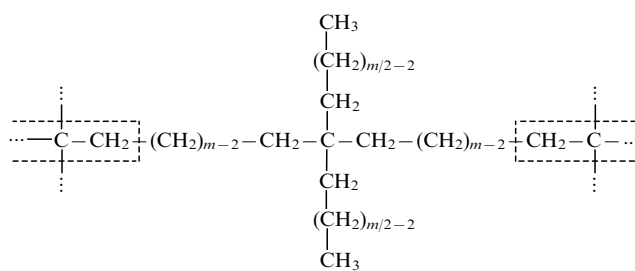


Figure 11. The dependences of T_g on α (for different m) for a tetrafunctional polyethylene network with dangled chains with a constant (a) and variable (b) number of cross-link points and for a trifunctional polyethylene network with dangled chains (c). m : (1) 4; (2) 5; (3) 6.

Linear chains are formed upon 'breaking' of linear fragments of the network; therefore, calculations for the former cross-link point should be carried out using a_i and b_j increments instead of K_i increments, *i.e.*,

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1} = 320.9 \times 10^{-3} \text{ } \text{\AA}^3 \text{ K}^{-1}.$$

Taking account of this fact and using Eqn (6), we get

$$T_g = \frac{\alpha(17.2 + 34.2m) + (1 - \alpha)(5.0 + 34.2m)}{\alpha(80.2m + 160.4m) + (1 - \alpha)(160.4m - 217.86)} \times 10^3$$

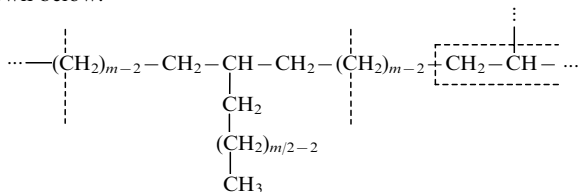
or

$$T_g = \frac{5.0 + 12.2\alpha + 34.2m}{160.4m + 298.1\alpha - 217.86} \times 10^3, \quad (27)$$

where α is the proportion of former cross-link points out of which two 'broken' chains issue.

Relationship (27) is valid if $\alpha \leq 0.25$. The $T_g(\alpha)$ dependence calculated using formula (27) is shown in Fig. 11b. It can be seen that the glass transition temperature rapidly decreases with the increase in the proportion of cross-link points out of which two 'broken' chains issue. This is explained by the fact that the branching point ceases to play the role of the cross-link point and the linear fragment between neighbouring cross-link points becomes twice as long.

Let us consider a trifunctional network with dangled chains. The scheme of such a hypothetical polyethylene-based network is shown below.



In this case upon 'breaking' the cross-linked chains the point from which the dangled chain issues ceases to play its role and becomes a constituent of a linear fragment with branching.

Using Eqn (6), we obtain

$$T_g = \frac{\alpha(25.652m + 17.1) + (1 - \alpha)(25.65m + 11)}{\alpha(24.8 + 120.3m) + (1 - \alpha)(120.3m - 152.76)} \times 10^3$$

or

$$T_g = \frac{6.1\alpha + 25.65m + 11.0}{177.56\alpha + 120.3m - 152.76} \times 10^3,$$

where α is the proportion of structures with dangled chains.

The $T_g(\alpha)$ dependences for the network with dangled chains are shown in Fig. 11c. The glass transition temperature of the network rapidly decreases with an increase in the proportion of dangled chains (especially for small m).

We have already considered hypothetical polyethylene-based networks in which the fragments between cross-link points and dangled chains are of the same chemical structure. Let us consider now a system in which the chemical structure of dangled chains differs from that of chains forming the network. Such a system based on an epoxy resin has been synthesised and studied.⁴ The ED-20 epoxy resin was cured with methyltetrahydrophthalic anhydride. To obtain a network with dangled chains, methyltetrahydrophthalic anhydride was partially replaced by oleic acid. The results of calculations and experimental studies of such networks have been reported in detail.^{4,6}

In addition to dangled chains, a network can also contain such defects as isolated loops. Different types of defects are illustrated by Fig. 12. Only those branching sites out of which the chains

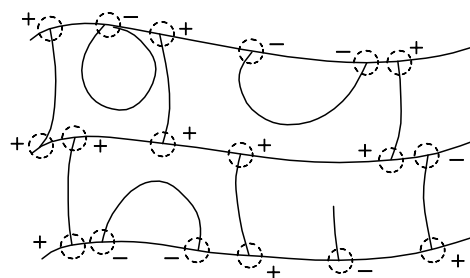
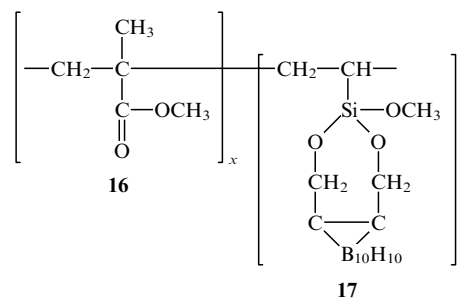


Figure 12. Schematic view of various network defects.

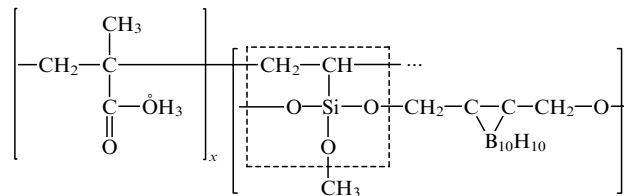
forming cross-links (*i.e.*, chains connecting neighbouring chains) issue are cross-link points. Such structures are marked by the 'plus' sign. The branching sites, out of which the chains issue representing either offshoots or isolated loops (formed through end attachment to the initial point or to some other point of the same chain) rather than cross-links, are not cross-link points (marked by the 'minus' sign).

Such defects must be taken into account when calculating the glass transition temperature using relationship (6). If the branching site is a cross-link point (in the sense mentioned above), K_i increments should be used. If the branching site does not play the role of a cross-link point, then a_i and b_j increments for the same atoms should be substituted in relationship (6).

It is possible to estimate the proportion of defects in an actual network by comparing the calculated and experimental T_g values. Let us perform such an analysis taking a network based on methyl methacrylate-1-methoxy-1-vinyl-1-sila-2,7-dioxa-4,5-(1,2-carborano)cycloheptane copolymer as an example. The chemical structure of this copolymer has the form⁴¹



When the copolymer is exposed to heat, ring opening occurs in the fragment **17** to form a network of the following chemical structure:



The cross-link point is marked by dashes.

The values of $\left(\sum_i \Delta V_i \right)$, $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)$ and $\left(\sum_i K_i \Delta V_i \right)$ for the fragments **16** and **17** of this network are given in Table 1.

Let us consider the dependence of the glass transition temperature on the chemical structure of the network in general form with taking account of the fact that the network has structural defects and branching (see Fig. 12). Then, relationship (6) can be written in the form

$$T_g = \left(\sum_i \Delta V_i \right) / \left[\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 + y \left(\sum_i K_i \Delta V_i \right)_{c-1} + (1-y) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right) \right], \quad (28)$$

where y is the proportion of branching sites that function as cross-link points. Comparing the calculated and experimental glass transition temperature, one can find the y value from the transformed expression (28):

$$y = \left[T_g^{-1} \left(\sum_i \Delta V_i \right) - \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 - \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1} \right] / \left[\left(\sum_i K_i \Delta V_i \right)_{c-1} - \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 \right],$$

where T_g is the experimental glass transition temperature.

When copolymers are used for the network formation, as in our case, the situation becomes more complicated. Let us assume that one of the copolymer components does not form a network. Then, in an ideal case (the degree of cross-linking is equal to 100%) we have

$$T_g = \left[(1-n) \left(\sum_i \Delta V_i \right)_{16} + n \left(\sum_i \Delta V_i \right)_{17} \right] / \left\{ (1-n) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{16} + n \left[\left(\sum_i a_i \Delta V_i + \sum_j b_j \right) + \left(\sum_i K_i \Delta V_i \right)_{17} \right] \right\}$$

(n is the proportion of the units of structure **17**).

If some of the branching sites do not act as cross-link points, then

$$T_g = \left[(1-n) \left(\sum_i \Delta V_i \right)_{16} + n \left(\sum_i \Delta V_i \right)_{17} \right] / \left\{ (1-n) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{16} + n \left[\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1 + y \left(\sum_i K_i \Delta V_i \right)_{c-1} + (1-y) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{17} \right] \right\}. \quad (29)$$

Let us use relationship (29) to calculate the proportions of active and inactive cross-link points [y and $(1-y)$, respectively]. According to our calculations,

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1,16} = 490.4 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}.$$

Substituting the $\left(\sum_i \Delta V_i \right)_{16}$, $\left(\sum_i \Delta V_i \right)_{17}$, $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_1$, $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{17}$, $\left(\sum_i K_i \Delta V_i \right)_{c-1}$, and $\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1,17}$ values (see Table 1) in formula (29), we get

$$T_g = \frac{96.8 + 112.1n}{255.8 - 420.5ny + 635.6n} \times 10^3. \quad (30)$$

The experimental and calculated dependences of T_g on the content of the component **17** for different proportions of active cross-link points y are shown in Fig. 13. The calculations were performed using formula (30). It can be seen that, e.g., if a proportion of the component **17** is 20%, the proportions of active and inactive cross-link points are equal to 58% and 42%, respectively; if a content of this component is 10%, the proportion of active cross-link points is equal to ~55%, etc. Thus, these networks (Ref. 41), despite being highly cross-linked, possess considerable defectiveness. If a content of the structure **17** in the copolymer is 20%, the proportion of the sol fraction is equal to 18.5%. Therefore, some portion of inactive cross-link points is contained in the branched copolymer, which is 'washed out' of the system. The remaining part of inactive cross-link points ($42\% - 18.5\% = 23.5\%$) is incorporated into the network and form branchings or isolated loops.

Let us take yet another example of assessing the network structure on the basis of comparing the calculated and experimental glass transition temperatures.⁴² Let us consider ebonites, since different types of networks can be formed in them and also because a considerable body of contradictory experimental data on their structure and mechanical properties has been accumulated. Let us calculate the T_g value of a polyisoprene-based ebonite assuming that the amount of sulfur used in the reaction corresponds to one sulfur atom per one polyisoprene repeating unit. Let us consider several variants of the formation of a network that may comprise four types of structures.

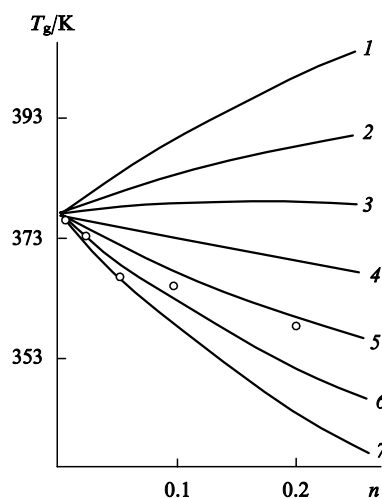
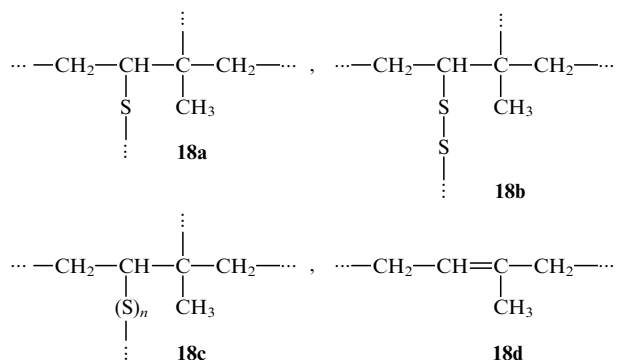


Figure 13. Dependences of T_g on the proportion of 1-methoxy-1-vinyl-1-sila-2,7-dioxa-4,5-(1,2-carborane)cycloheptane (n) in the **16–17** copolymer. The proportion of active cross-link points: (1) 1; (2) 0.9; (3) 0.8; (4) 0.7; (5) 0.6; (6) 0.5; and (7) 0.4. The points represent experimental values.

The structures **18a–c** contain respectively mono-, di-, and polysulfide bridges, and structure **18d** is the initial polyisoprene repeating unit. In the structure **18a**, all the atoms constitute the

cross-link point of the network; hence, $\left(\sum_i a_i \Delta V_i + \sum_j b_j\right) = 0$ for this structure. The values of all parameters of structures **18a–d** are listed in Table 1.

The glass transition temperature of the structure **18a** calculated using Eqn (6) coincides with the temperature of the onset of intense thermal degradation T_d (since all the atoms constitute the cross-link point of the network)

$$T_g = T_d = 673 \text{ K}.$$

Hence, if all sulfur is consumed for curing of the polyisoprene so that only monosulfide bonds are formed, then T_g should coincide with the temperature of the onset of intense thermal degradation, which is equal to 673 K. In practice, the glass transition temperature of ebonites lies in the interval 333–493 K (see Ref. 43); therefore it is likely that di- and possibly polysulfide bridges are formed in addition to the monosulfide bonds. Let us calculate the T_g value of a cross-linked system with different types of bridges between the polyisoprene chains.

Let us find a relation connecting the T_g value of ebonite with the mole fractions of bridges containing mono-, di-, and polysulfide groups. Let $\beta_1, \beta_2, \dots, \beta_n$ be the mole fractions of cross-link points (bridges) containing mono-, di-, and n -sulfide groups, respectively. With a given stoichiometric ratio of sulfur and polyisoprene, the appearance of one disulfide bond leads to one uncross-linked polyisoprene unit; the appearance of a trisulfide bond leads to two uncross-linked polyisoprene units, *etc.* Hence, the proportion of uncross-linked polyisoprene units will be equal to

$$\beta_u = \beta_2 + 2\beta_3 + \dots + (n-1)\beta_n = \sum_{i=2}^n \beta_i(i-1).$$

Then, having regard to the foregoing and this relation, we obtain

$$T_g = \left[\beta_1 \left(\sum_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i \Delta V_i \right)_2 + \dots + \beta_n \left(\sum_i \Delta V_i \right)_n + \left(\sum_i \Delta V_i \right)_4 \sum_{i=2}^n \beta_i(i-1) \right] / \left\{ \beta_1 \left(\sum_i K_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i K_i \Delta V_i \right)_2 + \dots + \beta_n \left[\left(\sum_i K_i \Delta V_i \right)_3 + \left(\sum_i a_i \Delta V_i \right)_3 \right] + \left(\sum_i a_i \Delta V_i + \sum_j b_j \right) \sum_{i=2}^n \beta_i(i-1) \right\}. \quad (31)$$

Here account is taken of the fact that

$$\sum_{i=2}^n \beta_i(i-1) = 1 - \beta_1 - \beta_2 - \dots - \beta_n = 1 - \sum_{i=1}^n \beta_i.$$

Let us consider several particular cases. If the network is formed only by mono- and disulfide cross-linking bridges, then

$$T_g = \left[\beta_1 \left(\sum_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i \Delta V_i \right)_2 + (1 - \beta_1 - \beta_2) \left(\sum_i \Delta V_i \right)_4 \right] / \left[\beta_1 \left(\sum_i K_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i K_i \Delta V_i \right)_2 + (1 - \beta_1 - \beta_2) \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_4 \right].$$

Taking account of the fact that $\beta_2 = 1 - \beta_1 - \beta_2$, finally we obtain

$$T_g = \left[(1 - 2\beta_2) \left(\sum_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i \Delta V_i \right)_2 + \beta_2 \left(\sum_i \Delta V_i \right)_4 \right] / \left[(1 - 2\beta_2) \left(\sum_i K_i \Delta V_i \right)_1 + \beta_2 \left(\sum_i K_i \Delta V_i \right)_2 + \beta_2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_4 \right]. \quad (32)$$

Relationship (32) relates the T_g value of the ebonite network to the mole fraction of disulfide cross-linking bridges β_2 . Substituting the numerical values of all the increments in this relationship, we obtain

$$T_g = \frac{92.2 + 8.2\beta_2}{136.9 + 299.7\beta_2} \times 10^3.$$

The dependence of T_g on β_2 is shown in Fig. 14. As the proportion of disulfide bonds increases, the glass transition temperature gradually decreases and becomes equal to ~ 330 K at $\beta_2 = 0.5$ (in the case of disulfide bridges only).

It has been reported that only bridges with a small number of sulfur atoms are formed (the average number is taken to be 2.6).⁴³ Taking account of this fact, let us evaluate the effect of the proportion of bridges with different length (up to three sulfur atoms) on T_g .

We shall designate the number of cross-linked units as

$$m_c = m_1 + m_2 + m_3,$$

where m_1, m_2 , and m_3 are the numbers of units connected by mono-, di-, and trisulfide bridges, respectively. The total number of units (both cross-linked and free) is equal to

$$m_a + m_2 + 2m_3 = m_1 + m_2 + m_3 + m_2 + 2m_3 = m_1 + 2m_2 + 3m_3.$$

Then

$$\beta_1 = \frac{m_1}{m_1 + 2m_2 + 3m_3}, \quad \beta_2 = \frac{m_2}{m_1 + 2m_2 + 3m_3},$$

$$\beta_3 = \frac{m_3}{m_1 + 2m_2 + 3m_3}, \quad \beta_4 = \frac{m_2 + 2m_3}{m_1 + 2m_2 + 3m_3}.$$

Dividing the numerators and the denominators of these expressions by m_3 and substituting the relations obtained in Eqn (31), we get

$$T_g = 10^3 \left[92.2 \frac{m_1}{m_3} + 111.1 \frac{m_2}{m_3} + 130.0 + 81.5 \left(\frac{m_2}{m_3} + 2 \right) \right] / \left[136.9 \frac{m_1}{m_3} + 172.8 \frac{m_2}{m_3} + 239.5 + 413.25 \left(\frac{m_2}{m_3} + 2 \right) \right].$$

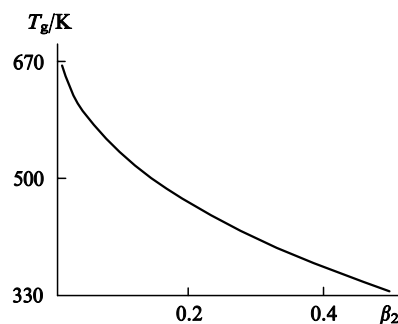


Figure 14. The calculated dependence of T_g of ebonites containing only mono- and disulfide cross-linking bridges on the proportion of the disulfide bonds.

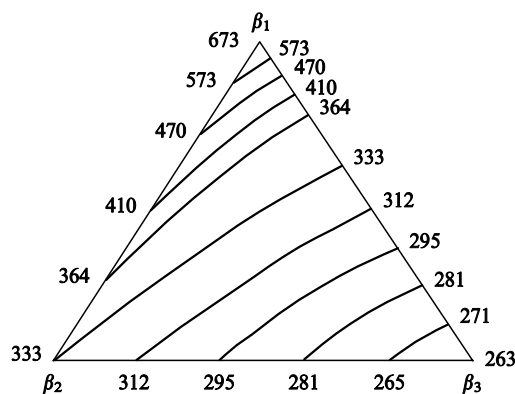


Figure 15. The triangle diagram characterising the effect of the composition of the ebonite network on T_g . The numbers at isolines are the T_g (K) values.

Let us consider a triangle similar to the Gibbs triangle; the proportions of bridges with different bonds are plotted on the sides of the triangle, while the isolines represent the lines of equal glass transitions temperatures (Fig. 15). It can be seen that the T_g values of ebonites can vary over a very wide range if mono-, di-, and trisulfide bridges are present. The maximum softening temperature corresponding to the presence of monosulfide bridges only and coinciding in this case with the temperature of intense degradation is equal to 673 K; the minimum T_g (263 K) is characteristic of a network containing only trisulfide bridges.

It is also possible to conceive the cases where the sulfide bridges can have variable lengths and there is certain distribution in bridge lengths in the actual system. Such a situation has been considered in the literature;⁴² the glass transition temperatures of ebonites were calculated taking into account the function of length distribution of sulfide bridges. It has been concluded that the bridges cannot contain large number of sulfur atoms and that the claims of other authors that the bridges are formed mainly by disulfide chains are correct.

It thus follows that the glass transition temperature of a polymer increases upon cross-linking in all cases. This is particularly noticeable when the number of repeating units in linear fragments between cross-link points is small. However, a slight increase in T_g upon cross-linking is also observed in the case of a large number of repeating units in linear fragments. The reasons for such a behaviour of T_g have been considered.^{6, 44, 45} According to Shefer and Gottlieb,³⁹ one of the reasons is the decrease in the concentration of end groups leading to a complete loss of chain mobility. Other reasons are associated with transformation of low-molecular-weight molecules resulting in the formation of offshoots and cross-links, with non-Gaussian chain statistics, and with cyclisation.^{46–53}

According to a theory proposed by Hale, Macosko, and Bair,⁴⁵ the glass transition temperature of a polymer network is determined using the following equation

$$T_g = \frac{T_{g,u}}{(1 - K_2 X_c)/(1 - Y X_c^2)},$$

where K_2 is the DiMarzio constant dependent on the chemical structure of the polymer network, X_c is the density of active cross-link points, and Y is the parameter accounting for the non-Gaussian 'behaviour'. The $T_{g,u}$ value is determined from the following equation

$$\frac{1}{T_{g,u}} = \frac{1}{T_{g,\infty}} + \frac{K_1}{M_n},$$

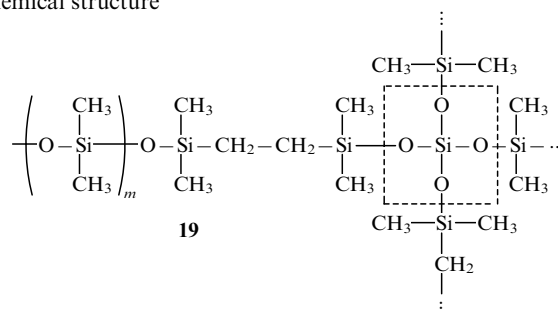
where $T_{g,\infty}$ is the glass transition temperature of a polymer with an infinite molecular weight, and M_n is the number-average molecular weight.

According to a theory proposed by Stutz, Illers, and Mertes, the T_g value is described by the following equation⁴⁴

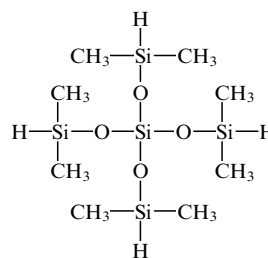
$$T_g = T_{g,u} \left(1 + \frac{K_2 X_c}{1 - X_c} \right),$$

where X_c is the density of cross-links defined as the mole fraction of all cross-links in the system divided by the network functionality.

Changes in the glass transition temperature of end-linked networks in the case of some violation of the stoichiometric ratio have been studied.⁴³ The polymer network had the following chemical structure



The experimental results of measuring the relative changes in T_g upon complete conversion of end groups in the reaction with a cross-linking agent are shown in Fig. 16. The following compound was chosen as cross-linking agent:



The authors of the study cited have concluded that their data correspond to the Hale–Macosko–Bair theory according to which changes in T_g become noticeable after the gel point; this is due to the contribution of elastically effective cross-link points

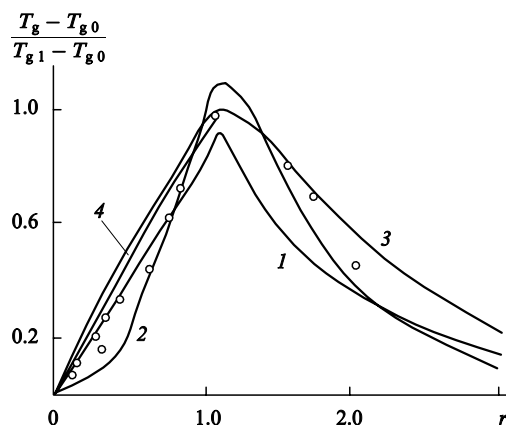


Figure 16. Relative changes in the glass transition temperatures of polymer networks estimated by different methods (r is the stoichiometric ratio). (1) the Stutz–Illers–Mertes method; (2) the Hale–Macosko–Bair method; (3) the Hale–Macosko–Bair method modified by Shefer and Gottlieb; and (4) the Askadskii–Matveev method.

absent in the pre-gel period. It can be said that this result corresponds to the conclusion of the Gibbs–DiMarzio theory, *viz.*, not any branching points but the elastically effective cross-link points make major contribution to the T_g value.

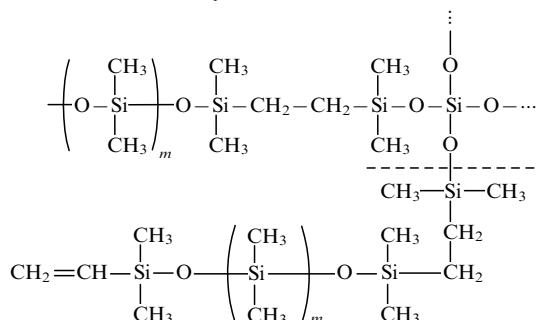
The Hale–Macosko–Bair theory modified by Shefer and Gottlieb makes it possible to approximate the dependence of the glass transition temperature T_g on the stoichiometric ratio r .

Let us consider the possibilities of application of this approach to the analysis of the changes in T_g upon cross-linking. The experimental dependence of the $(T_g - T_{g0})/(T_{g1} - T_{g0})$ ratio on the stoichiometric ratio r (here T_g is the glass transition temperature of the polymer network, T_{g0} is the glass transition temperature of the initial linear polymer, and T_{g1} is the glass transition temperature of the network at $r = 1$) can be described by Eqn (6). In this case, the initial linear polymer was polydimethylsiloxane with vinyl end groups and a number-average molecular weight M_n of 3500.

Let us consider a case with $r = 1$, where a tetrafunctional cross-link point is formed. The calculated parameters of the network with these points are given in Table 1. Substituting these values in Eqn (6), we obtain the dependence of the glass transition temperature T_g on the number (m) of polydimethylsiloxane repeating units between the cross-link points

$$T_g = \frac{714.4 + 144.2m}{4289 + 962m} \times 10^3. \quad (33)$$

If $r < 1$ (a deficit of cross-linking agent), then ‘dangled’ chains are formed as a result of the reaction between one functional group of linear polydimethylsiloxane and the cross-linking agent. The structure of such a system is shown below:



The following parameters were found for a dangled chain marked by a dashed line:

$$\left(\sum_i \Delta V_i \right)_{dc} = 274 + 72.1m,$$

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{dc} = (1634 + 481m) \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}.$$

According to the principle of calculation of the glass transition temperature (see above), if a chain issuing out of the branching point does not reach another branching point and remains dangled (*i.e.*, no cross-link between two chains is formed), then such a branching point cannot be considered as a cross-link point. In this case a_i and b_j increments should be used in Eqn (6) instead of K_i increments for the atoms constituting the branching point and we obtain

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1} = 319.8 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}.$$

In the presence of dangled chains Eqn (6) can be written in general form as follows:

$$T_g = \left\{ \left[\left(\sum_i \Delta V_i \right)_{c-1} + 2 \left(\sum_i \Delta V_i \right)_1 \right] r + \right. \quad (34)$$

$$\left. + 2 \left(\sum_i \Delta V_i \right)_{dc} (1-r) \right] / \left[\left(\sum_i K_i \Delta V_i \right)_{c-1} r + \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{c-1} (1-r) + 2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right) r + 2 \left(\sum_i a_i \Delta V_i + \sum_j b_j \right)_{dc} (1-r) \right] \}; \quad r \leq 1.$$

It is natural that if $r = 1$, then Eqn (34) becomes relationship (33). Substituting the values of all the parameters found preliminarily in Eqn (34) gives

$$T_g = \frac{583.0 + 131.4r + 144.2m}{3588 + 701r + 962m} \times 10^3. \quad (35)$$

It should be noted that end-group cross-linking of polydimethylsiloxane chains with a rather high molecular weight (M_n) of 3500 leads to a very small increase in the glass transition temperature.

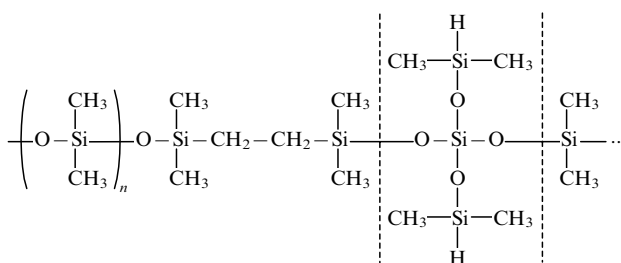
Let us express the $(T_g - T_{g0})/(T_{g1} - T_{g0})$ ratio using relationships (33) and (35). According to Eqn (35), $T_{g0} = 150.88 \text{ K}$ at $r = 1$; taking account of this fact, we obtain for $r \leq 1$

$$\frac{T_g - T_{g0}}{T_{g1} - T_{g0}} = \frac{(41.6 + 25.63r - 0.95m)(4289 + 962m)}{(3588 + 701r + 962m)(67.3 - 0.95m)}. \quad (36)$$

The results of calculations using relationship (36) are shown in Fig. 16. The experimental data as well as three theoretical dependences found by the Stutz–Illers–Mertes method, by the Hale–Macosko–Bair method, and by the Hale–Macosko–Bair method modified by Shefer and Gottlieb are also plotted in this figure. As can be seen, experimental and calculated dependences are in fairly good agreement; however, it is noteworthy that Eqn (36) contains no fitting parameters and that all the parameters of this equation are determined based on the chemical structure of the network without using experimental parameters.

Let us consider a situation when the cross-linking agent is present in excess ($r > 1$). Here, (1) trifunctional cross-link points rather than tetrafunctional cross-link points, (2) long chains between cross-link points, and (3) a network with cross-link points whose functionality varies from 0 to 4 can be formed. Clearly, a portion of the cross-linking agent does not react with end groups and this substance acts as plasticiser.

Let us consider only one case where long chains between cross-link points are formed. Such a situation is possible for $r = 2$. The system has the following chemical structure



The following parameters for the fragment between the dashed lines were found for the portion of the cross-linking agent constituting the chain and forming this structure:

$$\left(\sum_i \Delta V_i \right)_{c-1} = 184.1 \text{ Å}^3;$$

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j \right) = 1353.2 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}.$$

For polydimethylsiloxane (PDMS) chains with the $-(\text{CH}_2)_2-\text{Si}-(\text{CH}_3)_2$ fragments we have

$$\left(\sum_i \Delta V_i\right)_{\text{PDMS}} = 339.7 + 72.1m \text{ \AA}^3;$$

$$\left(\sum_i a_i \Delta V_i + \sum_j b_j\right)_{\text{PDMS}} = (2120.6 + 481m) \times 10^{-3} \text{ \AA}^3 \text{ K}^{-1}.$$

If $r = 2$, then the glass transition temperature is determined from the following relationship

$$T_g = \frac{523.8 + 72.1m}{3473.8 + 481m} \times 10^3. \quad (37)$$

If $m = 44$, which corresponds to a M_n of 3500, then the $(T_g - T_{g0})/(T_{g1} - T_{g0})$ ratio becomes negative. However, as can be seen in Fig. 16, the experimental value of this ratio is equal to 0.5 at $r = 2$; this means that the formation of entirely linear chains is impossible. In addition to linear chains, the system must also contain cross-links. Their proportion can be determined from relationships (35) for $r = 1$ and (37), and for this network ($m = 44$) we obtain

$$T_g = \frac{7059.2\alpha + 3696.2(1-\alpha)}{46617\alpha + 24637.8(1-\alpha)} \times 10^3. \quad (38)$$

Using the experimental value (0.5) of the $(T_g - T_{g0})/(T_{g1} - T_{g0})$ ratio and Eqn (38), we can find that $\alpha = 0.7$. Hence, this system contains a mixture of linear and cross-linked fragments. Thus, the approach described also makes it possible to solve the inverse problem, *viz.*, to determine the degree of cross-linking α from experimental data on changes in the glass transition temperature.

Thus, any changes in the network topology lead to changing the chemical structure of the entire system, which is of crucial importance in the case of highly cross-linked networks and considerably affects their properties. This approach takes into account all changes in the network structure, which makes possible to describe the properties with a good accuracy. The calculations do not require the use of the so-called fitting parameters, which are unknown beforehand and should be found from the experimental dependences. Alternative approaches for the description of the glass transition temperature of polymer networks have been analysed using a number of particular examples. Though they can be used to describe, *e.g.*, the dependence of the glass transition temperature on the degree of cross-linking with a good accuracy, they require introducing fitting parameters, *i.e.*, are devoid of predictive power.

V. The equilibrium rubbery modulus of polymer networks

1. Computational methods for estimating the equilibrium modulus

To estimate the equilibrium rubbery modulus E_∞ and the molecular weight of the network fragment M_c in the case of cross-linked elastomers with fairly sparse cross-links, the known equation of the classical theory of rubber elasticity is used

$$E_\infty = 3\rho \frac{RT}{M_c}, \quad (39)$$

where ρ is the density of the cross-linked elastomer, R is the universal gas constant, and T is the absolute temperature.

The application of Eqn (39) to highly cross-linked networks with linear fragments containing a very small number of repeating units (down to one or even less) leads to considerable discrepancies between the experimental and calculated E_∞ values.

Equation (39) can be used to describe the properties of highly cross-linked networks if the so-called front factor ϕ is introduced

$$E_\infty = \phi 3\rho \frac{RT}{M_c}.$$

However, the introduction of the front factor does not alter the situation for the better, since comparing the calculated and experimental E_∞ values allows one only to evaluate this front factor. Therefore, an attempt was made to obtain a generalised equation for estimating E and M_c that would be valid in the case of both sparse and highly cross-linked networks.⁵⁴

Let us perform a detailed analysis of the influence of a large number of cross-link points on the equilibrium rubbery modulus. It should be noted preliminarily that the van der Waals volume of cross-link points for sparse networks is incommensurably less than that of linear network fragments; therefore, it can be neglected when estimating the compressibility of a cross-linked system. This is impossible in the case of highly cross-linked networks, since the total van der Waals volumes of cross-link points and of linear fragments are nearly the same (the former may even be larger than the latter).

Considering the cross-linked elastomer as a system consisting of two subsystems (elastic and rotational-isomeric), let us analyse first the latter subsystem. It has been shown⁷ that the force constant of a rotational-isomeric subsystem can be determined if the difference in the energies of rotational isomers is known, which depends on the size of 'molecular defects' l_i^d in the polymer in the following way:

$$\Delta E_i = 4D_i a^2 (l_i^d)^2, \quad (40)$$

where D_i is the averaged energy of intermolecular interaction characteristic of the given type of atom, and a is the constant of the Morse potential

$$\varphi(R) = D[(e^{-a(R-r_0)} - 1)^2 - 1],$$

where D is the depth of the potential well, and r_0 is the equilibrium interatomic distance in the harmonic approximation.

To determine the size of the molecular defect l_i^d , let us consider the 'cylinder of interaction' between two hydrogen atoms bonded to carbon atoms (Fig. 17).⁵⁵ The volume of the cylinder is the sum of the volumes of interacting atoms ΔV_i and the defect volume itself. The volumes of the 'cylinders of interaction' for the crystalline (V_c^{cr}) and amorphous (V_c^{a}) polymers are respectively

$$V_c^{\text{cr}} = 2\Delta V_i + \delta_i^{\text{cr}} \Delta V_i, \quad V_c^{\text{a}} = 2\Delta V_i + \delta_i^{\text{a}} \Delta V_i,$$

where ΔV_i is the van der Waals volume of the i th atom, and the quantities δ_i^{cr} and δ_i^{a} enter into the relationships for the molecular packing coefficients for the crystalline and amorphous polymers.

$$k_c = \frac{\sum_i \Delta V_i}{\sum_i \Delta V_i + \sum_i \delta_i^{\text{cr}} \Delta V_i}, \quad k_a = \frac{\sum_i \Delta V_i}{\sum_i \Delta V_i + \sum_i \delta_i^{\text{a}} \Delta V_i}.$$

The δ_i^{cr} and δ_i^{a} values for each atom can be found in the literature.⁵⁴

The defect size is

$$l_i^d = \frac{V_c^{\text{a}} - V_c^{\text{cr}}}{2S_c} = \frac{\delta_i^{\text{a}} - \delta_i^{\text{cr}}}{2} \frac{\Delta V_i}{S_c},$$

where ΔV_i is the part of the van der Waals volume of the i th atom which is overlapped by the van der Waals volume of the atom chemically bonded to it; a factor of 2 appears in the denominator because the amplitude of the jump of the i th atom is equal to half the defect size, and S_c is the base area of the 'cylinder of interaction'.

To estimate l_i^d , let us consider the limiting case where the base radius of the 'cylinder of interaction' is equal to the van der Waals radius of the i th atom. In this case we have

$$l_i^d = \frac{1}{3} R_i (\delta_i^{\text{a}} - \delta_i^{\text{cr}}).$$

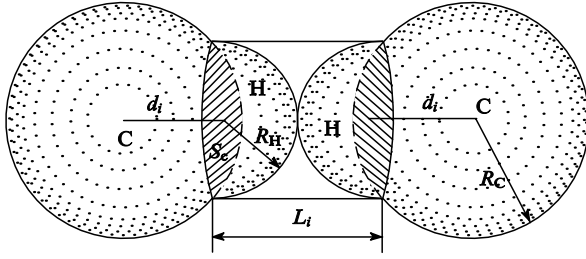


Figure 17. The ‘cylinder of interaction’ of two hydrogen atoms; d_i is the length of the chemical bond between the H and C atoms, and L_i and S_i are respectively the height and the base area of the ‘cylinder of interaction’.

For hydrocarbon polymers, $R_i = R_H$ (R_H is the van der Waals radius of the hydrogen atom equal to 1.17 Å) and the defect size l_i^d is a constant equal to 0.053 R_H . Substituting the l_i^d value obtained in expression (40), we can determine the contribution of the hydrogen atom to the energy difference of rotational isomers: $\Delta E_H = 4.56 \text{ kJ mol}^{-1}$. The value obtained corresponds in order of magnitude to spectroscopic data on the energy difference of rotational isomers.

For further analysis, we rewrite relationship (40) in the form

$$\Delta E_i = 4D_i a^2 R_i^2 \left(\frac{l_i^d}{R_i} \right)^2, \quad (41)$$

where R_i is the van der Waals radius of the i th atom, and l_i^d is the size of the defect formed by the given atom.

The aR_i value was estimated as ~ 6 (Ref. 7).

To evaluate the contribution of the rotational-isomeric subsystem to the temperature dependence of the modulus of elasticity of the polymer in the transition zone and in the rubber-like region, it is necessary to find l_i^d values for different atoms and types of the intermolecular interaction.

The calculations of melting points of polymers (T_m) showed⁷ that the energy of the intermolecular interaction D_i for a given type of atom depends on whether it is a constituent of the atomic group that forms a hydrogen bond or is involved in the dipole-dipole interaction. Therefore, the influence of specific interaction will manifest itself mainly through the energy of intermolecular interaction D_i of the given type of atom when ΔE_i is calculated using formula (41), while δ_i^a and δ_i^{cr} increments are not affected by the hydrogen bonds and dipole–dipole interactions.

If a repeating unit consists of a set of different types of atoms, it is necessary to introduce the concept of the effective energy difference ΔE_{ef} of rotational isomers, which can be found as follows. To estimate the modulus of elasticity of amorphous polymers, let us use the following relationship⁷

$$E = \left(\sum_i \Delta V_i \right) / \sum_i \frac{\Delta V_i S_i}{\alpha_i l_i}, \quad (42)$$

where ΔV_i is the van der Waals volume of the i th atom of the repeating unit; S_i is the van der Waals surface of the i th atom; through this surface the intermolecular interaction occurs (see Fig. 17); α_i is the force constant of the i th atom; and l_i is the characteristic bond length.

For the rubbery state, the α_i coefficient in the denominator of expression (42) should be replaced by the force constant of the rotational-isomeric subsystem α_{ri} (see Ref. 7),

$$\alpha_{ri} = \frac{RT}{q_i (l_i^d)^2}, \quad (43)$$

where $q_i = \exp(\Delta E_i/RT)$, and ΔE_i is the energy difference of rotational isomers. Taking into account relationship (43), the denominator of Eqn (42) takes the form $\sum_i \Delta V_i (l_i^d)^2 S_i q_i / RT l_i^d$.

Let us introduce the effective parameter q_{ef} in such a way that it be determined from the condition

$$\sum_i \frac{(l_i^d)^2 S_i q_i}{l_i} \Delta V_i = \frac{(l_{ef}^d)^2 q_{ef} S_{ef} \sum_i \Delta V_i}{l_{ef}}. \quad (44)$$

Taking into account relationship (40), we obtain the following formula for l_{ef}

$$(l_{ef}^d)^2 = \frac{\Delta E_{ef}}{4D_{ef} a^2},$$

where $D_{ef} = \alpha RT_m$, $S_{ef} = \langle S \rangle$, and $l_{ef}^d = \langle l \rangle$. The condition (44) can be written as follows:

$$\sum_i \frac{(l_i^d)^2 S_i q_i}{l_i} \Delta V_i \Big|_{T=T_m} = \frac{\Delta E_{ef} q_{ef} \langle S \rangle}{4\alpha RT_m a^2 \langle l \rangle} \sum_i \Delta V_i. \quad (45)$$

The left side of expression (45) and the quantities $\langle S \rangle$ and $\langle l \rangle$ in the right side are known. Therefore, the problem is reduced to the search for the solution of an equation of the type $b = xe^x$, where $x = \Delta E_{ef}/RT_m$, and b includes all the known terms of Eqn (45). This will make it possible to determine how different types of atoms affect ΔE_{ef} . If a hydrogen atom (and the corresponding ΔE_H value) is taken as the initial (the most typical) atom constituting polymers, then the appearance of other types of atoms with ΔE_i in the structure of the repeating unit will change ΔE_{ef} , the change being dependent on the statistical weight of these types of atoms in the repeating unit. The ΔE_{ef} value will either increase or decrease: $\Delta E_{ef} > \Delta E_H$ if $\Delta E_i > \Delta E_H$, and $\Delta E_{ef} < \Delta E_H$ if $\Delta E_i < \Delta E_H$.

Let us examine now the influence of the degree of cross-linking on the modulus of elasticity of a cross-linked polymer in the rubbery state. Considering a network polymer as a mixture of linear fragments and cross-link points, we write

$$\frac{1}{E_c} = \frac{\gamma}{E_l} + \frac{1-\gamma}{E_{c-1}} \quad \text{or} \quad E_c = \frac{E_l}{\gamma + (1-\gamma)E_l/E_{c-1}}, \quad (46)$$

where E_l and E_{c-1} are the moduli of elasticity for linear fragments and cross-link points, respectively, and γ is the concentration (fraction) of linear fragments.

Formula (46) was obtained by summing the compressibilities of linear fragments of the polymer chain and cross-link points, hence

$$\gamma = \left(\sum_i \Delta V_i \right)_l / \left(\sum_i \Delta V_i \right)_f.$$

The $\left(\sum_i \Delta V_i \right)_l / \left(\sum_i \Delta V_i \right)_f$ ratio can be written in the form

$$\frac{\left(\sum_i \Delta V_i \right)_l}{\left(\sum_i \Delta V_i \right)_f} = \frac{n \left(\sum_i \Delta V_i \right)_l^0}{n \left(\sum_i \Delta V_i \right)_l^0 + \left(\sum_i \Delta V_i \right)_{c-1}},$$

where n is the number of repeating units per cross-link point, and

$\left(\sum_i \Delta V_i \right)_l^0$ is the van der Waals volume of the repeating unit of the linear fragment.

Let us introduce the following designations: $\zeta = E_l/E_{c-1}$ and

$\beta = \left(\sum_i \Delta V_i \right)_{c-1} / \left(\sum_i \Delta V_i \right)_l^0$, where E_l is the modulus of

elasticity of a linear polymer and E_{c-1} is the modulus of elasticity of a cross-linked polymer consisting of nothing but cross-link points. Then we obtain the following relationship:

$$\gamma = \frac{n}{n + \beta}.$$

Expression (46) can be transformed to the form

$$\frac{E_l}{E_c} = \gamma + (1 - \gamma) \frac{E_l}{E_{c-1}} = \frac{n}{n + \beta} + \frac{\beta \zeta}{n + \beta}. \quad (47)$$

Since the polymer consisting of nothing but cross-link points has the modulus of elasticity many decimal orders of magnitude larger than that of the linear elastomer, then $\zeta \ll 1$ and for highly cross-linked networks $\zeta \ll \beta$. Hence the second term in expression (47) can be neglected, *i.e.*,

$$\frac{E_l}{E_c} = \frac{n}{n + \beta}. \quad (47a)$$

We revert now to the effective l_{ef} , q_{ef} , l_{ef}^d , and S_{ef} values. Taking into account the fact that the force constant of a rotational-isomeric subsystem is proportional to the mean-statistical number of the repeating units in the linear fragments between cross-link points (n), we can rewrite the relationship (42) in the form

$$E_l = \frac{l_{ef} RT}{(l_{ef}^d)^2 q_{ef} S_{ef} n},$$

and the modulus of elasticity of the rotational-isomeric subsystem of such a hypothetical polymer at $n_0 = 1$ and at temperature $T = T_0$ is

$$(E_l)_0 = \frac{l_{ef} RT_0}{(l_{ef}^d)^2 q_{ef}^0 S_{ef}}.$$

The ratio of these moduli is

$$\frac{E_l}{(E_l)_0} = \frac{T}{T_0} \frac{q_{ef}^0}{q_{ef} n}, \quad (48)$$

where $q_{ef} = \exp(\Delta E_{ef}/RT)$ and $q_{ef}^0 = \exp(\Delta E_{ef}/RT_0)$.

Substituting expression (48) in relationship (47a), we have

$$\frac{E_c}{(E_l)_0} = \frac{n + \beta}{n^2} \frac{T}{T_0} \frac{q_{ef}^0}{q_{ef}}. \quad (49)$$

For practical calculations account must be taken of the fact that the repeating network fragment consists of $n\Phi/2$ repeating units; therefore, with consideration of functionality Φ , expression (49) should be written as

$$\frac{E_c}{(E_l)_0} = \frac{2(n + \beta)}{\Phi n^2} \frac{T q_{ef}^0}{T_0 q_{ef}}. \quad (50)$$

Let us analyse Eqn (50) in more detail and compare it with the equation given by the classical theory of rubber elasticity (39). It can be seen that these equations are similar and Eqn (50) describes the modulus of elasticity for both sparse and highly cross-linked networks. In fact, if we write $n = M_c/M_0$, then from Eqn (50) we obtain

$$E_c = (E_l)_0 \frac{2}{\Phi} \frac{M_c/M_0 + \beta}{(M_c/M_0)^2} \frac{T}{T_0} \frac{q_{ef}^0}{q_{ef}},$$

where M_0 is the molecular weight of the repeating unit.

For sparse networks, $\beta \ll M_c/M_0$, then

$$E_c = (E_l)_0 \frac{2}{\Phi} \frac{M_0}{M_c} \frac{T}{T_0} \frac{q_{ef}^0}{q_{ef}}. \quad (51)$$

Comparing formulae (39) and (51), we get

$$(E_l)_0 = \frac{3\rho R \Phi T_0 q_{ef}^0}{2M_0 q_{ef}}. \quad (52)$$

If the modulus of elasticity is measured at $T = T_0$, then $q_{ef} = q_{ef}^0$, and Eqn (50) simplifies and takes the form

$$E_c = (E_l)_0 \frac{2(n + \beta)}{\Phi n^2}. \quad (53)$$

If chain fragments between cross-link points are long (sparse networks), the condition $\beta \ll n$ is fulfilled and Eqn (53) goes over into the following relationship

$$E_c = (E_l)_0 \frac{2}{\Phi n},$$

and, with consideration of relationships $T_0/T = q_{ef}^0/q_{ef}$ and $M_0 n = M_c$, we obtain

$$E_c = \frac{3\rho RT}{M_c}, \quad (54)$$

i.e., Eqns (54) and (39) coincide.

Relationship (53) is convenient for practical calculations of the modulus of elasticity of highly cross-linked networks; the $(E_l)_0$ value can be either calculated using Eqn (52) or determined from experimental data on the equilibrium modulus of elasticity of sparse networks where $n \gg 1$.

Let us perform several additional transformations. At $T = T_0$ and $q_{ef} = q_{ef}^0$, expression (52) takes the form

$$(E_l)_0 = \frac{3\rho R \Phi T}{2M_0}. \quad (55)$$

From relationships (53) and (55) we get

$$E_c = \frac{3\rho RT(n + \beta)}{M_0 n^2}, \quad (56)$$

and from formula (56), taking account that $M_c = M_0 n$, we obtain

$$E_c = \frac{3\rho RT(n + \beta)}{M_c n}. \quad (57)$$

Let us divide the numerator and the denominator of formula (57) by n ; then

$$E_c = \frac{3\rho RT(1 + \beta/n)}{M_c} \quad (58)$$

or

$$M_c = \frac{3\rho RT(1 + \beta/n)}{E_c}. \quad (59)$$

For a sparse network, $\beta \ll 1$ and $n \gg 1$; therefore, $\beta/n \rightarrow 0$ and the generalised equation (58) goes over into conventional Eqn (39).

In the case of highly cross-linked networks, the M_c value can be evaluated using formula (59). For the sake of convenience it can be transformed (considering that $n = M_c/M_0$) to the following form

$$E_c = \frac{3\rho RT(1 + \beta M_0/M_c)}{M_c}.$$

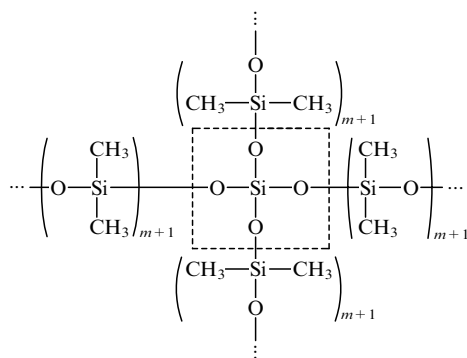
From this equation we get

$$M_c = \frac{3\rho RT + \sqrt{3\rho RT(3\rho RT + 4E_c M_0 \beta)}}{2E_c}. \quad (60)$$

For sparse networks, $\beta \rightarrow 0$ and formula (60) goes over into Eqn (39).

2. The equilibrium rubbery modulus of model networks

Let us consider a model polydimethylsiloxane-based network studied by Mark and Sullivan⁵⁶ as an example. The network structure is shown below

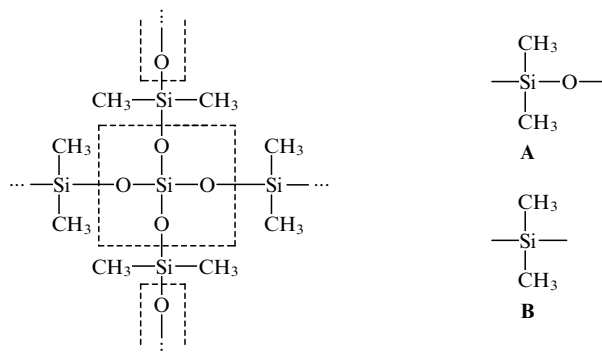


The cross-link point of the network is marked by dashed lines. For this network, we have

$$\left(\sum_i \Delta V_i\right)_{c-1} = 34.7 \text{ \AA}, \quad \left(\sum_i \Delta V_i\right)_1 = 72.1 \text{ \AA},$$

$$\beta = \frac{34.7}{72.1} = 0.481.$$

All details of the chemical structure of the network should be taken into account when calculating the equilibrium rubbery modulus of highly cross-linked networks using Eqn (53) and the glass transition temperature T_g using Eqn (6). The point is that at $m = 0$ this network has the following structure



In this case only a part of the unit **A** is a constituent of a linear chain fragment between neighbouring cross-link points of the network, since the oxygen atom of this unit is shared by the neighbouring cross-link point. For the quantity n defined as the

$\left(\sum_i \Delta V_i\right)_1^* / \left(\sum_i \Delta V_i\right)_1^0$ ratio in which the numerator is equal to the van der Waals volume of the group **B**, we get $n = 0.99$. If $m = 1$, then $n = 1.99$, etc. Taking account of this fact is of prime importance when calculating the glass transition temperature T_g using Eqn (6). In this case Eqn (6) goes over into the following formula

$$T_g = \frac{\left(\sum_i \Delta V_i\right)_{c-1}^* + m \left(\sum_i \Delta V_i\right)_1^0 + \left(\sum_i \Delta V_i\right)_1^*}{\left(\sum_i K_i \Delta V_i\right)_{c-1} + m \left(\sum_i a_i \Delta V_i\right)_1^0 + \left(\sum_i a_i \Delta V_i\right)_1^*},$$

where the second and the third terms in the denominator are the sets of increments for the units **A** and **B**, respectively (note that in the case of the network considered $\sum_j b_j = 0$).

To calculate the equilibrium rubbery modulus E_c using Eqn (53), it is necessary first to evaluate the $(E_l)_0$ value. It has been mentioned above that this can be done in two ways. The first way is to use formula (55), i.e., the $(E_l)_0$ value is determined entirely by computation. Substituting $\rho = 1.169 \text{ g cm}^{-3}$, $\Phi = 4$,

Table 2. Characteristics of polydimethylsiloxane networks.

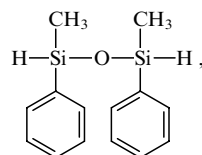
m	n	β	E_c/MPa	T_g/K
0	0.99	0.482	148	183
1	1.99	0.241	61.5	166
2	2.99	0.160	38.2	161
3	3.99	0.120	27.6	158
4	4.99	0.096	21.6	156
6	6.99	0.069	15.0	154
9	9.99	0.048	10.3	153

$M_0 = 74.15$, and $T = 293 \text{ K}$ in this formula, we obtain $(E_l)_0 = 230 \text{ MPa}$.

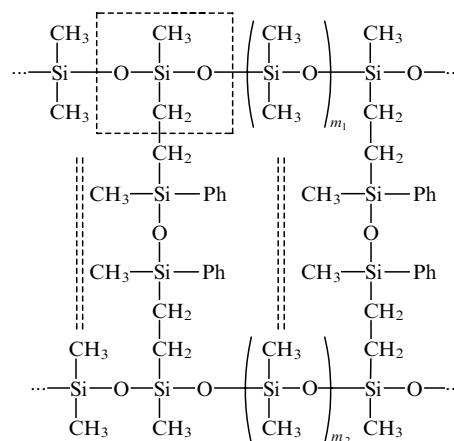
The second way is to use formula (53) and the experimental E_c value for a sparse network. Using the experimental E_c value obtained by Mark and Sullivan⁵⁶ and Eqn (53), we get $(E_l)_0 = 197 \text{ MPa}$. The calculations of E_c using formula (53) and this $(E_l)_0$ value lead to the values of the equilibrium moduli listed in Table 2. It can be seen that the E_c value increases rapidly and for a very highly cross-linked network ($n = 1$) large E_c values are reached as the distance between adjacent cross-link points of the network decreases. It should be noted that the glass transition temperature remains below room temperature.

In the preceding section, we have considered the possibilities of evaluating the equilibrium rubbery modulus for highly cross-linked networks based on their chemical structure. However, the inverse problem, viz., the estimation of the composition of the microphase that forms effective cross-link points of the network, can also be solved.

In fact, if the chemical structure of the cross-linking agent differs essentially from that of chains subjected to cross-linking, microphase separation can occur. Let us analyse several systems. Considerable attention has been focused recently on the so-called bimodal networks.^{57–59} The mechanical behaviour of such networks was studied by Sharaf and Mark.⁶⁰ These networks can be prepared by different methods, e.g., by random ‘along-the-chain’ cross-linking of polydimethylsiloxane chains containing reactive methylvinylsiloxane units. If the cross-linking agent has the chemical structure shown below,



then the following bimodal networks are formed:^{61, 62}



Tetrakisdimethylsiloxysilane is also used as cross-linking agent.^{63–65} The mechanical properties of networks with this cross-linking agent have been studied^{61–65} and it has been

shown^{63–65} that the experimental data are in good agreement with the results obtained using the Flory–Erman theory.^{66–68} However, Gottlieb *et al.*^{61, 62} have found that the values of the moduli of elasticity are considerably larger (by 10%–15%) than those predicted by the Flory–Erman theory based on the density of cross-links. The discrepancy can be due to neglecting the contribution of active entanglements.⁶⁰ With this contribution taken into account, the values calculated using the Flory–Erman theory and the experimental ones coincide.^{61, 62}

Other approaches explaining the discrepancy between the calculated and experimental data are also possible. For instance, the following explanation of the discrepancy mentioned is proposed. It is based on assumptions made by Sharaf and Mark^{57–59} that short segments between cross-link points located along the molecule subjected to cross-linking can act as elastically effective chains by themselves. In accordance with this, it has been postulated that the length distribution of the network chains is bimodal.^{57–59} Several investigators interpret large values of the modulus of elasticity obtained in the case of small deformations as a consequence of the contributions of short chains formed by the cross-linking agent (Fig. 18a).⁶⁰

Another explanation of the experimental fact that the modulus of elasticity increases (all things being the same) due to the presence of short chains between cross-link points can be based on the approach described above. According to this approach, the equilibrium rubbery modulus is calculated using generalised Eqns (56) or (58). In this case, the definition of the cross-link point of the network given in the Introduction is used. However, when the chemical structure of linear chains and that of the cross-linking agent differ essentially, the concept of ‘a cross-link point of the network’ can become more complicated. According to the initial definition of ‘a cross-link point of the network’, which is valid when calculating glass transition temperatures, this cross-link point is marked by dashed lines. However, the possibility of microphase separation should be considered when analysing and calculating the equilibrium rubbery modulus. Here, one microphase is the polydimethylsiloxane microphase, while the other is that formed by the cross-linking agent. In this case (see Fig. 18b), the cross-link point of the network consists of the cross-linking agent with the adjacent CH₂ groups; this cross-link point is marked by double dashed lines.

In order that a microphase be able to act as a cross-link point, it must be rigid. Such a situation occurs in the case of block copolymers. For instance, in polystyrene–polybutadiene block copolymers the polystyrene domains act as cross-link points while the polybutadiene component plays the role of the rubber matrix. It is possible to calculate the possibility of microphase separation computationally from the difference of the surface energies of microphases. According to calculations of the surface energies for polydimethylsiloxane chains and for the complicated cross-link point (see Fig. 18b) using the method proposed in the literature,^{69, 70} the surface energy of polydimethylsiloxane chains is equal to 20.7 dyn cm^{−1} while that of the cross-linking agent is

equal to 30 dyn cm^{−1}. The difference between these energies is quite sufficient for microphase separation.

Assuming that rigid domains play the role of cross-link points, the van der Waals volume of such a cross-link point is equal to 315.8 Å³. The van der Waals volume of the polydimethylsiloxane repeating unit is equal to 108.15 Å³; therefore, the β value in Eqn (56) will be equal to 2.92. Now it is necessary to evaluate the $(E_i)_0$ value using Eqn (55). Substituting all the parameters required, we get that $(E_i)_0 = 149$ MPa at room temperature. Then, Eqn (56) can be written as follows:

$$E_c = 149 \frac{2(173 - a \cdot 2.92)}{3 \times 173^2},$$

where a is the number of the structures **1** in the complicated cross-link point.

Since the mole fraction of methylvinylsiloxane units was equal to 0.0057 (Ref. 56), a factor of 173 appears in the denominator of the last relationship. The fact that the experimental moduli are 15%–25% larger than those predicted by theory indicates that the complicated cross-link point contains 9–15 units of the cross-linking agent. This example shows that the approach described above also makes it possible to solve the inverse problem by comparing the calculated and experimental values of the equilibrium rubbery modulus, to assess the network structure, and to determine the structure of the cross-link point.

Thus, on going to highly cross-linked networks, when the linear fragment contains less than five repeating units, the account of the influence of the chemical structure of the cross-link point becomes necessary for a correct evaluation of the equilibrium rubbery modulus. Using this approach, one can eliminate the unpredictable front factor usually introduced into the classical equation of the rubber elasticity theory to obtain coincidence between the calculated and experimental values of the equilibrium rubbery modulus. The use of generalised Eqn (58) makes it possible to predict the equilibrium rubbery modulus value with a good accuracy, thus providing a way of designing the chemical structure of the network for the preparation of materials with unusual properties.

VI. Different-modulus and gradient-modulus polymers based on highly cross-linked networks

In this section we will consider the use of computational schemes that make it possible to evaluate the glass transition temperatures T_g and the equilibrium rubbery moduli E of highly cross-linked networks in designing polymeric materials with unusual properties. The case in point will be the design and preparation of two types of elastic different-modulus polymeric materials: (1) materials for which the modulus of elasticity is constant for each specimen but varies over a very wide range from one specimen to another, and (2) materials in which the modulus of elasticity changes gradually in a prescribed manner within the same specimen in which no layers and interfaces are present.

For example, gradual transition from rubber to plastic or *vice versa* is required within the same specimen. Such a transition will allow one to design complex different-modulus constructions without using traditional methods of joining, *viz.*, gluing, welding, *etc.* The problem of realisation of this idea is associated with two fundamental peculiarities of the behaviour of polymeric materials that require clarification.

The temperature dependence of the modulus of elasticity of a typical polymer is represented schematically in Fig. 19; unfortunately, in the glassy state region the modulus of elasticity depends slightly on the chemical structure of the polymer and varies within the limits $(2–3) \times 10^3$ MPa. Therein lies the first problem of preparing different-modulus and gradient-modulus materials. Within the temperature zone of transition from the glassy to the rubbery state, the modulus of elasticity decreases sharply in the narrow temperature interval ($\Delta T = 20–30^\circ$). In this connection, it may appear at first glance that the problem of obtaining polymers



Figure 18. A scheme of a topological structure of polydimethylsiloxane networks cross-linked by a short-chain cross-linking agent. (a) the formation of bimodal networks according to Sharaf and Mark;⁶⁰ (b) the topological structure of the same network in the case of microphase separation.

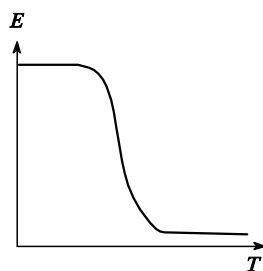


Figure 19. Temperature dependence of the modulus of elasticity.

with different moduli of elasticity varying, *e.g.*, in the interval from 3×10^3 to 3 MPa, is simple, *viz.*, it is merely necessary to obtain polymers with glass transition temperatures close to room temperature (if different-modulus materials must be used at room temperature). However, as is known, materials possess pronounced viscoelastic behaviour in the transition zone; in addition, their mechanical properties change sharply as the temperature either slightly decreases (transition to plastic) or increases (transition to rubber). Therein lies the second problem of obtaining different-modulus materials, which, in addition to the wide range of changes in the modulus of elasticity, must possess elastic rather than viscoelastic properties and retain the predetermined gradient of properties over a wide temperature range.

Theoretically, the materials free of plasticisers or fillers and possessing the moduli of elasticity varying over a wide range can be obtained by designing and preparing highly cross-linked network structures containing bulky rigid cross-link points connected by flexible linear chains of controlled lengths (Fig. 20). This follows from the generalised Eqn (58), which can be used for evaluating the equilibrium rubbery modulus E of cross-linked systems.

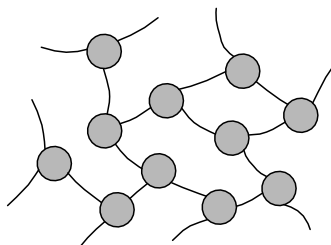
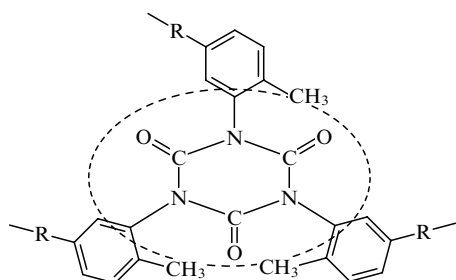


Figure 20. A scheme of a structure of a network containing bulky cross-link points and short and flexible linear chains.

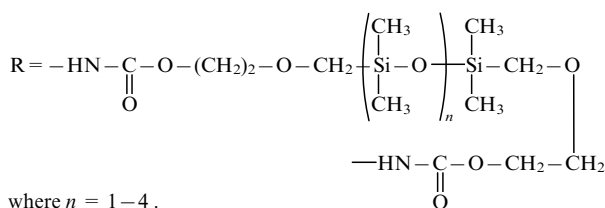
According to Eqn (58), large E value can be achieved on going to highly cross-linked networks with bulky cross-link points where $n \rightarrow 1$ and $\beta > 1$. In this case, linear fragments between cross-link points should be very flexible to retain the low glass transition temperature.

Cross-linked polyisocyanurates of the following chemical structure were synthesised^{71–77} as structures containing rigid bulky cross-link points connected by flexible linear ($-R-$) chains:



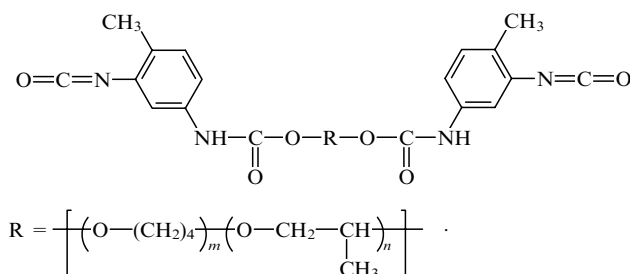
The trifunctional isocyanurate ring plays the role of a cross-link point (outlined by dashes).

Short organosilicon chains with $n = 1-4$ were used as linear fragments.^{71,72}



In other studies, cross-linked copolymeric polyisocyanurates were obtained.^{73–76}

Oligomeric diols were used as one of the initial components in the synthesis of these materials. Reactions of these diols with a diisocyanate (in particular, with toluylene 2,4-diisocyanate) resulted in macrodiisocyanates with urethane backbone



Commercial oligomeric rubbers with hydroxyl end groups (*e.g.*, the PF-OP-15 polyether, an oligomeric tetrahydrofuran-propene oxide copolymer) can be used as diols.

Macrodiisocyanates obtained from oligomeric rubbers undergo polycyclotrimerisation *in situ* and copolymerisation with diisocyanates of any structure (aromatic, alicyclic, or aliphatic) that are capable of forming cross-linked polyisocyanurates at a sufficient rate to yield cross-linked polymers. Actually, copolymers of mixed structures are prepared. The polymer simultaneously contains a network built of the products of homopolycyclotrimerisation of both the oligomer and the diisocyanate and a network with linear chains randomly distributed in the structure as a result of reaction of the oligomer with the diisocyanate.

The content of rigid cyclic structures in the network formed increases with the increase in the excess of diisocyanate with respect to the oligomeric macrodiisocyanate in the initial reaction mixture. Thus, the ratio of flexible (polyether) and rigid (isocyanurate rings with adjacent cyclic diisocyanates) fragments can be arbitrarily changed, which permits controlling the mechanical properties over a wide range. To check the possibility of controlling the properties of polymer networks in this way, glass transition temperatures of these cross-linked systems with variable chemical composition were calculated preliminarily using Eqn (6). Gradual decrease in T_g with an increase in the proportion of flexible rubber fragment can be seen in Fig. 21.

Calculations of the equilibrium modulus of elasticity using Eqn (53) have shown⁷⁴ that if T_g is below room temperature, the equilibrium modulus E_∞ can reach high values, intermediate between those of rubber and plastic. Such kind of preliminary calculations was carried out for networks with organosilicon linear fragments.^{71,72} As a result, the following expression relating the T_g value of the network to the number of dimethyl-siloxane units (n) in the linear fragment was obtained for the structure in question

$$T_g = \frac{751 + 108.15n}{2450 + 721.5n} \times 10^3. \quad (61)$$

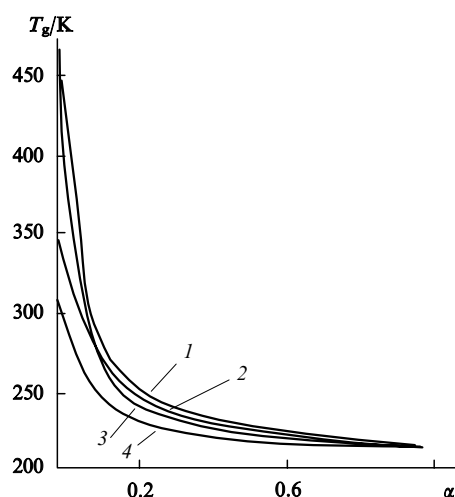
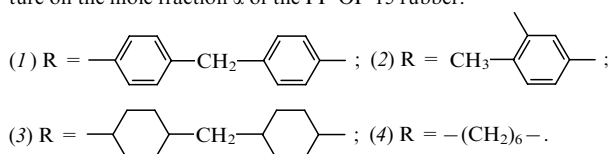


Figure 21. Dependence of the calculated glass transition temperature T_g of polyisocyanurate polymers based on diisocyanates of different structure on the mole fraction α of the PF-OP-15 rubber.



The results of calculations carried out using expression (61) are listed in Table 3. It can be seen that the T_g values are below room temperature and decrease as n increases approaching the glass transition temperature of polydimethylsiloxane.

The values of the equilibrium moduli which fall into the range from 3 to 886 MPa depending on the n value are also listed in Table 3.

Experimental studies of cross-linked polymers with the structure considered above confirmed the correctness of the assumptions made and calculations carried out.^{71, 72} Thus, the E_∞ values of the networks obtained with organosilicon linear fragments change over a range from 3 to 3×10^3 MPa (Fig. 22) depending on the length of the linear fragment.

Microphase separation due to considerably different surface energies of organosilicon chains ($\sim 21 \text{ dyn cm}^{-1}$) and isocyanurate cross-link points ($\sim 35 \text{ dyn cm}^{-1}$) is of great importance for such materials; its development was confirmed by X-ray photoelectron spectroscopy, electron microscopy, and dynamic mechanical analysis.^{71, 72}

The microphase separation can occur both in linear block copolymers (or polymer mixtures) and in polymer networks. Two clearly defined maxima are observed in these cases in the temperature dependence of the loss factor $\tan \delta$.

Table 3. Calculated and experimental characteristics of cured macrodiisocyanates.

n	T_g/K	E/MPa	
		Calculated	Experimental
0	310	—	—
1	271	884	886
2	268	249	283
3	232	123	149
6	206	40	43
9	193	22	24
19	174	8	7
43	161	3	3
∞	150	—	—

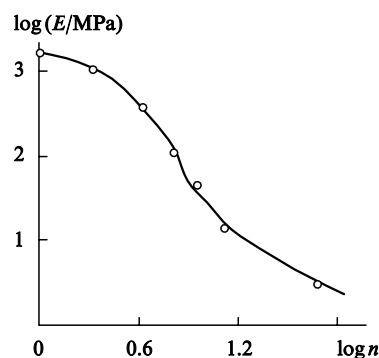


Figure 22. Dependence of the modulus of elasticity E on the number of dimethylsiloxane units n in linear fragments of polyisocyanurate networks.

The temperature dependence of the loss factor $\tan \delta$ for block specimens of the polyisocyanurates under consideration with different lengths of linear organosilicon fragments is shown in Fig. 23. The low-temperature peak is shifted towards low temperatures as the length of the linear fragment increases approaching the glass transition temperature of poly(dimethylsiloxane). The high-temperature maximum associated with the glass transition of the entire system is virtually independent of n starting from $n = 2$.

Thus, there are two rather clearly defined transition temperatures, which can be considered as the glass transition temperature of the polydimethylsiloxane microphase in the polymer network and the glass transition temperature of the microphase containing isocyanurate cross-link points with adjacent spacers. This suggests that the microphase separation caused by incompatibility of the polydimethylsiloxane fragments and isocyanurate cross-link points with adjacent spacers exists in the system.

Taking into account the fact that the transition temperatures in both microphases are shifted towards each other, one can calculate the compositions of the microphases provided that the transition temperature coincides with the glass transition temperatures of microphases of given compositions. Since the transition temperature of the microphase formed mainly of organosilicon fragments is higher than that of polydimethylsiloxane itself, it is obvious that the polydimethylsiloxane microphase contains neighbouring fragments.

What is the structure of these fragments? Glass transition temperatures of the following structures were calculated⁷² to answer this question

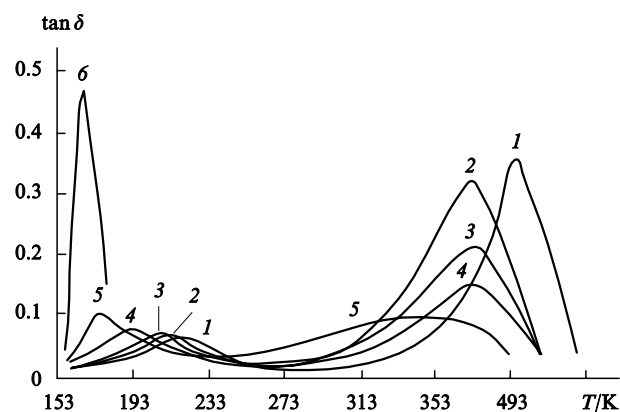
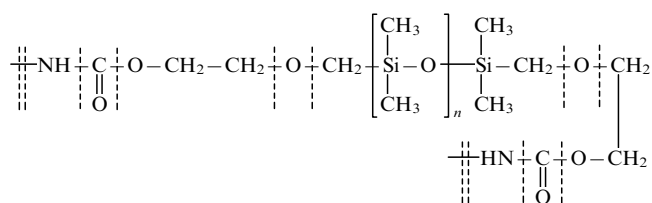


Figure 23. Temperature dependence of the loss factor $\tan \delta$ for block specimens of polyisocyanurate networks with different lengths of linear organosilicon fragments. n : (1) 1.2; (2) 2.1; (3) 3.2; (4) 5.4; (5) 9.2; (6) 22.



Glass transition temperatures of polydimethylsiloxane fragments with adjacent chain fragments indicated by dashed lines were calculated stepwise for different n using formula (6). These fragments were 'elongated' until the calculated glass transition temperature coincided with the experimentally determined temperature of the first transition. It turned out that the calculated and experimental transition temperatures coincide when the polydimethylsiloxane domains contain chain fragments marked by double dashed lines, the structure of these fragments being independent of n , i.e., of the length of the organosilicon chain. Such an approach to estimating the composition of microdomains can be extended to any objects characterised by microphase separation.

If microphase separation occurs in the system, then the concept of 'a cross-link point of the network' from the viewpoint of its chemical structure should be extended when calculating the equilibrium rubbery modulus. In fact, a rigid microphase (*e.g.*, consisting of isocyanurate cross-link points with adjacent spacers) plays the role of cross-link points provided that the glass transition temperature of this microphase is above room temperature. The presence of such a 'macro-cross-link point' leads to a considerable increase in the β value in Eqn (53), which favours the increase in the equilibrium rubbery modulus.

Such an analysis has been carried out for the system considered above⁷² and it was found that T_g of rigid domains is equal to 306 K and that their van der Waals volume is equal to 751 Å³.

Taking into account the van der Waals volume of the polydimethylsiloxane repeating unit ($180.15 \text{ \AA}^3$) we obtain $\beta = 751/180.15 \approx 4.2$.

The equilibrium rubbery moduli were determined experimentally⁷² from the stress relaxation curves approximated using physically well-founded memory functions.^{78–81}

The dependence of the modulus of elasticity of polyisocyanurate networks on the average number of repeating units in polydimethylsiloxane chains connecting the cross-link points is shown in Fig. 22. As was mentioned above, the range of numerical values of the modulus of elasticity for such networks exceeds the range characteristic of the zone of transition from the glassy to the rubbery state. However, despite this fact, these materials possess elastic mechanical behaviour characteristic of polymeric glasses rather than viscoelastic behaviour characteristic of all polymers in the transition zone. This is confirmed by the stress relaxation curves (Fig. 24). The first specimen was a

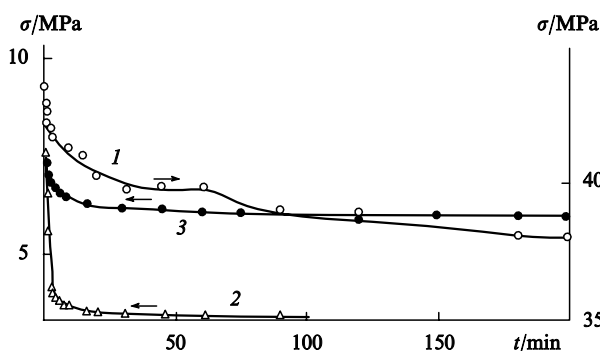


Figure 24. Stress relaxation curves for the ED-20 epoxy resin cured with methyltetrahydrophthalic anhydride (1) and a mixture of poly(sebacic anhydride) and azelaic acid (2), and for a polyisocyanurate network with linear organosilicon fragments with $n = 6.2$ (3).

conventional ED-20 epoxy resin cured with methyltetrahydrophthalic anhydride. This system has a glass transition temperature of 120 °C and is a glassy polymer at room temperature. Fast stress (σ) relaxation is observed in the initial period, then the drop in σ slows down, and the stress changes only slightly. The second specimen was an ED-20 epoxy resin cured with a mixture of poly(sebacic anhydride) and azelaic acid taken in such a proportion that the transition zone for this specimen was in the interval from -5 to 34 °C. The stress relaxation curve is characteristic of the transition zone, *i.e.*, fast stress relaxation virtually down to zero is observed.

The third specimen was a polysilycynurate network with linear organosilicon fragments ($n = 6.2$). With this size of linear chains, the initial stress σ_0 is nearly equal to that of the viscoelastic material (7.5 MPa). However, the mechanical behaviour is fundamentally different, *viz.*, fast but small stress relaxation is observed in the initial period and then the stress virtually ceases to drop, *i.e.*, the material behaves as an elastic glassy polymer.[§]

Let us consider the properties of gradient-modulus materials based on the oligomeric PF-OP-15 rubber and toluylene 2,4-diisocyanate.

To obtain gradient-modulus materials, the initial components are gradually measured out thus achieving the targeted control of the chemical composition of the network within the same specimen.

This allowed one to prepare specimens in which the modulus of elasticity changed from 4.5 MPa (which is characteristic of rubbers) to 2000 MPa (which is characteristic of plastics).^{75, 76} The change occurred smoothly within the same material (with no interfaces and intermediate layers).

The dependence of the modulus of elasticity on the content of toluylene 2,4-diisocyanate in the initial reaction mixture is shown in Fig. 25 as an example. It can be seen that the modulus of elasticity changes linearly along the length of the specimen so that a gradual transition from rubber to plastic occurs with no interfaces, as was mentioned above.

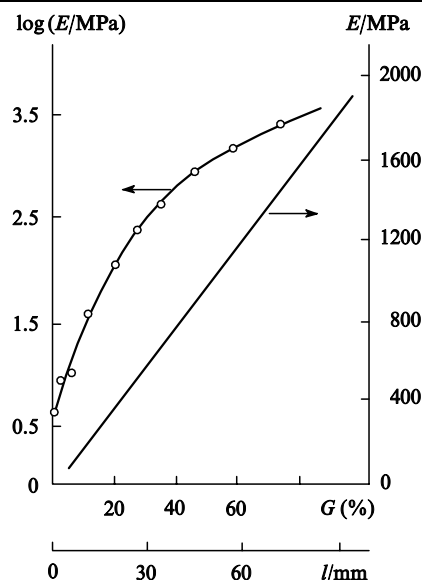


Figure 25. Dependence of the modulus of elasticity varying along the specimen length (l) on the content of toluylene 2,4-diisocyanate (G) in a mixture with oligomeric macrodiisocyanate.

To analyse the character of mechanical behaviour of the materials obtained, the stress relaxation curves were studied for

§ It is well to bear in mind that there are no absolutely elastic polymeric materials (except for ideal crystals). Therefore the terms 'elastic behaviour' and 'elastic material', as applied to the polymers, are conditional. The term 'elastic behaviour' is used in reference to such a behaviour where the stress relaxation occurs at a very slow rate.

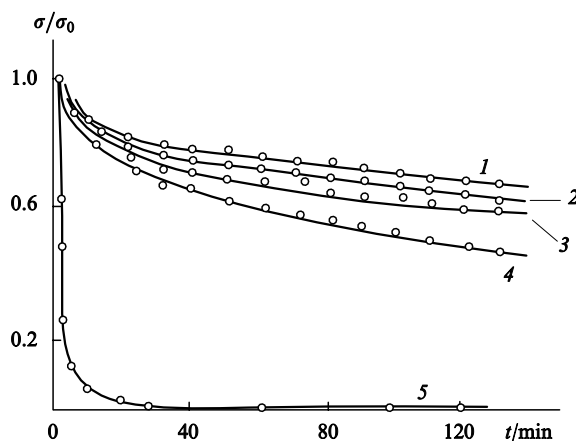


Figure 26. Stress relaxation curves for polyisocyanurate networks obtained from oligoether diisocyanate, toluylene diisocyanate at a content of the latter compound of 6% (1), 46% (2), and 27% (3); for the ED-20 epoxy oligomer cured with methyltetrahydrophthalic anhydride (4); and for an ED-20-based epoxy viscoelastic polymer cured with a mixture of poly(sebacic anhydride) (27.3%) and azelaic acid (13.8%) (5).

microspecimens cut from the initial macrospecimen in regions with different gradients of the modulus of elasticity (Fig. 26). For comparison, a stress relaxation curve for the viscoelastic material [ED-20 epoxy resin cured with poly(sebacic acid anhydride) in the presence of azelaic acid] is also shown in this figure. The glass transition temperature of this network is close to room temperature (the same temperature is characteristic of the material whose relaxation behaviour is illustrated by Fig. 24 [specimen (2)]). The stress relaxation curves were plotted in 'relative stress–time' coordinates; the relative stress was calculated as σ/σ_0 , where σ is the current relaxing stress, and σ_0 is the initial stress developed at the instant of termination of 'instantaneous' initiation of the deformation.

Fast relaxation of the relative stress nearly down to zero is observed for the conventional viscoelastic material, while a slower drop in the stress characteristic of polymeric glasses or rubbers followed by a very slow rate of stress relaxation is observed for the cross-linked polymers synthesised.^{75,76}

Thus, despite the fact that a part of the material within the same specimen is characterised by the modulus of elasticity corresponding to the transition zone, this part possesses elastic mechanical behaviour similar to that of glasses or rubbers rather than viscoelastic behaviour characteristic of all polymers in the transition zone.

The dynamic mechanical analysis of the networks obtained shows that they have very small $\tan \delta$ values, like elastic materials, and that the value of the storage modulus E' is characteristic of the transition zone.

Films based on cross-linked polyisocyanurates with the gradient of the modulus of elasticity perpendicular to the film plane were obtained. These films formed by highly cross-linked polymer networks possess good mechanical properties (a strength of 50 MPa and a limiting elongation of 90%). Such gradient-modulus materials are devoid of brittleness, which is the major drawback of highly cross-linked polymer networks.

Thus, it is possible to obtain polymeric materials possessing new properties using the principles of the molecular design of polymer networks and performing targeted synthesis of the networks. The curves shown in Fig. 27 illustrate the mechanical behaviour of conventional and new polymeric materials over a wide temperature interval. As was mentioned above, irrespective of their chemical structure, conventional materials in the glassy state have approximately the same moduli of elasticity $[(2-3) \times 10^3 \text{ MPa}]$. On heating of these materials to their glass transition temperatures, the moduli of elasticity decrease sharply

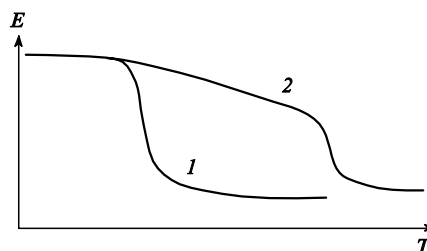


Figure 27. Temperature dependence of the modulus of elasticity for conventional polymers (1) and networks with bulky cross-link points and short and flexible linear fragments (2).

in the narrow temperature interval $\Delta T \approx 20-30^\circ$ and the materials undergo transition to the rubbery state.

A fundamentally different picture is observed for new materials. At low temperatures, the new materials (like conventional ones) are also in the glassy state. However, on heating to the temperature of the first relaxation transition the modulus of elasticity decreases very slowly (up to the temperature of the second relaxation transition). Only after passing this temperature a sharp decrease in the modulus of elasticity occurs and the material undergoes transition to ordinary rubbery state. In this case the temperature interval, in which the slow drop in the modulus of elasticity is observed, is ~ 200 degrees. This interval is the major operating range for these materials. Despite the fact that within this interval the moduli of elasticity take the values characteristic of the zone of transition from the glassy to the rubbery state, the materials possess elastic rather than viscoelastic behaviour. It is possible that in this case a new physical state is observed different from the glassy and rubbery states. It is needless to say that this assumption is tentative, though the distinction in the mechanical behaviour of conventional materials and those under consideration is beyond doubt.

VII. Optical sensitivity of highly cross-linked networks

The stress-optical coefficient C_σ , *i.e.*, the coefficient of proportionality between birefringence Δn and the mechanical stress σ that induces birefringence, is one of the characteristics of the optical sensitivity of materials

$$\Delta n = C_\sigma \sigma.$$

The stress-optical coefficient C_σ is a fundamental characteristic of the materials used in the photoelasticity method of stress investigation. In this method, a model of an actual construction made of transparent, optically sensitive materials is loaded as required. As a result, birefringence appears in the material the model is made of and the stress-strain state of the construction can be judged from the birefringence pattern. In the case of three-dimensional models, the deformation freezing method is rather efficient. A model is heated to the temperature at which the constituent material undergoes transition to the rubbery state; it is then loaded and cooled under load to room temperature, which is about $80-100^\circ$ lower than the glass transition temperature for conventional optically sensitive materials. The deformations and optical anisotropy appearing upon loading the model are frozen. Then the model is sliced and these specimens are investigated thereafter.

Without dwelling on other modifications of the photoelasticity method of stress analysis, we should note that their progress is only possible as new polymeric materials with desired optico-mechanical properties have become available. Two types of materials (elastic and viscoelastic ones) are required to solve different problems. Different-modulus polymeric materials with the ratio of the moduli of elasticity from 2 to 10 and possessing elastic properties both under static and under dynamic loads are

required for studying the stress fields in laminated elastic media by the dynamic photoelasticity method. Such materials have come into use in dynamic photoelastic studies recently.⁷¹ The problem of their preparation is that all polymeric glasses irrespective of their chemical structure have nearly the same moduli of elasticity ($\sim 10^3$ MPa).

It might seem that different-modulus materials could be prepared if polymers were synthesised that possess the behaviour characteristic of the zone of transition from the glassy to the rubbery state at the test temperature (*e.g.*, at room temperature). Since the modulus of elasticity decreases sharply in this zone, it is always possible to choose a material with the desired modulus of elasticity. However, materials in the transition zone possess extremely high viscoelasticity, whereas elastic materials are required for solving this problem by the photoelasticity method of stress analysis. Polymer networks of specific chemical structure (highly cross-linked networks possessing extremely large rubbery moduli have low glass transition temperatures much below room temperature) fulfil these two incompatible requirements. The present state-of-the-art studies in the field of predicting the properties of such systems makes it possible to predict the structure of highly cross-linked networks that would meet these two contradictory requirements.^{72, 82}

Using the above approach, the glass transition temperatures and the moduli of elasticity of cross-linked carbosilicon organosilicon polyisocyanurates with short linear fragments of different lengths were predicted.^{71, 72} The structure of these networks is shown in page 705. The relaxation properties of these materials have already been compared to those of the viscoelastic material. Let us consider mechanical and optical properties of the networks under creep conditions.

The time dependences of mechanical and optical creep are shown in Fig. 28. It can be seen that a gradual increase in the compliance values is observed after loading the viscoelastic material, whereas fast creep relaxation is observed for silicon-containing cross-linked polyisocyanurates in contrast to typical viscoelastic polymer.

Thus, it can be pointed out that elastic behaviour, complicated only by weak indications of viscoelasticity, is characteristic of carbosilicon organosilicon polyisocyanurates.^{71, 72}

Table 4 lists the values of the equilibrium moduli of elasticity (E_∞) found by fitting the stress relaxation curves using new memory functions,⁷⁸ which make it possible not only to obtain high correlation coefficients but also to calculate such physical characteristics of a material as the number of microdefects, the initial entropy of the system, *etc.* The stress-related values of

Table 4. Optico-mechanical characteristics of cross-linked macrodiisocyanates.

n	Static load		Dynamic load		
	E_∞/MPa	$\sigma_0^{1.0}/\text{MPa}$ (295 K)	$\eta/\text{m s}^{-1}$	E_d/MPa	$\sigma_0^{1.0}/\text{MPa}$
1.2	866	1.26	1980	4822	2.6
2.5	283	1.14	1700	3454	2.3
3.8	149	1.08	1270	1897	2.1
5.4	—	0.80	1000	1140	1.8
6.2	43	0.69	800	727	1.6
9.2	24	0.41	570	357	1.0

material strip $\sigma_0^{1.0}$ are also given in this table. As can be seen from the table, the stress-optical sensitivity ($\sim 1/\sigma_0^{1.0}$) in the series of polyisocyanurates differing only in the number of dimethylsiloxane units between cross-link points of the network increases as the length of the linear fragment n increases. It seems most likely that the increase in optical sensitivity, despite the decrease in the concentration of the groups possessing high anisotropy of polarizability (isocyanurate ring, aromatic rings), is associated with an increase in the mobility of the macrochain, which depends both on the concentration of cross-link points in the network and on the number of dimethylsiloxane units with low potential energy barrier to rotation about the Si—O—Si bond.⁸³

Dynamic characteristics of optico-mechanical properties of the polymers can differ appreciably from the static ones because of the influence of the time factor. Thus, the duration of the processes that occur under the action of short-term impulse loads and are recorded in the optical birefringence pattern model are from several to hundreds of microseconds. In this case conventional quasi-static creep and stress relaxation tests cannot reproduce the essence of the phenomena occurring in the polymeric material upon dynamic action.

The photogram analysis shows that longitudinal and transverse waves propagate along the rods made of cross-linked polyisocyanurates at a constant velocity. The values of the velocity of propagation of longitudinal waves C_p and the dynamic moduli of elasticity E_d calculated using the following equation

$$E_d = \rho C_p^2,$$

where ρ is the density of the material, are listed in Table 4. As can be seen, the velocities of propagation of longitudinal waves C_p and

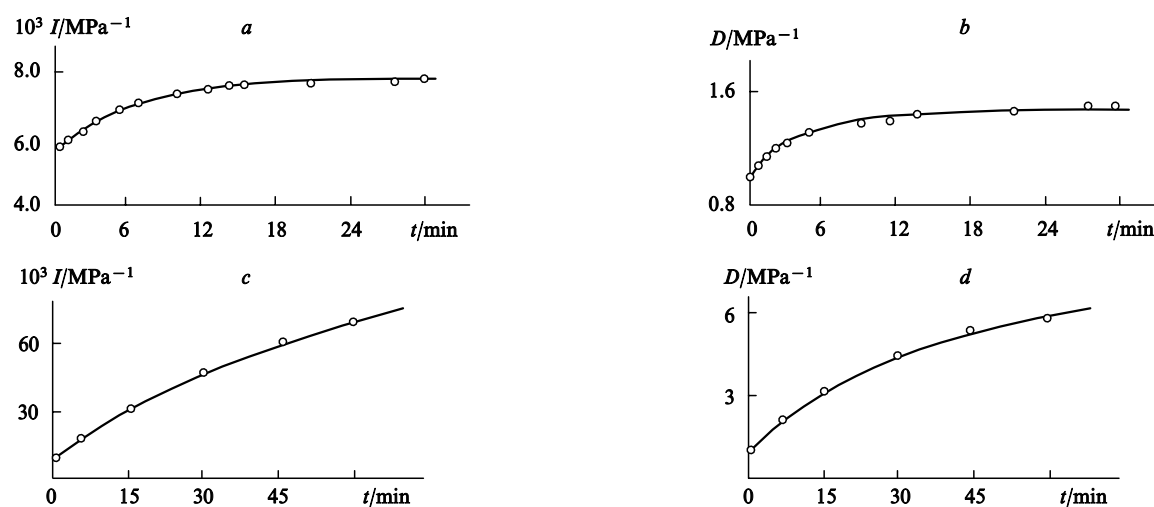


Figure 28. The mechanical $I(t)$ (a, c) and optical $D(t)$ (b, d) creep curves for polyisocyanurate networks with $n = 6.2$ and $\sigma = 1.4$ MPa (a, b) and for the viscoelastic polymer based on the ED-20 epoxy oligomer cured with a mixture of poly(sebacic anhydride) (27.3%) (c, d) and azelaic acid (13.8%).

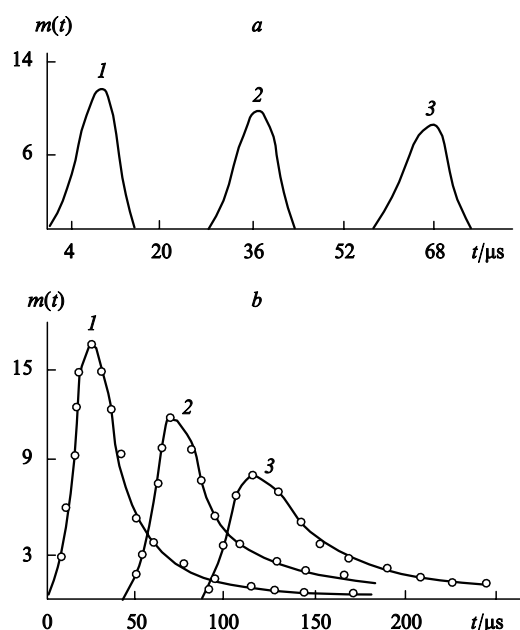


Figure 29. Changes in impulse birefringence pattern $m(t)$ at different cross-sections l of the rods made of a cross-linked polyisocyanurate with $n = 2.5$ for $l = 50$ (1); 100 (2); and 150 (3) mm (a); those for an ED-20-based viscoelastic polymer cured with a mixture of poly(sebacic anhydride) (27.3%) and azelaic acid (13.8%) for $l = 60$ (1); 110 (2); and 160 (3) mm (b).

the dynamic moduli of elasticity E_d of the materials presented vary over a wide range.

Thus, optically sensitive materials based on the cross-linked polyisocyanurates with short chains between cross-link points differ substantially from the traditional ones. The latter have different static moduli of elasticity but virtually the same dynamic moduli of elasticity, which limits the field of their application when solving certain dynamic problems.

To evaluate the viscoelastic properties of cross-linked polyisocyanurates under conditions of dynamic action, let us consider the birefringence patterns under the impulse loading $m(t)$ at different cross-sections l of the rods.⁸² For comparison, the impulse values $m(t)$ are plotted on the same graph (Fig. 29) with the shift in time, which takes account of the velocity of wave propagation in the materials. In contrast to the typical viscoelastic polymer, slight changes in the shape of impulses and their durations observed with increasing distance covered in the rods are characteristic of specimens of cross-linked polyisocyanurates with $n = 1-9$; this indicates their weak viscoelasticity under impulse loading. Hence, optically sensitive cross-linked polyisocyanurates are suitable for studying the stress-strain state of laminated media by the dynamic photoelasticity method.

Previously, we have considered elastic polymeric materials. However, optically sensitive materials possessing viscoelasticity are required for solving a number of problems. It is natural that viscoelastic behaviour is mostly characteristic of the zone of transition from the glassy to the rubbery state.

The currently available methods of creep simulation by the photoelasticity method (the photocreep method) are based on a specific selection of materials possessing both high optical sensitivity and pronounced viscoelastic properties. To solve this problem, it is necessary to have polymer networks for which the test temperature falls into the zone of transition from the glassy to the rubbery state. Viscoelasticity of the materials will increase as the test temperature approaches the glass transition temperature. Therefore, it is necessary to have a set of polymeric materials with

preset glass transition temperatures not equidistant from the test temperature. The preparation of such materials has been reported in the literature.⁸⁴⁻⁸⁸

In addition to physical characteristics considered above [density (the molar volume), the glass transition temperature, and the equilibrium rubbery modulus], the molar (or specific) heat capacity, the coefficient of volume expansion in the glassy and in the rubbery states, the dielectric constant, the refractive index, the energy of intermolecular interaction, *etc.*, can also be calculated for highly cross-linked polymer networks. These properties are calculated using the same relationships as for linear polymers with account of the fact that in the case of networks their repeating fragments rather than the 'monomer' units of the polymers play the role of the repeating units.

The ability to calculate the characteristics mentioned above makes it possible to solve the inverse problem, *viz.*, to judge the structure of a network (especially of a complex network) from the experimental characteristics. Analysis of the structure of phenol-formaldehyde resins is an example of such an approach.⁸⁹

VIII. Analysis of the structure of cross-linked polymers (taking cured phenol-formaldehyde resins as an example)

Phenol-formaldehyde (PF) resins belong to the oldest representatives of highly cross-linked polymer networks; however, interest in their structure and properties has persisted up to the present.⁹⁰ Numerous studies have been dedicated to the analysis of the structure and properties of PF resins; however, there is no agreement concerning the chemical structure of the network formed by these resins as yet. This is probably due to the fact that the network may have different structures depending on the course of curing of PF resins. In addition, OH groups capable of forming hydrogen bonds are present in the network structure. Hydrogen bonds can be formed both due to intermolecular interaction of the OH groups in the neighbouring chains of PF resins and due to interaction between the OH groups within the same repeating unit.

It is convenient to clarify the sense of such concepts as the inter- and intramolecular interaction from the viewpoint of the approach presented using a simplified scheme (Fig. 30). Figure 30a illustrates the case of intermolecular interaction resulting in the formation of a network of physical (hydrogen) bonds between the chains. It is natural that the formation of this network favours an increase in the glass transition temperature. Figure 30b illustrates the case where two OH groups are within the same unit of a linear fragment of PF resin; the hydrogen bonding occurs within this unit while no formation of a network of physical bonds between the neighbouring chains occurs. Of course, different types of intermolecular interaction (hydrogen bonding) can actually co-exist and appreciably affect the properties of PF resins (see below).

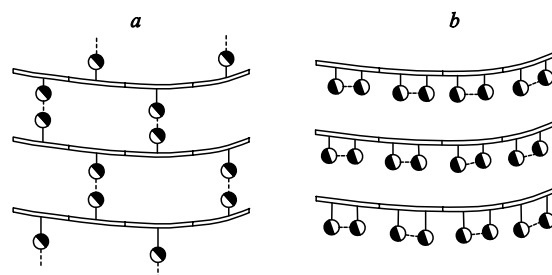
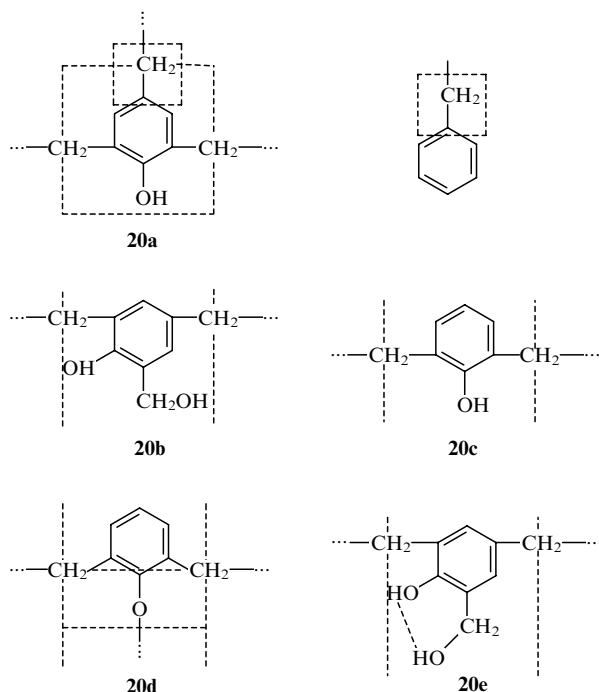


Figure 30. A scheme of a network of hydrogen bonds; (a) hydrogen bonding between neighbouring chains; (b) hydrogen bonding within the same repeating unit.

The cured PF resin can contain the following structures (the cross-link point is shown near the structure **20a**):



The structure **20a** constitutes only the network, the repeating fragment of which is marked by dashed lines. The cross-link point is specified within the repeating fragment (in accordance with our definition of the chemical structure of the cross-link point).

Let us calculate the glass transition temperature of the network using Eqn (6). It is reasonable that the entire cross-link point contains three of these sets of atoms. The data for structure **20a** are given in Table 1.

Substituting the values of the parameters for the ideal structure **20a** in Eqn (6), we get

$$T_g = \frac{101.1}{21.5 \cdot 3 + 71.6} \times 10^3 = 743 \text{ K}.$$

The calculated T_g is much higher than the experimental T_g values. The experimental values of the parameters are listed below: $T_g = 343\text{--}433 \text{ K}$, $\rho = 1.24\text{--}1.33 \text{ g cm}^{-3}$, $n = 1.57\text{--}1.63$, $\alpha = (18.0\text{--}22.5) \times 10^{-5} \text{ K}^{-1}$, $C_p = 29\text{--}48 \text{ cal mol}^{-1} \text{ deg}^{-1}$.

Hence, the actual network differs in structure from the ideal one.

The possible structure **20b** of PF resins corresponds to a linear polymer (the repeating unit is marked by dashed lines). The data for this structure are listed in Table 1.

If both OH groups are involved in the formation of the hydrogen bonds between the chains (see Fig. 30), then

$$\begin{aligned} \sum_j b_j &= 2b_h + b_m; \\ \sum_j b_j &= (-139.6 \times 2 + 16.0) \times 10^{-3} = \\ &= -263.2 \times 2 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}. \end{aligned}$$

Substitution of the values of all parameters in Eqn (5) gives the following T_g value of the ideal linear structure **20b**:

$$T_g = \frac{123.05}{505.4 - 263.2} \times 10^3 = 508 \text{ K}.$$

As for the structure **20a**, this value is beyond the experimental temperature interval in which the α -transition for PF resins is observed.

The structure **20c** forms only linear chains; their repeating unit is enclosed by dashed lines. The following relationship is valid for such a structure

$$\begin{aligned} \sum_j b_j &= b_h + b_m = (-139.6 + 16.0) \times 10^{-3} = \\ &= -123.6 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}. \end{aligned}$$

By substituting the values of the parameters in Eqn (5) we can obtain T_g of the ideal structure **20c**.

$$T_g = \frac{99.05}{331.9 - 123.6} \times 10^3 = 476 \text{ K}.$$

This value is somewhat higher than the observed temperature interval of α -transition for PF resins.

The structure **20d** forms a network the repeating fragment of which is shown by dashed lines (the cross-link point of the network is enclosed by dashed lines). All parameters for the structure **20d** are given in Table 1. Substituting the values of the parameters in Eqn (6), we get the T_g value of an ideal network based on the structure **20d**

$$T_g = \frac{91.25}{56.5 + 120.7} \times 10^3 = 515 \text{ K}.$$

Thus, the glass transition temperature of such a highly cross-linked polymer network is rather high.

The structure **20e** has the same molecular formula as the structure **20b**; however, hydrogen bonding occurs within the same repeating unit. Such a structure was described by Nikolaev.⁹¹

If hydrogen bonds are formed between the neighbouring OH groups within the same repeating unit, then no formation of the physical network between the chains due to the hydrogen bonds occurs. Then the following should be taken into account when

determining the $\sum_j b_j$ value for calculating the glass transition

temperature: the fact that the structure **20e** is linear requires the introduction of the b_m increment to account for the m -substitution in the aromatic ring; in addition, there are two branchings from the aromatic ring, which requires introducing two b_d increments. Then

$$\begin{aligned} \sum_j b_j &= b_m + 2b_d = 16.0 - 2 \times 55.4 = \\ &= -94.8 \times 10^{-3} \text{ Å}^3 \text{ K}^{-1}. \end{aligned}$$

Substituting the values of all parameters of the structure **20e** in Eqn (6), we obtain

$$T_g = \frac{123.05}{505.4 - 94.8} \times 10^3 = 300 \text{ K}.$$

This T_g value is below the temperature interval of α -transition for cured PF resins.

None of the calculated glass transition temperatures of possible ideal structures of PF resins fall into the interval in which experimental values are observed. This suggests that the cured PF resin has a more complex structure than the ideal structures considered above, which has been noted by most investigators. It is most likely that the actual structure of PF resins consists of a set of the considered ideal structures.

To establish the most plausible actual structure of PF resins, let us calculate, in addition to T_g , such characteristics of cured PF resins as density ρ , the refractive index n , the coefficient of volume

Table 5. Calculated characteristics of ideal structures of cured PF resins.

PF structure	T_g / K	ρ / g cm ⁻³	n	$10^4 \alpha$ / K ⁻¹	C_p^s / kcal mol ⁻¹ deg ⁻¹
20a	743	1.253	1.621	1.30	31.9
20b	508	1.250	1.583	1.89	42.4
20c	476	1.205	1.604	2.02	31.4
20d	515	1.301	1.645	1.86	26.1
20e	300	1.250	1.583	3.20	42.4

expansion α_G , and the molar heat capacity C_p^s . These characteristics were chosen with account of their sensitivity to the changes in the structural formula of the substance and of the fact that both the increase and decrease in the values of other characteristics can be observed for different ideal structures of PF resins with the increase in the glass transition temperature. The latter is of importance for searching the most plausible structure of PF resins using the experimental design method.

The calculated densities of PF resins for structures **20a–20e** are listed in Table 5.

The refractive index n was calculated using the following equation⁷

$$\frac{n^2 - 1}{n^2 + 2} = \frac{k R_f}{N_A \left(\sum_i \Delta V_i \right)_f}, \quad (62)$$

in which the molar refraction of the repeating fragment R_f is the sum of the refractions R_i of particular atoms and increments for different types of bonds (double and triple bonds).

The n values for different structures found using Eqn (62) are listed in Table 5.

The calculations of the molar heat capacity C_p^s in the glassy state of the polymer were carried out using the following relationship⁹²

$$C_p^s = \sum_i C_{p,i}^s \Delta V_i - 0.77,$$

where $C_{p,i}^s$ are the partial heat capacities characteristic of each atom and ΔV_i are the van der Waals volumes of the atoms.

The coefficient of volume expansion α is related to the glass transition temperature by the following relationship⁷

$$\alpha = \frac{0.096}{T_g}.$$

Comparison of calculated and experimental values of the characteristics of possible ideal structures of PF resins (see Table 5) allows one to conclude that a cured PF resin represents a set of structures rather than an ideal network. The experimental design method of construction of simplex lattices and polynomial 'composition–property' models was applied to multicomponent systems to find such a set of structures.⁸⁹

It has been found⁸⁹ that one possible relation between the relative content of ideal structures corresponding to the permissible set of network structures has the form $\alpha_1 = \alpha_5 = 0.345$, $\alpha_3 = 0.2$, and $\alpha_4 = 0.11$, where α_1 , α_3 , α_4 , and α_5 are the mole fractions of the structures **20a**, **20c**, **20d**, and **20e**, respectively.

The following values have been found for the actual network, viz., $T_g = 429$ K, $\rho = 1.248$ g cm⁻³, $n = 1.6057$, $\alpha = 2.238 \times 10^{-4}$ K⁻¹, and $C_p^s = 34.8$ cal mol⁻¹ deg⁻¹. All these values fall into the range of experimental values (see Table 5).

Taking into account the narrow limits of the permissible set of ideal structures of cured PF resin, it is possible to conclude that the actual network structure considered is close to the most plausible one.

Thus, comparing the experimental and calculated characteristics of complex highly cross-linked network systems allows one to draw certain conclusions on their structure.

IX. Conclusion

The study of the influence of the chemical structure of highly cross-linked polymer networks on their properties shows that the passage from sparse networks to highly cross-linked networks occurs when the number of the repeating units between the cross-link points is reduced to 4–5. Changes in the properties become particularly noticeable as the number of repeating units is reduced to 1–2 or becomes less than 1. Changes in the chemical structure of a highly cross-linked network to an extent that it only vaguely resembles that of the initial network is the main reason for principal changes in the network properties.

Numerous studies of the structure and properties of highly cross-linked networks have shown that the classical theory of rubber elasticity becomes inapplicable to the description of the dependence of the equilibrium rubbery modulus on the distance between the cross-link points. The same is also valid when solving the inverse problem (estimation of the distance between the cross-link points from the experimentally measured equilibrium rubbery modulus). This required the development of altogether new approaches and methods for assessing the structure and properties of highly cross-linked polymer networks. An analysis of the potentialities of the equations and computational schemes proposed has shown that the distance between the cross-link points can be estimated with a good accuracy by comparing experimental and calculated glass transition temperatures. The proposed generalised equation for evaluating the equilibrium rubbery modulus makes it possible to perform calculations with a good accuracy for both highly cross-linked and sparse networks. All the relationships considered in this review require no fitting parameters and allow one to analyse the properties on the basis only of the chemical structure of the network. Mention should be made of yet another important circumstance, viz., any change in the network topology (the appearance of dangled chains, branchings, isolated loops, and cycles) results in changes in its chemical structure and, as a consequence, in changes in the physical properties.

This approach is of fundamental importance for designing cross-linked polymers with unusual properties. Primarily it concerns gradient-modulus polymeric materials in which the modulus of elasticity changes by a factor of 1000–10 000 within the same specimen in a prescribed manner. In this case it has been possible to eliminate the major drawback of the polymers in the zone of transition from the glassy to the rubbery state and possessing pronounced viscoelasticity. In addition to the moduli of elasticity characteristic of the transition zone, the new materials obtained possess elastic behaviour rather than viscoelastic behaviour.

Yet another example is the use of this approach for predicting the unusual properties of cross-linked polymers followed by the synthesis of these materials that have found application in the photoelasticity method.

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Polychlorobiphenyls: problems of the pollution of the environment and technological neutralisation methods

L N Zanaveskin, V A Aver'yanov

Contents

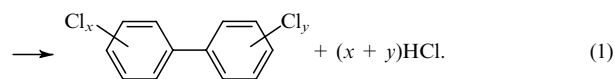
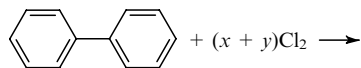
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Abstract. The principal sources of the pollution of the environment by polychlorobiphenyls are indicated and their ecological danger is estimated; the output in the manufacture and applications of polychlorobiphenyls are quoted. The known methods for the neutralisation of polychlorobiphenyls are examined. The methods considered are analysed and their practical significance for industry is estimated. The bibliography includes 277 references.

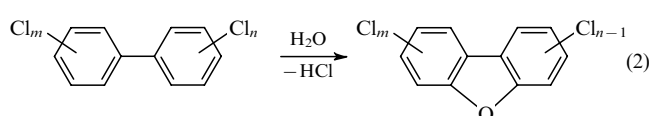
I. Introduction

Polychlorobiphenyls (PCB) possess a series of unique physical and chemical properties: exceptional thermophysical and electrical insulating characteristics, thermal stability, inertness to acids and bases, fire resistance, satisfactory solubility in fats, oils, and organic solvents, high compatibility with resins, plasticity, resistance to corrosion, and an excellent capacity for adhesion.^{1–9} All these features are responsible for their wide-scale employment as dielectrics in transformers and capacitors,^{1, 3, 7, 10–18} as hydraulic liquids,^{10, 13, 16–20} as heat exchangers and refrigerants,^{1, 3, 6, 9, 10, 12–14, 16–18, 20} as lubricating oils,^{3, 6, 16, 17, 20} as components of varnishes, paints, and adhesive compositions,^{6, 10, 14, 15–17, 20–24} as plasticisers and fillers in plastics and elastomers,^{1, 3, 6, 16, 17, 20, 24} as antipyrenes,^{1, 9, 15, 20, 25} and as solvents.^{1, 6, 16, 22}

The industrial synthesis of PCB is based on the substitutional chlorination of biphenyl in the presence of electrophilic substitution catalysts.^{7, 26}



Polychlorodibenzofurans (PCDF) are formed as side products:⁷



There are 209 individual PCB differing in the number and positions of chlorine atoms in the molecule. Depending on the content of chlorine atoms, PCB have different numbers of isomers (Table 1).

Table 1. The number of possible PCB isomers for different contents of chlorine atoms in the molecules.²⁷

Name of PCB	Molecular formula of PCB	No. of isomers
Monochlorobiphenyl	C ₁₂ H ₉ Cl	3
Dichlorobiphenyl	C ₁₂ H ₈ Cl ₂	12
Trichlorobiphenyl	C ₁₂ H ₇ Cl ₃	24
Tetrachlorobiphenyl	C ₁₂ H ₆ Cl ₄	42
Pentachlorobiphenyl	C ₁₂ H ₅ Cl ₅	46
Hexachlorobiphenyl	C ₁₂ H ₄ Cl ₆	42
Heptachlorobiphenyl	C ₁₂ H ₃ Cl ₇	24
Octachlorobiphenyl	C ₁₂ H ₂ Cl ₈	12
Nonachlorobiphenyl	C ₁₂ HCl ₉	3
Decachlorobiphenyl	C ₁₂ Cl ₁₀	1

Technical PCB mixtures produced by industry consist of 50–70 individual compounds. Most of them contain between 3 and 8 chlorine atoms, although there are small amounts of both more and less chlorinated PCB. These mixtures are known under different names: Arochlor (USA), Phenochlor (France), Chlophen (Federal Republic of Germany), Kanechlor (Japan), Fenchlor (Italy), and Sovol (Russia). The proportions of PCB in the Arochlors are presented in Table 2.

The world manufacture of PCB has increased successively from 1929 to 1970 when these compounds were recognised as

L N Zanaveskin The 'Sintez' Research Institute, Ugreshskaya ul. 2, a/Box 56, 109432 Moscow, Russian Federation. Fax (7-095) 279 46 84. Tel. (7-095) 279 83 29

V A Aver'yanov Tula State University, prosp. Lenina 92, 300600 Tula, Russian Federation. Fax (7-087) 233 13 05. Tel. (7-087) 225 18 40

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Table 2. Approximate composition of various Arochlors (%).

PCB	[Cl] (mass %)	Brand of Arochlor			
		1242	1248	1254	1260
C ₁₂ H ₉ Cl	18.8	3	—	—	—
C ₁₂ H ₈ Cl ₂	31.8	13	2	—	—
C ₁₂ H ₇ Cl ₃	41.3	28	18	—	—
C ₁₂ H ₆ Cl ₄	48.6	30	40	11	—
C ₁₂ H ₅ Cl ₅	54.4	22	36	49	12
C ₁₂ H ₄ Cl ₆	59.0	4	4	34	38
C ₁₂ H ₃ Cl ₇	62.8	—	—	6	41
C ₁₂ H ₂ Cl ₈	66.0	—	—	—	8
C ₁₂ HCl ₉	68.8	—	—	—	1

pollutants of the environment.¹⁶ Towards the end of the 1980s, the total amount of PCB produced was estimated as 1 million tonnes.^{16,17} Analysis of the pattern of the consumption of PCB in various countries showed that about 40% of this amount, *i.e.* 400 000 tonnes enter the environment, while the remaining 600 000 tonnes, at the time when the estimate was made, was still being used or was stored in settling tanks.¹⁷ According to later estimates, even after the prohibition of the manufacture of these products in the USA, Japan, and a number of European countries, the content of PCB in the environment hardly changed.

The nature and dynamics of the distribution of PCB in the environment is in many respects determined by their physical properties such as persistence, chemical inertness, fairly high vapour pressure, and capacity for diffusion.^{1–9,26–33} The persistence of PCB makes it possible to include them among typical xenobiotics which are not very susceptible to the action of a wide variety of microorganisms and animal enzyme systems.³⁴ Persistence combined with lipophilicity promotes the bioaccumulation of PCB in the fatty tissues of man and animals in amounts dangerous for vital activity.^{9,10,16,17,35–37} Chemical inertness is responsible for the resistance of PCB to the action of environmental abiotic factors, the relatively high vapour pressure facilitates their spreading in the atmosphere, while their capacity for diffusion favours their migration in the soil and in subterranean and surface waters.

Despite the gradual reduction of the applications of PCB in the economy, they continue to pollute the environment^{4,10} and nowadays these toxic products, which have spread virtually throughout the entire terrestrial globe, are present in the organism of each of us.^{10,16} As PCB are incorporated in the biological chains, the weakly chlorinated components are progressively lost by virtue of their selective biotransformation.^{8,9,28,37,38} The most dangerous highly chlorinated PCB therefore accumulate in the human and animal organisms.

According to data of the World Health Organisation,²⁸ the principal ways in which PCB enter the environment are as follows: vaporisation from plasticisers; evolution on combustion of industrial and domestic waste and also when transformers, capacitors, and other industrial equipment in which PCB are used are switched on; leakage together with other industrial waste; the

removal of PCB to rubbish dumps and aeration fields; other unmonitored pathways.

The environment is polluted mainly *via* the first three pathways. The typical PCB concentrations in various objects in the environment²⁷ are as follows: in the air of agricultural regions 0.05 ng m⁻³, in the air of cities 1–5 ng m⁻³; on the surface of soil 2–50 µg kg⁻¹; in plants 10 µg kg⁻¹; in water 2 ng litre⁻¹; in fatty tissues 1 ng kg⁻¹; in human breast milk 10 µg kg⁻¹; in the organisms of marine animals 5–50 ng kg⁻¹; in the fat of the otter 5–200 ng kg⁻¹.

The potential danger of PCB is associated with their use in open systems, with possible spillage, with leakage and vaporisation from capacitors, transformers, and other elements of equipment in the course of their cleaning, emptying, and filling, with the breakdown of hermetic seals in equipment, and with the occurrence of fires in plant where PCB are employed as dielectric liquids or heat exchangers.^{7,8,16,17,36–42} An example of mass poisoning of people by PCB as a consequence of the breakdown of hermetic seals in heat-exchange apparatus in the course of the refining of rice oil is known. This incident, which has entered history as the 'Yusho incident', occurred in Japan in 1968. The symptoms of poisoning were an increase in the size and hypersecretion by mammary glands, nausea, vomiting, enlargement and porphyria of the liver, pathological changes in the peripheral nervous system and in the composition of blood, and disturbance of the functioning of adrenal glands.

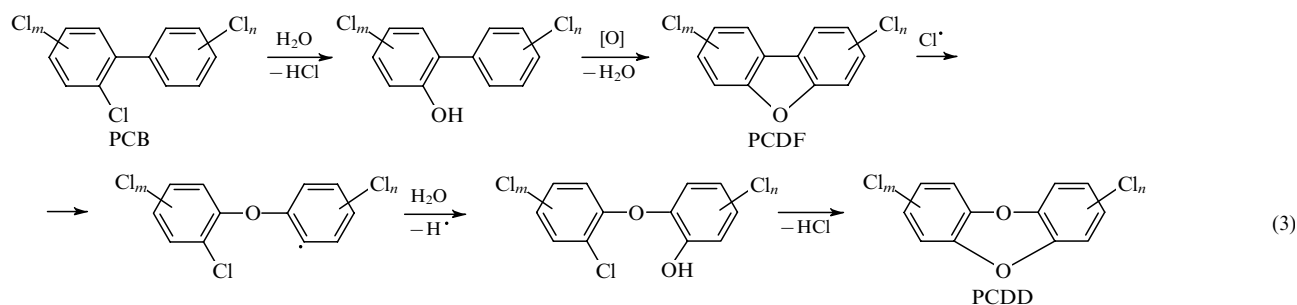
Thermal overloading or fires in plant (transformers, capacitors) in which PCB-containing materials were employed as dielectrics or refrigerants constitutes a major hazard to the environment, because uncontrolled combustion of PCB results in the formation of the highly toxic polychlorodibenzodioxins (PCDD) and polychlorodibenzofurans (PCDF).^{7–9,39,40,42–45} According to certain ideas,^{7,46,47} such transformations may occur in accordance with processes (3).

The combination of persistence, chemical stability, and lipophilicity of PCB creates the possibility of their bioaccumulation in lipid-rich liver, kidney, adrenal gland, lung, and brain tissues of man and animals.^{1,4,8,15,28} The concentration of PCB in human blood and milk has been noted.^{1,7,16,28}

Until recently, the toxicity of PCB remained controversial. Some investigators denied the existence of a connection between various diseases and the presence of PCB in human and animal organisms, others attributed a number of serious toxicological effects, causing chronic illnesses, to the action of PCB.^{1,5,7,9,15,16,24,35,48,49}

More rigorous studies carried out recently made it possible to discover a whole spectrum of the toxic effects of PCB on man and laboratory animals, including lethal effects, harmful influence on reproduction and development, liver porphyria, weight loss, dermatological effects, suppression of the immune system, disturbance of the functioning of the kidneys, atrophy of the thymus, carcinogenesis, disorganisation of the homeostasis of the steroid hormones, and a mutagenic effect.^{37,45,50}

The massive effect of PCB on ecosystems as a whole and on man in particular is intensified by constantly operating factors such as the increase in the content of PCB in water and aqueous ecosystems as a result of the entry of surfactants into the latter,² the biotransformation of PCB in the environment into still more



toxic products,⁵¹ and the accumulation of PCB in human and animal organisms as a consequence of their accumulation in the food chains.³⁷ The increase in the level of PCB in living organisms and the destruction of animals induced by this, sometimes on a mass scale, noted in a number of regions of the planet (particularly in the aquatic systems of the Pacific Ocean), indicates the potential danger of the bioaccumulation of PCB to populations of living organisms and whole ecosystems.^{7, 18, 37} It has to be borne in mind that, by virtue of their chemical and thermal stability and exceptional operating properties, the PCB-containing materials produced earlier by industry will continue in use for a long time yet (more than 20 years) in active closed systems.⁵²

Thus the danger of the accumulation of PCB in living organisms and the threat of the destruction of populations and whole ecosystems, as well as the potential possibility of leakages or a series of discharges from settling tanks and active plant have raised the problem of the pollution of the environment by these compounds to the class of global environmental problems.

Bearing in mind the very serious level of environmental danger, Canada, the USA, Japan, the countries of the EEC, and other states have developed measures regulating the manufacture, use, processing, and destruction of PCB.^{8, 18, 35, 53–63} These measures include the following: complete prohibition of the manufacture of PCB, gradual replacement of PCB by alternative materials with less toxic properties, the monitoring of materials containing PCB in the course of their employment, storage, transport, and distribution, the development of effective ecologically safe technologies for the processing and neutralisation of PCB-containing materials, the monitoring of the neutralisation and processing of waste, and the development of new rules for the operation of plant in which PCB is employed taking into account more stringent requirements for the ecological safety of industries.

The possibility of the gradual removal of PCB-containing materials from the sphere of man's economic activity and of a universal ban on their manufacture depends on the solution of the problem of the replacement of PCB by new materials with similar operating characteristics but with a significantly lower toxicity. The question of the search for substitutes of PCB-based dielectric materials is most acute.

New compositions and individual compounds have been obtained and tested in recent years. They have been recommended as substitutes for PCB in transformers and capacitors. For example, these are mineral and silicone oils,^{9, 17, 64–66} high-molecular paraffins,^{9, 65} alkylated biphenyls and terphenyls,^{9, 17} esters of phosphoric, phthalic, and other carboxylic acids,^{9, 17} and esters of polyhydric alcohols.⁶⁵ While less toxic, these substances approach PCB as regards their dielectric properties but are inferior to them in chemical inertness and resistance to combustion.

Less toxic polychlorotoluenes⁶⁷ and chloromethylbenzenes⁶⁸ have been proposed for the replacement of PCB in hydraulic systems.⁶⁸ The report of the promising application of absolutely nontoxic and chemically stable perfluorinated organic compounds as components of lubricating oils merits attention.⁴¹

However, overall the search for new materials to be used as substitutes for PCB for various purposes has been fragmentary.

In the system of measures designed to lower the degree of pollution of the environment, the conservation of PCB removed from the sphere of economic activity in settling tanks or storage sites occupies a definite place.^{5, 35, 69–77} In practice, various storage methods are employed, but the safest is the method involving enclosure in glass.⁷¹ However, there is no information about the ecological risk when this operation is performed. Thus enclosure in glass may entail the formation of toxic PCDD and PCDF and their subsequent diffusion together with PCB into the environment. The hardening method is widely used in the storage of PCB, but it cannot guarantee their complete isolation from the environment.^{70, 76, 77} The main disadvantages of the method involving the storage of hardened PCB are as follows: as a consequence of the appreciable volatility and diffusibility as well

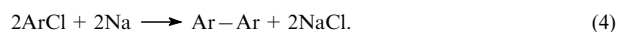
as the leaching of PCB, one cannot rule out the possibility of their entry into soil, underground and surface waters, and the atmosphere; the need to search for storage sites remote from populated areas, definite requirements for geological structures at the storage sites, and the continually rising cost of this operation;^{69, 72, 74} One should also take into account the negative attitude of the population to the possibility of storage of any waste on adjacent territories.

The storage of undecomposed PCB in settling tanks is a less reliable method of their conservation. The inevitability of the diffusion of PCB from the settling tanks is aggravated by the probability of accidents at the storage sites.

The most promising procedure for lowering the amount of PCB in the environment involves their conversion into environmentally safe products. One may identify the following methods for the processing of PCB: chemical and electrochemical dechlorination, thermal, photochemical, and radiation-chemical and biotechnological methods, oxidation, and hydrogenolysis. These methods may include operations involving the concentration of PCB before treatment. Such operations include extraction, adsorption, dialysis, vaporisation, distillation, and filtration.^{5, 18, 25, 63, 50, 77–88} Operations of this kind acquire particular importance when the removal of residual PCB from transformers and capacitors is required. By virtue of the application of extraction by liquids at the critical temperature and pressure, the effectiveness of the extraction of PCB from plant to be cleaned has increased in recent years.^{80, 85, 87}

II. Reagent-based neutralisation methods

Diverse reagents, reaction conditions, catalytic systems, and apparatus are used in the chemical methods for the neutralisation of PCB. The reagents are usually alkali metals (Na, K, Li),^{9, 52, 80, 89–97} with the aid of which a version of the Wurtz reaction takes place:⁹⁸



In this method, use is made of the dechlorinating effect of the alkali metal (in particular, sodium). The organic dechlorination products are high-molecular polynuclear compounds.

According to the ideas developed by Oku *et al.*,⁹⁹ the mechanism of reaction (4) includes the following stages:



In the presence of compounds containing relatively mobile hydrogen (hexane, cyclohexane, other hydrocarbons), the aryl radicals are involved in a chain of new reactions:



The main result is the substitution of the chlorine atoms in PCB by hydrogen *via* reaction (7). Thus hydrocarbons with fairly reactive C–H bonds regulate the average molecular mass of the dechlorination products, but are themselves decomposed in this process. The regulating function of hydrocarbons is important because it permits the retention of the possibility of further dechlorination of PCB at advanced stages of the reaction with respect to chlorine, whereupon contact between the sodium atoms and the chlorine atoms still present in the polynuclear chlorination products becomes sterically hindered.

In order to decompose PCB, the alkali metal is usually dispersed in the bulk of the material being treated or a hydrocarbon solvent is used as the reaction medium. A version of the process in a flow system using the alkali metal (Na or K) deposited on an inert material as the reagent has also been described.⁸⁹ This method is characterised by a high degree of decomposition of

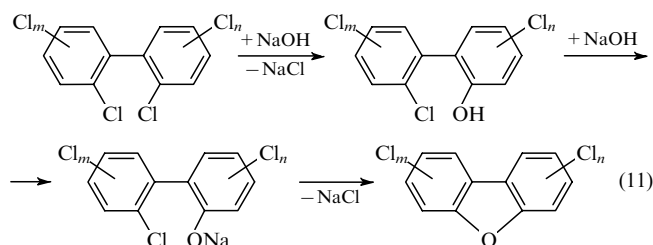
PCB, but its application is held back by a series of limitations and deficiencies — the high cost of the neutralisation process, increased danger of the process, and conversion of the treated compounds into high-molecular products which lower the quality of the materials being purified. Furthermore, alkali metals may interact with valuable components of the materials being purified, exerting a negative effect on their operating characteristics.¹⁰⁰

There are data concerning the use of alkaline earth and other metals, such as Mg, Ca, Fe, Sb, Zn, and Pb^{101, 102} in a molten salt and in the vapour phase^{101, 103} for the dechlorination of PCB. As regards safety and dechlorination efficiency alkali metal naphthalides and anthracides have a definite advantage over alkali metals.^{18, 77, 104–107} The higher efficiency of the dechlorination by the naphthalides and anthracides is due to the possibility of increasing the degree of dispersion of the reagent down to the molecular level. On the other hand, the metals in the compounds specified are chemically bound and this makes them more inert to oxygen and water, which increases the safety of the process in its turn. Compounds between alkali metals and carbon are a variety of reagents of this type.¹⁰⁸ The main disadvantages of the dechlorinating agents listed is the difficulty of isolating them from the reaction mass and the fact that high-molecular products, exerting a negative influence on the quality of the neutralised material, are formed with participation of the given reagents.

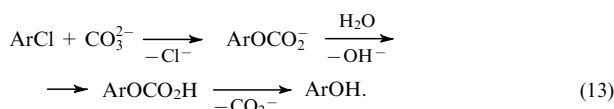
Strong bases — alkali and alkaline earth metals and oxides and hydroxides,^{77, 80, 101, 102, 109–115} alkoxides, glycolates, and polyglycolates^{18, 77, 80, 85, 95, 116–123} — constitute a large group of reagents. Alkali metal carbonates or hydrogen carbonates make up yet another group.^{124, 125} Their dechlorinating activity is based on the nucleophilic substitution of the chlorine in PCB. Thus, when aqueous solutions of alkalis are used, the main reaction proceeds in accordance with the equation



Aqueous solutions of alkalis are insufficiently effective and are quite expensive. Furthermore, the presence of chlorine in the 2- and 2'-positions in the PCB being neutralised creates structural preconditions for the formation of PCDF:



Alkali metal glycolates, polyglycolates, carbonates, and hydrogen carbonates are more effective dechlorinating agents, since the polarisability of their anions is greater.^{110, 126}



In contrast to alkali metals, as well as compounds of alkali metals with naphthalene, anthracene, and carbon, these reagents do not require the use of special safety measures, the processes involving them can be readily controlled, and the products obtained after dechlorination can be readily separated from the purified material. In most cases, the methods for the employment of such reagents are universal in relation to the object being treated: they can be applied in the detoxification of soils, sludges, sewage, and simply PCB-containing materials. The disadvantages of these methods are as follows: the need to neutralise the excess alkaline agent with formation of salt waste, the possibility of the impairment of the operating quality of the materials being

neutralised as a consequence of the formation of hydrolysis and alcoholysis products, the rapid wear of the equipment working in corrosive media at high temperatures.

In view of the existence of the last problem, the process involving the detoxification of PCB-containing materials by alkaline agents, initiated with ultrasound under milder conditions, merits attention.¹¹⁵ The influence of alkaline reagents on the quality of the processed materials imposes certain limitations on their content of PCB: it should not exceed 1 mass %.¹⁰⁰

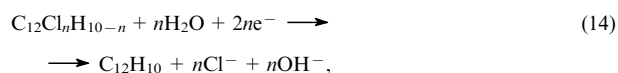
The oxidation–reduction processes with participation of a wide variety of oxidants and reductants constitute a separate group of methods for the chemical detoxification of PCB-containing materials. The oxidants include hydrogen peroxide, sodium iodate,^{125, 127} permanganates, persulfates and perborates,⁴⁹ and peracetic acid,¹²⁸ while the reductants comprise the hydrides of alkyl derivatives of alkaline metals,⁹⁵ alkali and alkaline earth metal hydroborates,^{49, 129} and alcohols.^{130, 131} When alcohols are used as the reducing agents, the attainment of the necessary rate of the process requires either more severe conditions (170–200 atm, 150–350 °C) or the radical reduction reaction must be carried out in the presence of alkali metal hydroxides and chemical initiators.

The methods indicated require the application of expensive reagents and can hardly be recommended for industrial application.

Methods for the processing of PCB involving their interaction with elemental sulfur in the vapour phase at high temperatures are of undoubted practical interest.^{59, 130, 132} An environmentally safe polymeric product is obtained and can be used as an additive to asphalt, a binder for concrete, a vulcanising agent for raw rubber, and as a material for the preparation of resistors. The products SCl_2 and CS_2 formed together with the polymer can be readily separated from the latter together with the unreacted elemental sulfur, which is returned to the process. This method is suitable exclusively for the treatment of concentrated PCB, but the possibilities for its wide-scale application are restricted by the available elemental sulfur resources.

III. Electrochemical methods

The majority of the known methods for the electrochemical oxidation and reduction of PCB are used within the framework of laboratory research.^{77, 133–141} Certain results are promising as regards energy expenditure¹³⁴ and apparent yields,¹⁴² but overall the prospects for the application of these methods in industry are at the present time small owing to the insufficiently high degree of conversion of PCB^{137, 141} and the high requirements which must be met by the purity of the initial PCB. However, the interest in the electrochemical methods has persisted for several reasons. Firstly, it is possible to organise the process under the conditions of cathodic reduction:



which imparts to it resource-saving qualities. Secondly, electrochemical devices are suitable for the creation of mobile systems for the processing of waste at the site of their formation and accumulation. Thirdly, such devices have an advantage in the conversion of dielectric liquids, lubricating oils, and other spent PCB-containing materials into a valuable hydrocarbon fuel.

IV. Pyrolytic methods

Among the pyrolytic methods for the decomposition of PCB, the process in which a hollow tube heated from the outside by electrodes or other electrically heated elements merits attention.^{16, 122, 142–144} Porous graphite may be used for the preparation of the tube. In order to avoid the breakdown of the material of the reactor, a stream of nitrogen or other inert gas is passed from the outside into the porous surface.

The PCB decomposition products are a solid carbon residue and gases, mainly HCl and Cl₂, as well as a certain amount of organochlorine compounds. The gases are trapped in series-connected absorbers irrigated with water and an alkaline solution and also in an adsorber with activated charcoal. In order to ensure the effective destruction of the PCB and a decrease in process temperature, it is recommended that a small amount of oxygen be added to the initial mixture.¹²²

In order to attain the quantitative decomposition of PCB, in certain cases the pyrolytic processes are carried out on solid catalysts, activated charcoal, metallic Zn, Ni, Cu, Fe, Al, Pb, Pt, Rh, and Cr or the oxides, carbonates, and silicates of these metals.^{145–147}

One of the difficulties in the application of pyrolytic methods is the difficulty of achieving an effective supply of heat to ensure the specified temperature. This problem can be solved successfully if the process is carried out in salt melts.^{87, 148} Nevertheless pyrolysis in melts has hardly come to be widely used, since equipment wears rapidly in a salt medium and the high temperatures needed to apply these methods render industries of this kind dangerous.

The plasma pyrolysis occurring at temperatures from 5000 to 25 000 °C involves the complete decomposition of PCB; H₂, CO, CO₂, HCl, CH₄, H₂O, and elemental carbon being formed as the products.^{87, 149–151} The presence of oxygen-containing compounds in the products is associated with the use of alcohols as solvents for the preparation of the initial mixtures.¹⁵¹

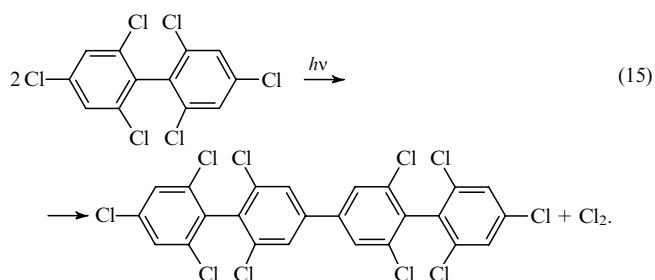
A novel method for the pyrolysis of PCB has been put forward in France.¹⁵² The process is carried out at 1500 °C in the presence of water vapour. The main reaction products are chlorine and C₁–C₂ hydrocarbons. The chlorine is absorbed by a solution of alkali while the hydrocarbons are used as a fuel.

In the communications quoted above, devoted to pyrolytic decomposition methods, the degree of decomposition of PCB is quoted as the sole criterion of the effectiveness of the processes and this parameter is in all cases close to 100%. The lack of any kind of data on the composition of the products with different degrees of conversion hinders even a preliminary interpretation of the process mechanisms. Certain conclusions about the initial period of the pyrolytic decomposition of PCB can be made on the basis of the results of a detailed study of the pyrolysis of chlorobenzenes in the region of relatively low temperatures.^{153, 154} The principal pyrolysis products under these conditions are chlorobiphenyl and dichlorobiphenyl and the reactions responsible for their formation are reversible. Adopting the principle of microreversibility as a guide,¹⁵⁵ the proposed mechanism of the pyrolysis of chlorobenzenes can be extended also to the pyrolysis of polychlorobiphenyls.

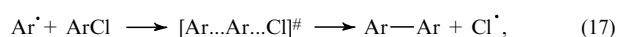
An important advantage of the pyrolytic methods compared with the widely used combustion is the absence of the highly toxic PCDF and PCDD from the products. However, the large energy consumption in these processes increases their cost and impairs their ecological parameters. Furthermore, the pyrolytic process is relatively unselective and is therefore unsuitable for the dechlorination of materials with a low PCB content. To a certain extent, these disadvantages are overcome by employing catalytic pyrolysis, but the formation of pyrolytic carbon leads to rapid deactivation of the catalyst.

V. Radiation and photochemical dechlorination methods

The radiation and photochemical dechlorination methods are being rigorously investigated.^{2, 77, 156–181} Their successful application does not require additional chemical reagents.^{77, 156–165} The processes can be described by the following stoichiometric equation in relation to the dechlorination of 2,2',4,4',6,6'-hexachlorobiphenyl:¹⁸²



Thermokinetic analysis^{155, 183} made it possible to put forward the following mechanism of the photochemical dechlorination:

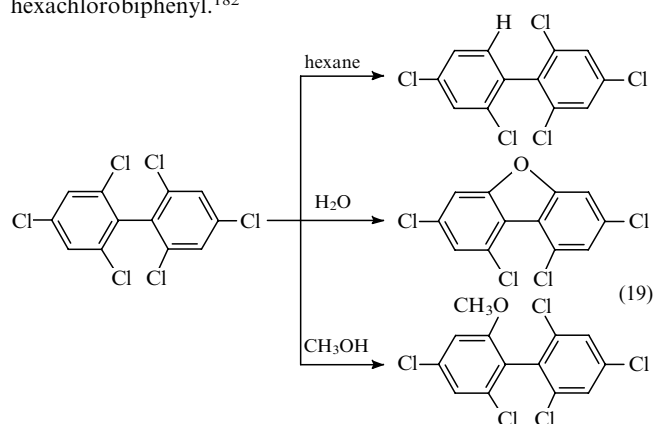


Evidently in the dechlorination initiated by γ -quanta the reactions involving the homolysis of the C–Cl bond are accompanied by competing reactions in which the C–H and C–C bonds are homolysed.

An advantage of the radiation and photochemical methods compared with the reagent-based dechlorination methods is simpler composition of the products and the absence of salt waste. However, the very low quantum or radiation-chemical yields of these processes lead to large energy expenditures and hence an impairment of the economic parameters of the industrial processes. In this connection, the search for photocatalytic systems and methods whereby the reagent concentration fields can be altered in the initiation stage in order to achieve the selective absorption of energy quanta and their effective utilisation for the generation of the necessary intermediates are of definite interest.^{156, 157, 159, 160, 163–167, 173, 184} On the other hand, the possibility of economising on the energy by increasing the quantum and radiation-chemical yield is limited because the rate constants for reaction (17) are low at the low temperatures characteristic of these processes¹⁵³ and conditions for the occurrence of chain processes are not therefore realised.

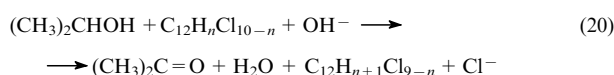
Radiation and photochemical dechlorination may find a practical application for the neutralisation of industrial and domestic sewage, provided that more effective and selective methods are developed for the application of energy to PCB-containing materials. In this sense, the report on the detoxification of waste waters in the presence of titanium dioxide on treatment with ultrasound under normal conditions merits attention.¹⁸⁵

The nature of the products of the photochemical and radiation-chemical dechlorination changes in the presence of compounds containing comparatively mobile hydrogen (cyclohexane, other hydrocarbons, alcohols, water, sodium tetrahydroborate, etc.)^{169, 172, 173, 175, 176, 179–184, 186} Some of the reactions occurring are indicated schematically below in relation to 2,2',4,4',6,6'-hexachlorobiphenyl.¹⁸²

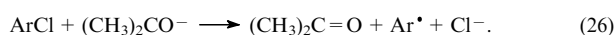
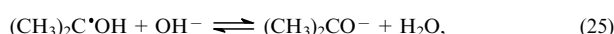
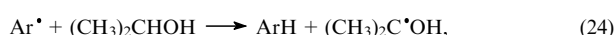
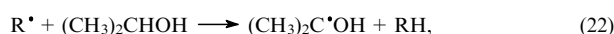
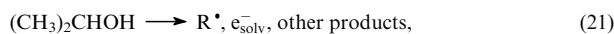


As can be seen, in the presence of hydrocarbons chlorine is replaced by hydrogen, which in fact gives rise to the neutralisation effect. On the other hand, when water and alcohols are used, there is a risk of the formation of the highly toxic PCDF. Evidently this risk exists also under the conditions of the photochemical and radiation-chemical dechlorination of PCB in an oxidising medium.^{46, 166} From the standpoint of the protection of nature, it is therefore useful to employ only hydrocarbons as the reagents. Nevertheless, despite the high reactivity of hydrocarbons in radical reactions, the quantum and radiation-chemical yields remain low and this prevents the introduction of such processes into industry.

When caustic alkali is added to the PCB–alcohol reaction system, the radiation or photochemical dechlorination of PCB by the alcohol proceeds *via* a radical-chain mechanism:^{170, 177–181, 186, 187}



Here the quantum yield increases by two–three orders of magnitude.¹⁷⁹ This effect can be accounted for by the operation of the following mechanism (in relation to the radiation-chemical dechlorination of PCB by the 2-propanol–NaOH system):



It is seen from the scheme presented that the function of alkali is associated with the production of the anion $(\text{CH}_3)_2\text{CO}^-$, which effectively dechlorinates the PCB molecule and regenerates the initial $\text{Ar}^\bullet$ radical by means of electron transfer *via* reaction (26). A significant economy in energy is achieved in this dechlorination method,^{188, 189} but the additional consumption of expensive reagents limits its application.

One should bear in mind that the use of visible and ultraviolet light to initiate the reactions is relatively ineffective owing to the lack of transparency of the majority of the reaction media to waves in this range, while the technique of radiation-chemical initiation is too expensive and the effect obtained does not compensate for the expenditure. When chemical reagents are used as initiators, the caustic alkali–alcohol system may be recommended for the detoxification of sewage and materials with a low PCB content.

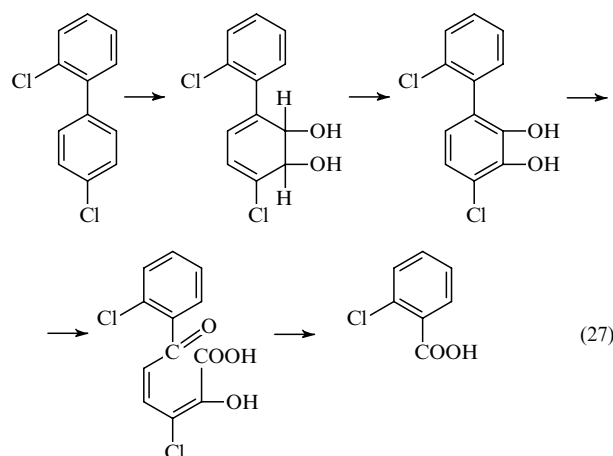
In conclusion of the consideration of dechlorination processes initiated by photochemical reactions, we may mention the method for the decomposition of PCB in the plasma of a radiofrequency glow discharge developed in Japan.¹⁹⁰ The nature of the products formed under these conditions is determined by the nature of the dechlorinating agent. In an oxygen plasma, PCB decomposes to CO_2 , CO , ClO_2 , Cl_2 , and HCl , while in the presence of water vapour CO_2 and HCl are formed. The use of a hydrogen plasma leads to the formation of C_2 – C_7 hydrocarbons (alkanes, alkenes) and HCl . The application of these processes ensures the quantitative binding of PCB without risk of the formation of PCDD and PCDF. Dechlorination in a plasma is most attractive because the hydrocarbons obtained may be used as a fuel. The prospects for this method are associated exclusively with the processing of concentrated PCB. There are so far no data on its industrial tests, which is apparently due to the low productivity of the process and the large energy expenditures.

VI. Biotechnological methods

During the last two decades, investigators have shown a steady interest in the problem of the search for effective PCB biodecomposition methods. This can be accounted for, firstly, by the high resistance of PCB and, secondly, by the fact that biological purification is the concluding stage in many detoxification processes, including the purification of sewage. The object neutralised usually consists of complex mixtures of toxicants and the decomposition of the PCB present in them limits the entire process as a whole.

A series of investigations have been devoted to the problem of the biodegradation of PCB.^{3, 9, 37, 38, 51, 77, 85, 191–202} It has been shown that both pure cultures of micro organisms and their mixtures can be used for the detoxification of PCB-containing materials. The microflora from the bottom deposits in rivers, lakes, and soils and the active sludge from the purification equipment in the cellulose-paper industry and undertakings of the food industry are used as mixtures of microorganism cultures.^{77, 192–198, 200–202} None of the natural strains isolated is capable of fully decomposing PCB, the highly chlorinated PCB being the most resistant to biodegradation.^{100, 200}

The difficulty of the study of the biodegradation mechanism is associated with the complexity of the processes investigated, which constitute a chain of consecutive-parallel reactions, each of which is catalysed by its own enzyme. Nevertheless, many groups of investigators who have studied the aerobic decomposition of PCB by microorganisms maintain a single view on the sequence of reactions leading to the decomposition of these compounds.^{203–214} This sequence includes the following stages: the interaction of an oxygen molecule with one of the aromatic rings of PCB with formation of the corresponding dihydrodiol; the transformation of the dihydrodiol into a dihydric phenol; the cleavage of the aromatic ring and the formation of the chlorinated 2-hydroxy-6-oxo-6-phenylpenta-2,4-dienecarboxylic acid; the formation of chlorobenzoic acid:



The above scheme has been confirmed by mass-spectrometric studies of the intermediate and final biodecomposition products, as well as by chemical tests on the latter.²⁰³ At the same time, on the basis of this scheme one cannot answer the fundamental question concerning the possibility of the intensification of biodecomposition processes.

An increase in the effectiveness of the decomposition of PCB may be promoted by the application of substrates such as sodium acetate²⁰⁰ or inorganic nitrogen and phosphorus compounds²¹⁵ as nutrients for the microorganisms, as well as by the use of mixtures of different cultures^{200, 201} and by the combination of PCB biodegradation processes with other biotechnological processes, for example composting.²¹⁶

The biodegradation methods are very convenient for the dechlorination of PCB dispersed in the environment, for example in soils and water sources, and also for the detoxification of

subterranean waters, sewage, sludge, and domestic waste with a low PCB content.^{3, 9, 51, 77, 85, 192, 194, 195, 200, 216}

The rate of biotechnological purification of sewage can be increased by employing emulsifying agents, which increase the solubility of PCB and PCB-containing oils in water.⁷⁷ The creation of highly productive biotechnological PCB degradation methods is possible if more active strains of microorganisms are cultured. For the productivity achieved at the present time, the biotechnological method for the decomposition of PCB is most reasonably employed at the end of the dechlorination process in combination with other methods, for example chemical and photochemical.^{77, 123, 130, 202} This is favoured also by the high degree of decomposition of PCB molecules containing fewer chlorine atoms in the concluding stage.

Another problem arising when biodegradation methods are employed consists in the preservation of the vitality of the PCB-decomposing microorganisms in the soil, where they should compete effectively with soil microorganisms.

Finally, certain difficulties arise owing to the interaction of PCB molecules with compounds in the bottom deposits and the soil. Such interaction prevents the microbiological decomposition of PCB.

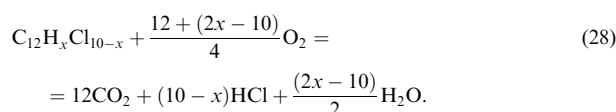
VII. Oxidative methods

Among the methods for the neutralisation of PCB-containing materials, the oxidative procedures predominate. They can be divided into combustion proper and special oxidation methods. The latter include catalytic oxidation, plasma methods, ozonisation, and oxidation under hypercritical conditions.

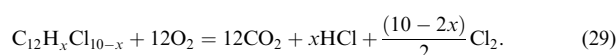
Combustion predominates not only among the oxidative methods but in general among the methods for the detoxification of PCB and PCB-containing materials. This is due to the universality of this procedure as regards the types of materials processed, the ease of controlling the process, and its suitability for various technological versions and conditions of the neutralisation process, which facilitates the creation of mobile apparatus and ensures the possibility of employing the heat of the combustion process, complete decomposition of the PCB in the cycle, *etc.*

The processes involving the combustion of PCB and polychlorobiphenyl-containing mixtures have been the object of numerous investigations^{5, 6, 9, 16, 18, 42, 48, 50, 55, 56, 74, 77, 85, 87, 143, 217–232} in the course of the last three decades, the aim of which consisted in the search for conditions ensuring the most complete oxidation. The requirements which must be met by the PCB combustion processes are fairly rigorous. Thus, according to the standards established by the Environmental Protection Agency in the USA the degree of destruction of PCB in these processes should not be less than 99.9999%.²³³ This is achieved by selecting the optimum ratios of PCB, the oxidants, and the additional fuel as well as the temperature and residence time of the mixture in the combustion chamber.²³⁴ We shall examine the principles governing this choice.

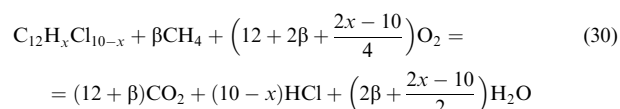
The ratios of the components of the initial mixture are determined primarily by stoichiometric considerations.²³⁴ Thus exhaustive oxidation of the $C_{12}H_xCl_{10-x}$ molecule to CO_2 , H_2O , and HCl should be described by the equation



This equation has a physical significance only for $x > 5$. When $x = 5$, water is not formed. For $x < 5$, the combustion process proceeds in the direction of the formation of molecular chlorine²³⁵ in accordance with the equation



The formation of molecular chlorine is undesirable for two reasons. Firstly, it has a highly corrosive effect on the material of the apparatus used in the combustion processes. Secondly, its quantitative extraction from effluent gases is a difficult problem and requires the use of expensive alkaline agents. Direct combustion of the majority of the commercial PCB mixtures should lead irreversibly to the formation of appreciable amounts of molecular chlorine. The virtually complete suppression of the formation of molecular chlorine in the combustion of highly chlorinated PCB can be achieved by introducing into the initial mixture of PCB and the oxidant an additional hydrocarbon fuel, which is an external source of the hydrogen atoms lacking in the PCB molecules.^{235, 236} If methane is used as such a fuel, the PCB combustion process can be described by the equation



The introduction of a fuel, the amount of which is expressed by the stoichiometric coefficient β , should not only make good the deficiency of the hydrogen in PCB but should also ensure the required temperature of the flame and its stability.

In its turn, the combustion temperature is determined from the condition for the complete suppression of the formation of PCDD and PCDF. The Environmental Protection Agency in the USA recommends that this requirement be satisfied by ensuring a temperature in excess of 1200 °C and a residence time in the combustion chamber longer than 2 s.^{46, 233, 237} A definite excess of the fuel relative to PCB and an excess of the oxidant relative to the fuel are necessary for this purpose.^{235, 236} There is no need to go far beyond the limit of 1200 °C, because this leads to an excess consumption of fuel and rapid wear of the equipment. A certain excess of the oxidant (oxygen, air) is needed for the exhaustive degradation of PCB and the suppression of soot formation.^{235, 236} However, this excess should not be enormous, because, in accordance with the Deacon equilibrium



the undesirable formation of chlorine is possible at a high oxygen concentration.

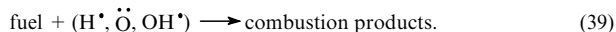
There have been few studies devoted to the quantitative aspects and mechanisms of the combustion processes of halohydrocarbons and they are concerned mainly with halomethanes.^{235, 236, 238–240} We suggest that the ideas developed in these investigations cannot be extended to haloarenes, because the chemical properties of the latter differ too much from those of halomethanes. On the other hand, two phenomena observed in the study of the combustion of halohydrocarbons may have a bearing also on the combustion of PCB.

The first concerns the inhibiting effect of halohydrocarbons. By extending the ideas developed in a series of investigations,^{236, 241–244} it is possible to put forward the following mechanism of the inhibition of the combustion of the PCB–fuel mixture,



Reactions (32) and (33) reflect the role of HCl (the product of the combustion of any chlorohydrocarbon) as a trapping agent for the $H \cdot$ and $OH \cdot$ free radical species responsible for the combustion process. Reactions (34) and (35) describe the involvement of chlorine atoms in chain termination and hence also in the inhibition of the combustion process.

The second observed phenomenon is the acceleration of the combustion of chlorohydrocarbons by water vapour:



Water vapour initiates the formation of the $\text{H}^\bullet$, $\text{O}^\bullet$, and $\text{OH}^\bullet$ radicals which are responsible for the oxidation process. The mechanism examined explains the suppression of the formation of chlorine in the chlorohydrocarbon combustion process.^{245, 246} Firstly, by virtue of the occurrence of reaction (36), the concentration of chlorine radicals falls and hence their recombination [reaction (34)] with formation of Cl_2 diminishes. Secondly, water vapour behaves as a donor of hydrogen atoms [reactions (36) and (37)] and hence it makes good the deficiency of hydrogen in PCB.

The technological formulation of the process depends in many respects on the state of aggregation of the material being neutralised. The simplest apparatus consists of a hollow combustion chamber fitted with a special burner with attachments for the supply of the PCB-containing material, the fuel (when this is necessary), and air (oxygen).^{217, 231} It is used to neutralise PCB-containing liquid waste and sewage. The joint combustion of concentrated sewage and liquid PCB-containing waste makes it possible to avoid the formation of PCDD and PCDF.²³¹ A two-chamber apparatus, consisting of a rotary furnace and a final combustion chamber,^{6, 18, 42, 77, 179, 183} in which a temperature higher by 200 °C than in the first chamber is maintained to ensure the completion of the process and the suppression of the PCDD and PCDF formation reactions, is used in certain cases. The two-chamber apparatus proved to be the most effective device for the combustion of liquid waste and its universal application has been recommended by the Environmental Protection Agency in the USA.¹⁸³

The most widely used procedure for the destruction of PCB-containing solid and liquid waste is combustion in cyclone and cement furnaces and incinerators. By virtue of the high temperature and a fairly long contact time, the complete decomposition of PCB and the intermediate PCDD and PCDF is achieved in rotating cement furnaces,^{54, 77, 174, 176} while the limestone present in the initial charge binds quantitatively the acid gases formed on combustion (Cl_2 , HCl , *etc.*). The addition of PCB-containing materials to the initial charge improves the quality of the cement obtained.⁷⁷ The materials combusted served as an additional source of heat and this makes it possible to economise on the main fuel.¹⁷⁴

An interesting method involving the combination of the combustion of PCB-containing materials with a blast furnace process has been proposed.¹⁷⁴ As in the cement furnaces, here the problem of the recovery of the heat is solved successfully and the acid gases formed are bound by the limestone used as the flux.

The highest efficiency of the combustion of solid PCB-containing waste is achieved in special furnaces consisting of three series-connected reaction units: a rotating furnace, a final combustion furnace, and a chamber for the combustion of gaseous products.^{18, 183} Such devices are suitable for the combustion of materials. In the version described, they are used for the combustion of domestic rubbish, whilst liquid PCB-containing waste can be supplied directly into the final combustion chamber. Gas, petroleum products, or coal can be used as the fuel for the combustion of any PCB-containing waste.¹⁸ In most cases, the effluent acid gases are absorbed in two series-connected scrubbers irrigated with water and an aqueous solution of alkali.^{184, 242} Limestone is sometimes added to the initial mixture to bind the acid gases.^{77, 171} A fluidised bed regime may be established to intensify the process in the combustion chamber,⁷⁷ but the melting point of the inert material used in this case imposes certain limitations on the combustion conditions. For example, the melting point of sand is 1100 °C.

The combustion furnaces can be combined into a single aggregate with any heat consuming unit. Thus examples of the

combustion of PCB-containing oils in boiler aggregates,²¹⁶ for heating aluminium furnaces,²²³ and for the generation of the additional heat in the lime preparation process⁷⁷ are known. The combustion methods are very convenient to use in devising mobile systems designed for the processing of local sources of pollution by PCB on trailers and in ocean-going vessels.^{77, 219}

The main deficiency of the combustion method is the risk of the formation of the highly toxic PCDD and PCDF during the oxidative degradation of PCB.^{18, 218, 235, 247} In a number of instances, the absence of PCDD and PCDF among the combustion products was noted^{54, 217, 221} and these data have been confirmed by kinetic and thermodynamic calculations, according to which these compounds should not be formed at temperatures above 1200 °C and for contact times longer than 2 s.²³⁷ Nevertheless, in the highly productive plant which actually exists it is difficult to ensure the ideal functioning of the combustion reactors, *i.e.* a uniform temperature throughout the volume of the chamber and an identical residence time in the reaction zone for all the particles in the reaction stream. For this reason, there is always a probability of the formation of the highly toxic PCDD and PCDF. A greater uniformity of the temperature field in the combustion chamber can apparently be ensured by employing a fluidised bed technique or by carrying out the process in the melt of an inert material, for example glass.⁷⁷

The complete suppression of the formation of PCDD and PCDF is achieved when PCB are combusted in an oxygen and water vapour atmosphere.²²⁰

One of the deficiencies of the combustion processes is a low selectivity, so that their use for the destruction of PCB is fully justified only for a fairly high content of the latter in the materials being neutralised.⁸⁷ The Environmental Protection Agency in the USA determined the lower limit of the PCB content in spent materials at the level of 500 mg of PCB per kilogram of the material.²²⁴

Among other deficiencies of the combustion processes, one may note the high cost, the additional consumption of fuel, the rapid wear of equipment in corrosive media (Cl_2 and HCl) and at high temperatures, and also the irreversible loss of the hydrocarbon component.^{68, 230} The last deficiency is of a fundamental character, because the aim of the overall strategy in the development of the world technology is the creation of resource-saving industries.

Only a few scattered studies have been devoted to the field of the catalytic oxidation of PCB.^{12, 232, 237, 248–252} The application of catalysts makes it possible to lower appreciably the process temperature and hence to reduce the capital and energy expenditure. It is remarkable that PCDD and PCDF are not formed under catalytic conditions, and the emission of nitrogen oxides is appreciably reduced. RuO_2 , $\text{Cr}_2\text{O}_3/\text{Al}_2\text{O}_3$, $\text{CuO}/\text{Al}_2\text{O}_3$, Co_3O_4 , the mixed catalysts CuCr_2O_4 , Pt-Pd , and metal chlorides on an inert porous support, which are capable of being converted into the corresponding oxides on heating in air, are used as catalysts. Despite promising results, systematic studies on the characteristic features of the catalytic PCB oxidation processes are lacking and this hinders an assessment of the prospects for their application.

The methods for the oxidative decomposition of PCB in plasma or electric arc discharges are of undoubted interest.^{11, 151, 252, 253} The complete conversion of PCB into gaseous products (CO , CO_2 , H_2O , HCl , Cl_2 , ClO_2) without risk of the formation of PCDD and PCDF is ensured under these conditions. However, such processes are characterised by low selectivity and high energy expenditures, so that their application is justified only if it is necessary to detoxify concentrated PCB-containing materials.

The neutralisation of PCB by the ozonisation method has been tested in relation to aqueous solutions of these toxicants.^{77, 254, 255} At the usual temperatures, the degree of decomposition of PCB reaches 97.0%–99.4%. The acceleration of this process is promoted by UV irradiation and by the addition of potassium hydroxide to the solution. This method is of interest for the detoxification of sewage, since simultaneous ozonisation ensures its disinfection.

PCB can also be oxidised by employing a mixture of oxygen (air) with water as the reagent under conditions ensuring the attainment of hypercritical parameters of the latter.⁷⁷ In this state, the hydrogen bonds are significantly weakened and the dielectric constant diminishes to 3–10. As a result, water becomes a good solvent for the organic mass and the oxygen supplied to such a system rapidly oxidises the substrate. The exothermicity of the process makes it possible to maintain the temperature at a level of $\sim 550^\circ\text{C}$. When this method is used, the formation of PCDD and PCDF is ruled out and the complete decomposition of PCB is ensured. However, additional studies are needed in order to analyse the material and energy balances and to elucidate the economic desirability of the development of the method.

VIII. Hydrogenolysis of polychlorobiphenyls

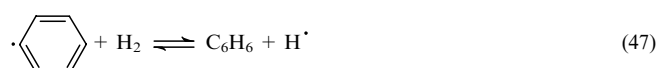
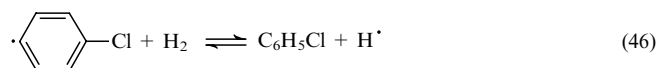
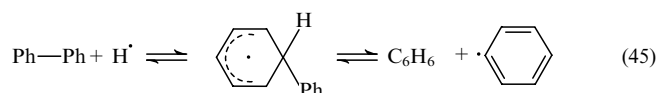
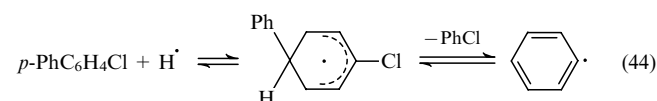
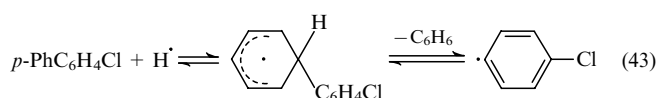
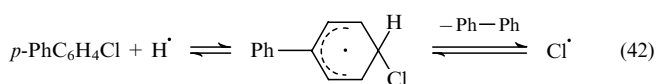
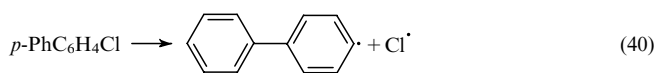
The interest in detoxification of organochlorine waste by the dechlorination method has increased in recent years.²⁵⁵ This has been induced by a series of evident advantages of this process compared with other procedures for the conversion of organochlorine compounds, including PCB. Firstly, hydrogenolysis proceeds fairly 'smoothly' under comparatively mild conditions up to the complete conversion of the initial organic reagent. Secondly, the reaction is selective in relation to the object processed, which makes it possible to achieve successfully the dechlorination of organochlorine compounds within any range of their concentrations. If other undesirable organoelement compounds are present in the reaction mixture, then they can be readily converted into the corresponding hydrocarbons by hydrogenolysis. Thus there is a possibility of the regeneration of the spent lubricating oils and other PCB-containing materials. Thirdly, in the hydrogenolysis the formation of PCDD and PCDF is ruled out. Fourthly, this method has an evident resource-saving character.

Processes involving the hydrogenolysis of organohalogen compounds have been the objects of numerous investigations. Nevertheless, the number of studies in which the chemical behaviour of PCB in these reactions has been considered is limited.^{49, 80, 129, 256–271} The aim of the majority of studies was to solve applied problems in the detoxification of PCB-containing materials.

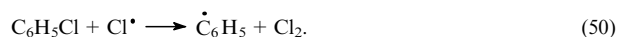
The hydrogenolysis of PCB can be achieved by the thermal, catalytic, and the usual chemical methods. In the last case, expensive alkali and alkaline earth metal hydrides and hydroborates^{49, 100, 186, 267} as well as silanes and polymethylsiloxanes^{129, 268} are used as the dechlorinating agents. These methods are more in the nature of preparative procedures and cannot be considered as a basis for industrial application.

There have been several studies devoted to quantitative aspects of the thermal hydrogenolysis of chloroarenes, including chlorobiphenyls.^{259, 272–274} The results of the investigation of the pyrolytic decomposition of arenes and chloroarenes should be regarded as a component of these studies.^{152, 275} The gas-phase thermal hydrogenolysis of PCB by hydrogen at $700–925^\circ\text{C}$ leads to the formation of benzene and hydrogen chloride as the final products with insignificant soot formation.²⁵⁹

Analysis of the results obtained in the studies quoted above and of the thermal kinetic data presented in some of them makes it possible to postulate the following mechanism of the thermal hydrogenolysis (in relation to 4-chlorobiphenyl):



Detailed investigation of the behaviour of PCB at different hydrogen concentrations^{153, 259, 275} has shown that reactions (43)–(45) are reversible. The processes which are the reverse of the above reactions may be regarded as stages in the thermolysis of chlorobenzenes. The pyrolysis of chlorobenzenes should then be supplemented by stages involving initiation and the formation of HCl:



Under the pyrolysis conditions, the concentration of molecular hydrogen is extremely low and equilibrium (41) is significantly displaced to the left, which leads to high $[\text{Cl}\cdot]/[\text{H}\cdot]$ ratios. This induces in its turn the displacement of equilibrium (43)–(45) also to the left, *i.e.* in the direction of the products of the thermolysis of chlorobiphenyls.

The main difficulty in the occurrence of thermal hydrogenolysis is the supply of heat for the creation of the required temperature regime. However, at the current level of the technology of high-temperature processes, this difficulty has been overcome. There have been promising communications concerning the possibility of replacing hydrogen in the thermal hydrogenolysis of PCB by the cheaper methane and other alkanes.^{257, 263, 275} A tubular furnace, in the intertubular space of which it is possible to combust the methane employed, is entirely suitable for the organisation of such a process.

Numerous versions of the catalytic hydrogenolysis of organochlorine compounds have been described in the literature.^{256, 271} The processes are carried out both in the liquid and gas phases, usually on metals such as Pt, Pd, Rh, Ru, Ir, Os, Ni, Co, Fe, Re, Mn, Mo, W, Cr, V, Cu, Ag, and Au. The properties of the catalysts can be varied widely by fusing them with other metals, by adding promoting agents, and by selecting supports.

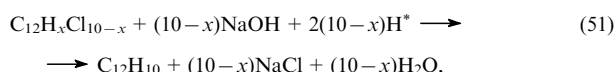
A detailed analysis of the characteristic features of the catalytic hydrogenolysis of various aromatic chloro-compounds, including PCB, has been carried out in mutually complementing reviews^{256, 271} and we shall therefore confine ourselves here to a brief description of the existing ideas.

The kinetics of the catalytic hydrogenolysis of a series of chloroalkanes, chloroalkenes, and chloroarenes indicate that the majority of the process proceed *via* the Langmuir–Hinshelwood mechanism with dissociative adsorption of hydrogen on the catalyst surface. The extensive experimental data accumulated provide guidelines in the search for more effective catalysts and for the extension of the ideas developed to new objects.

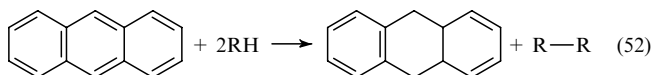
Many experimental data have been obtained in recent years on the catalytic hydrogenolysis of polychlorobiphenyls.^{258, 260–262, 264, 265, 270, 276} The reactions take place in the gas and liquid phases and in the latter case alkalis may be added to the reaction mass in

order to bind the hydrogen chloride formed. Supported Group VIB and Group VIII metals, Raney nickel, and the nickel--molybdenum alloy catalyst have been used successfully as catalysts. The hydrogenolysis of PCB on nickel, deposited on kieselguhr, in the gas and liquid phases has been studied in detail.²⁷⁶

The possibility of the quantitative dechlorination of certain PCB to biphenyl under mild conditions indicates major prospects for catalytic hydrogenolysis. The heat of reaction is sufficient to maintain the necessary, comparatively low, temperature in the reaction zone. In connection with the problem of increasing the useful life of the catalyst and of the restoration of its activity in the regeneration cycle, attention has been drawn to a study²⁷⁷ of the hydrogenolysis of PCB with the aid of a combined reagent comprising alkali and a hydrogen-transferring agent. The authors regard this process as an alternative to the usual catalytic hydrogenolysis. Hydrocarbons incorporating highly mobile hydrogen atoms (alkanes containing tertiary C—H bonds or alkylarenes with benzyl C—H bonds) are used as the hydrogen donor. The role of the hydrogen-transferring agent is performed by anthracene, phenanthrene, alkylnaphthalenes, and also graphite, soot, or transition metals (in the first place iron). The overall process can be described by the equation



where H* are active hydrogen atoms evolved by the hydrogenating form of the transferring agent, for example the dihydroanthracene formed on interaction with the hydrogen donor, *i.e.*



or the adsorbent (carbon, transition metals). In the latter case, the version proposed by the authors differs little from the usual heterogeneous-catalytic hydrogenolysis, because transition metals (the classical catalysts for these processes) promote the dissociative adsorption of H₂ and the formation of atomic hydrogen as the active surface intermediate. The idea of hydrogen transfer with the aid of polycyclic aromatic compounds is attractive, but the prospects for the technological application of this process are obscure, because problems arise associated with the application of expensive alkali and the difficulties in the separation of the reaction mass and the utilisation of the products of the conversion of the hydrogen donors.

* * *

The examination of the problem of the pollution of the environment by PCB and of the known methods for their neutralisation has shown that, in the practical solution of this ecological problem, it is possible to apply both individual methods for the processing of PCB and their various combinations. The use of two and more methods is most rational, for example, in the utilisation of articles containing high PCB concentrations. Such methods may be combustion and biological purification, dechlorination, oxidation, *etc.* A concrete technology for the neutralisation of PCB, determined by the state of aggregation of the material, the concentration of PCB in it, the specified degree of purification, and other technological and ecological factors, must be selected in each case.

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Oxidative methods in the synthesis of vicinal di- and polycarbonyl compounds

V D Filimonov, M S Yusubov, Ki-Van Chi

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Abstract. The review systematises and summarises the oxidative methods for the synthesis of compounds with vicinal carbonyl functions. The oxidative reagents used for this purpose, their scope and limitations are discussed. The bibliography includes 307 references.

I. Introduction

Alicyclic and cyclic 1,2-dicarbonyl and vicinal polycarbonyl compounds have been known for over 150 years. The properties of many of them have been well studied, and some have found practical use as biologically active compounds, intermediates in the synthesis of various heterocyclic compounds, analytical reagents, photopolymerisation initiators *etc.* Bis-1,2-diketones find use as monomers for the preparation of thermostable polyphenylquinoxalines.

Some representatives of this class (*e.g.*, ‘oxocarbons’ and ‘pseudooxocarbons’) are rather exotic compounds but present considerable interest for theoretical organic chemistry.^{1–3} To date, vicinal polycarbonyl compounds with five carbonyls have been obtained. Activity in this field of research does not cease.

Methods for the synthesis of 1,2-, bis-1,2- and polycarbonyl compounds^{1,4} and cyclic oxocarbons and pseudooxocarbons² have been reviewed.

The present review systematises and summarises the literature data on the oxidative methods for the synthesis of di- and polycarbonyl compounds with preservation of the carbon skeleton of the starting substrates. The existing methods for the synthesis of these compounds are divided into the following main groups: (1) introduction of a carbonyl group at the α -position with respect to the existing one in aldehydes, ketones, carboxylic acids and their α -substituted (hydroxy-, halogeno-, *etc.*) derivatives; (2) oxidative transformations of epoxides and vicinal compounds containing the CHX-CHY moiety; (3) oxidation of the alkyl groups and compounds with multiple bonds. The reagents used for oxidation are described for each of the above substrate types. Generally, we refer to studies not included in the

reviews mentioned above.^{1,2,4} However, in some instances we mention them in order to give a full picture of the existing reagents and the most reliable methods.

One should bear in mind that vicinal di- and polycarbonyl compounds tend to undergo hydration, and their mono- or dihydrates, *i.e.*, *gem*-diols, are commonly obtained as the final products. It is also typical of vicinal di- and polycarbonyl compounds to exist as various types of enols; the ratio of the carbonyl and enol forms has not been always determined with certainty.

II. Oxidation of carbonyl compounds and their derivatives

Syntheses of vicinal di- and polycarbonyl compounds are most commonly based on substrates already containing at least one carbonyl group.

1. Oxidation of the α -methyl and α -methylene groups of aldehydes, ketones and carboxylic acids

The reagents known for the preparative oxidation of the α -methyl and α -methylene groups of aldehydes and ketones are listed in Table 1. Nitrogen oxides and aromatic nitrosamines were the first reagents used for the oxidation of ketones (more seldom, aldehydes). They had been used rather widely in the synthesis of 1,2-dicarbonyl compounds before such reagents as selenium dioxide and DMSO appeared.^{1,2,4,5}

Since the turn of the century, treatment of 1,3-diarylpropan-2-ones with ‘nitrous gas’, which is generated from nitric acid and arsenic oxide at -30°C , has been known to give ‘isonitrosodimers’. The latter decomposed on heating to give nitrogen and aromatic vicinal triketone hydrates.⁶ This reaction was used in the synthesis of diethyl oxomalonate from diethyl malonate and N_2O_3 (yield 75%).⁷ It was pointed out that the oxidation of diethyl malonate is more convenient if NO_2 is used.¹ Later, diaryl triketones were obtained in high yields using an equimolar mixture of NO and NO_2 .⁸

In 1901, the oxidising effect of *p*-nitrosodimethylaniline on the methylene group of certain β -diketones and/or β -oxo esters, which resulted in contiguous tricarbonyl derivatives, was discovered. Examples of such reactions have been presented in reviews.^{1,5} Despite the high toxicity of the reagent, the method is sometimes used even now. For example, the following scheme for the preparation of dioxo esters (**1a–c**) from esters has been implemented.⁹

V D Filimonov, M S Yusubov Tomsk Polytechnical University, 634004 Tomsk, prosp. Lenina 30, Russian Federation. Fax (7-382) 241 52 35. Tel. (7-382) 241 56 37. E-mail: filim@org.chtd.tpu.edu.ru
Ki-Van Chi Ulsan University, 680-749 Ulsan, Republic of Korea. Tel. (10-82522) 44 77 53. E-mail: kwchi@uou.ulsan.ac.kr

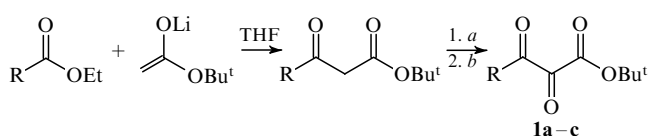
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Table 1. Reagents used for the oxidation of carbonyl compounds and their derivatives into vicinal di- and polycarbonyl compounds.

Substrate	Reagent	Product
RCOMe	AlkONO, NaNO ₂ –H ⁺ , HalNO, HSO ₄ NO, NH ₄ CrO ₃ Cl, nitrosonium salts, SeO ₂ , H ₂ SeO ₃ , PhSeSePh–(NH) ₄ S ₂ O ₈ –MeOH, HBr–DMSO	RCOCHO
RCOCH ₂ R and cyclic ketones	KMnO ₄ –Al ₂ O ₃ , NH ₄ CrO ₃ Cl, O ₂ –V ₂ O ₅ or V ₂ O ₅ , nitrosonium salts, SeO ₂ , H ₂ SeO ₃ , HBr–DMSO, NBS–DMSO	RCOCOR
β-Diketones	NO–NO ₂ , 4-Me ₂ NC ₆ H ₄ NO, ¹ O ₂ – <i>hν</i> –Bu ₄ NF, PhIO, SeO ₂ , H ₂ SeO ₃ , HBr–DMSO, NBS–DMSO	Vic. triketones
β-Oxo esters	NO–NO ₂ , 4-Me ₂ NC ₆ H ₄ NO, KMnO ₄ –Al ₂ O ₃ , Bu ^t OOH–V ₂ O ₅ –SiO ₂ , CrO ₃ , O ₂ –Co(OBz) ₂ , PhSeSePh–(NH) ₄ S ₂ O ₈ –MeOH	R ¹ COCOCOOR ²
R(Me ₃ SiO)C=CR(OSiMe ₃)	Br ₂ –CHCl ₃	RCOCOR

Note. NBS is *N*-bromosuccinimide.



R = 1-allyl-3-indolyl (**a**), 4-Me₂NC₆H₄ (**b**), 1-methyl-2-pyrrolyl (**c**);
(a) 4-Me₂NC₆H₄NO, KOH, EtOH; (b) HCl, CH₂Cl₂.

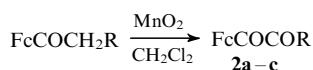
It was noted that compounds **1a–c** could not be obtained by the photooxidation of the phosphorylides of intermediate β-diketones.⁹

Certain ketones react with pentyl nitrite to give α-nitroso derivatives (oximes); this reaction with an excess of the reagent under mild conditions gives α-diketones.¹⁰ This procedure made it possible to synthesise 1-phenylpropane-1,2-dione from propiophenone and camphorquinone from camphor. Alkyl nitrites react with ketones as sources of the nitrosonium ion (NO⁺). Ketones are also successfully oxidised with other reagents that generate NO⁺ *in situ*, for example, inorganic nitrites in the presence of acids, nitrosyl halides and nitrososulfates. Some of aryl methyl ketones were oxidised with these reagents under mild conditions into arylglyoxals or their acetals.¹¹ Acetals are formed in 50%–70% yields in the reaction of acetophenones with MeONO in a mixture of MeOH with HCl at 0–5 °C in 4 h. Heating of aryl methyl ketones with NaNO₂ in HCl at 60 °C gives the corresponding arylglyoxals directly in yields higher than 60%.¹¹

The oxidative properties of organic nitrosonium salts are similar to those of nitrosodimethylaniline and alkyl nitrites. Their use as oxidants of alcohols, amines and ketones is covered in a review,¹² and we shall not dwell on this topic.

Such a popular oxidant as potassium permanganate generally cleaves ketones to carboxylic acids or (in basic media) transforms them to oxocarboxylic acids.⁵ However, KMnO₄ immobilised on alumina can selectively oxidise the α-methylene groups of ketones. Oxidation of cyclohexanone in dichloromethane at room temperature for 120 h results in cyclohexane-1,2-dione in 58% yield.¹³ The same reagent oxidises ethyl phenylacetate in 161 h to give ethyl phenylglyoxylate in an almost quantitative yield. However, phenylacetic acid undergoes decarboxylation under these conditions to give benzaldehyde.¹³

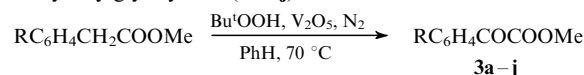
Ferrocenyl diketones (**2a–c**) were first obtained¹⁴ in 50%–65% yields upon the oxidation of the corresponding ferrocenyl ketones with MnO₂ in boiling dichloromethane.



Fc is ferrocenyl; R = Ph (**a**), 4-C₆H₄Ph (**b**), Fc (**c**).

Yet another example of a fundamental change in the properties of an oxidant after its immobilisation on a support was

demonstrated for V₂O₅ adsorbed on montmorillonite or SiO₂, which is an efficient catalyst for the oxidation of the methylene group of methyl phenylacetates with *tert*-butylhydroperoxide to give alkyl arylglyoxylates (**3a–j**).¹⁵

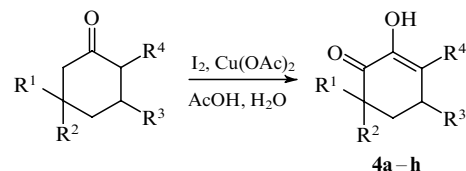


R = H(**a**), 2-MeO(**b**), 4-MeO(**c**), 4-Me(**d**), 4-NH₂(**e**), 4-NO₂(**f**), 2-Cl(**g**), 4-Cl(**h**), 2-PhCH₂(**i**), 4-PhCH₂(**j**).

Choudary *et al.*¹⁵ claimed that they were the first to oxidise the α-methylene group in arylacetic esters to the carbonyl group. However, as early as in 1957 phenylacetic acid was transformed to the acid **3a** in 86% yield upon treatment with air in the presence of cobalt benzoate at 110–115 °C.¹⁶ Diethyl malonate is oxidised with N₂O₃ as discussed above.

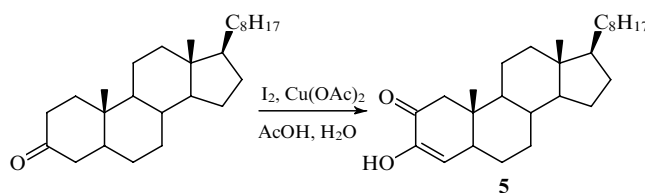
Butan-2-one is oxidised on V₂O₅ under aerobic and anaerobic conditions at 250–350 °C to butane-2,3-dione.^{17,18} Experiments involving ¹⁸O₂ showed that the resulting diketone did not contain this isotope. Acetic acid and acetaldehyde are the main side products, which are formed mainly due to the decomposition of butanedione. To a smaller extent, these products result from the oxidation of the original ketone in the enol form.

Copper acetate has been long used for the synthesis of 1,2-dicarbonyl compounds from α-hydroxy ketones (see Section III). An equimolar mixture of I₂ and Cu(OAc)₂ oxidises the α-methylene group in cyclohexanone and its derivatives on boiling in aqueous acetic acid for 15 h to give the corresponding cyclohexane-1,2-diones (**4a–h**) in up to 70% yields.¹⁹



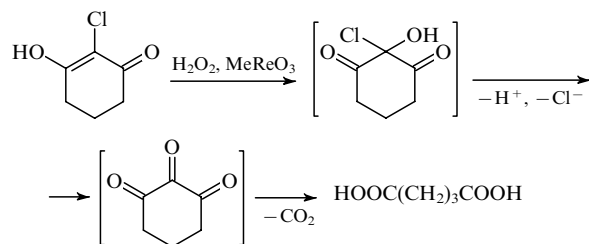
R¹ = R² = R³ = H, R⁴ = (**a**), Me (**b**), Et (**c**), cyclo-C₆H₁₁ (**d**), Ph (**e**);
R¹ = R² = H, R³ = R⁴ = Me (**f**); R¹ = R⁴ = H, R² = R³ = Me (**g**);
R¹ = R² = R³ = Me, R⁴ = H (**h**).

The same procedure made it possible to obtain cholestane-2,3-dione (**5**) from cholestan-3-one in 40% yield.¹⁹

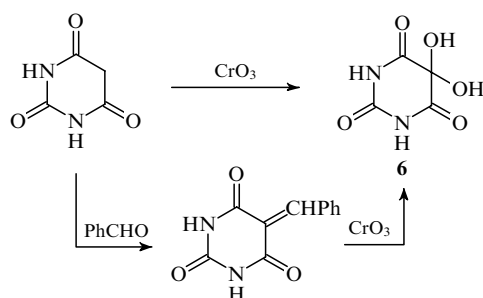


According to IR, ¹H and ¹³C NMR spectral data, compounds **4a–h** and **5** exist in the enol form.¹⁹

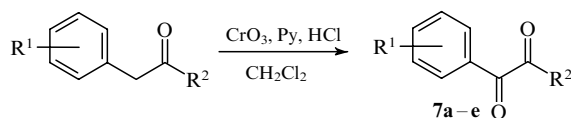
Oxidation of cyclic α -chloro β -diketones with hydrogen peroxide in the presence of MeReO_3 resulted in their decomposition to dicarboxylic acids *via* intermediate contiguous tricarbonyl compounds, which were detected in some instances by NMR spectroscopy.²⁰



The methylene group in barbituric acid can be oxidised with CrO_3 to give alloxan (**6**). The same result was obtained in the oxidation of benzylidenebarbituric acid (yield 75%–84%).^{21,22}



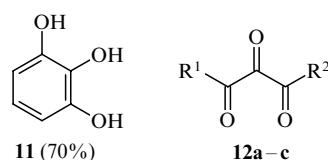
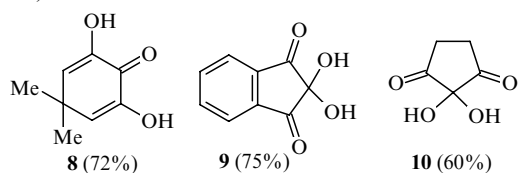
The other known reagent based on CrO_3 , namely, pyridinium chlorochromate introduced in practical organic synthesis in 1977 by Corey, oxidises successfully various benzyl ketones (but not aliphatic ketones) in boiling CH_2Cl_2 .²³



Compound	R ¹	R ²	Yield (%)
7a	H	Ph	80
7b	H	Me	85
7c	H	Et	80
7d	4-MeO	Me	60
7e	2-Me	Me	65

A similar reagent, ammonium chlorochromate ($\text{NH}_4\text{CrO}_3\text{Cl}$), transforms acetophenone to phenylglyoxal rather easily (DMF, 75 °C, 6 h) in 80% yield.²⁴ The same authors²⁵ used this reagent to oxidise butan-2-one to a mixture of ethylglyoxal and butane-2,3-dione and to oxidise 3-methylbutan-2-one to isopropylglyoxal.

A new method for the photooxidation of the methylene group of acyclic and cyclic β -diketones by singlet oxygen was suggested in 1985.^{26,27} The reaction occurs successfully only in the presence of tetrabutylammonium fluoride. Presumably, the fluoride anion enhances the nucleophilic properties of the enol forms, thus activating the electrophilic attack by singlet oxygen. This method gave high yields (60%–97%) of tricarboxyl compounds (**8**–**11**, **12a–c**).

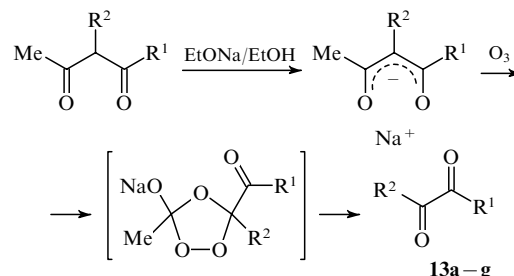


$\text{R}^1 = \text{R}^2 = \text{Ph}$ (**12a**); $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$ (**12b**); $\text{R}^1 = \text{R}^2 = \text{Me}$ (**12a**).

It should be noted that the similar photooxidation of five- and six-membered cyclic α -diketones results in ring opening to give aldehyde or oxo carboxylic acids, probably *via* intermediate *endo*-peroxides.^{26–29}

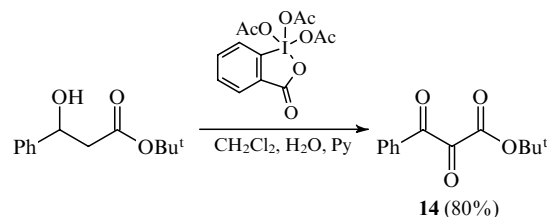
It is well known that the oxidation of acyclic ketones with oxygen in the presence of bases serves as a method for the synthesis of carboxylic acids. Oxidation of 3-methyl- and 3-ethylpentane-2,4-diones gives a mixture of acetic acid and the corresponding 3-hydroxy 2-ketones and 2,3-diketones.³⁰ This process is not a preparative method for the synthesis of diketones. However, it was found that cyclohexanone and cyclopentanone dissolved in dimethoxyethane undergo oxidation with atmospheric oxygen in the presence of Bu^tOK at -20°C to give the diketone **4a** and cyclopentane-1,2-dione, respectively.³¹ The yields of cyclopentanedione and especially diketone **4a** are low due to ring opening resulting in dicarboxylic acids. The similar reactions with cycloheptanone and cyclooctanone also give the corresponding diketones, but only as intermediates, which undergo subsequent aldol condensation. The stability of the diketone **4a** and cyclopentane-1,2-dione under these conditions is explained³¹ by the predominance of the enol forms.

1,2-Diketones and α -oxo esters (**13a–g**) are obtained in moderate to high yields (21%–83%) by the ozonolysis of Na-salts of β -diketones and β -oxo esters followed by treatment of the intermediate ozonides with hydrogen peroxide or dimethyl sulfide.³²



$\text{R}^1 = \text{OEt}$; $\text{R}^2 = \text{Bu}$ (**a**), PhCH_2 (**b**), 4-EtOCH₂C₆H₄CH₂ (**c**), $(\text{EtO})_2\text{P(O)CH}_2\text{CH}_2$ (**d**); $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Bu}^t$ (**e**), PhCH_2 (**f**), 4-EtOCH₂C₆H₄CH₂ (**g**).

Compounds of hypervalent iodine are used very widely in organic synthesis, particularly as oxidising reagents for the α -hydroxylation of carbonyl compounds (see *e.g.*, the reviews^{33–36}). Much less is known about direct oxidation of ketones with these reagents to α -dicarbonyl compounds. The use of 1,1,1-triacetoxy-1- λ^5 -benzo-1,2-iodoxol-3-one ('periodinane' or the Dess–Martin reagent) in moist CH_2Cl_2 in the presence of pyridine for the oxidation of *tert*-butyl 2-hydroxy-2-phenylpropionate to the corresponding dioxo ester **14** was reported.³⁷

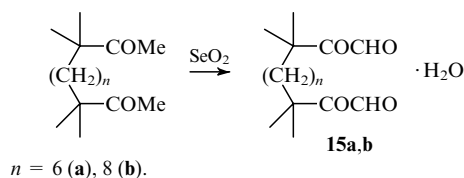


Diacetoxy- λ^3 -iodanylbenzene oxidises 1,3-indanedione in alcohols in the presence of H_2SO_4 to the corresponding 2,2-dialkoxyindanediones.³⁸

The kinetics and mechanism of the oxidation of cyclopentanone and cyclohexanone to the corresponding 1,2-diketones with bromoamine-T (4-MeC₆H₄SO₂NNaBr) in acidic media was studied.³⁹ Enolisation of the starting ketones was found to be the limiting step of the oxidation.

Selenium dioxide is a much more versatile reagent for the synthesis of vicinal polycarbonyl compounds. Its extensive use in practical organic synthesis started in the early 30's, and this reagent is still important today. Both SeO₂ and selenious acid (H₂SeO₃), which is prepared by concentrating aqueous solutions of selenium dioxide, are used in syntheses of dicarbonyl compounds. Both reagents selectively oxidise the α -methyl groups of aliphatic and aromatic ketones and acetaldehyde as well as the α -methylene groups of cyclic ketones. Oxidation can be carried out by heating the reagent and substrates in the absence of solvents. However, the reaction is more commonly performed in such solvents as water, ethanol, acetic acid and dioxane; sometimes, xylene, acetic anhydride and pyridine are used. A wide range of aryl methyl ketones with various donor and acceptor substituents in the ring are oxidised with SeO₂ to the corresponding arylglyoxals in yields usually exceeding 70%.^{4, 5, 40} However, *ortho*-acetylacetophenone, unlike the *para*-isomer,⁴ gives 2-hydroxy-1,4-naphthoquinone rather than bisglyoxal.⁴¹ It is reported in patent literature that the oxidation of acetophenone with SeO₂ in C_{1–9} aliphatic alcohols at 100 °C gives the corresponding phenylglyoxal acetals.⁴² Acetaldehyde is oxidised with H₂SeO₃ to glyoxal (isolated as a bisulfite derivative in 72%–74% yield⁴³). It can be noted that glyoxal is also formed from acetone by refluxing the latter with SeO₂ in xylene in the presence of water.⁴⁰ Selenious acid in aqueous dioxane readily oxidises cyclohexanone at room temperature to give cyclohexane-1,2-dione (yield 60%).⁴⁴ The use of SeO₂ in this reaction gives nearly the same yield but requires more drastic conditions (refluxing for 6–8 h).⁴⁵

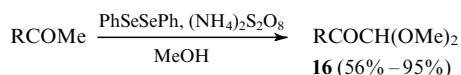
Selenium dioxide has also been used to oxidise many β -diketones (acetylacetone, benzoylmesitoylmethane, dimesitoylmethane, 5-hydroxy-4-phenylcyclopent-4-ene-1,3-dione, *etc.*) to the corresponding 1,2,3-triones.¹ Bisglyoxals (**15a,b**) used in the synthesis of cyclic vicinal tetraketones were also obtained with this reagent.⁴⁶



The possible mechanisms of oxidation with selenium dioxide have been discussed in reviews.^{4, 40}

Despite the high efficiency and selectivity combined with mild conditions of the reaction, SeO₂ has a serious drawback noted in many works, namely, the difficulty of purification of the final products from selenium that is formed. Black selenium that is evolved can be filtered off, but a small amount of colloidal selenium ('red selenium') remains in solution and cannot be removed even by distillation. This necessitates an additional work-up of the products, *viz.*, shaking with mercury or inactive Raney nickel or treatment with potassium cyanide, SO₂, potassium hydrogensulfite in acidic media or thiourea.^{5, 40}

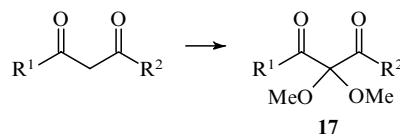
Yet another selenium-based oxidant, diphenyl diselenide, has been suggested recently.⁴⁷ It proved to be very efficient (in catalytic or stoichiometric quantities) for the preparation of α -oxo acetals **16** from the corresponding methyl ketones in the presence of ammonium peroxodisulfate (NH₄)₂S₂O₈.



The reaction is carried out in boiling methanol and is applicable to a broad range of aromatic and heterocyclic methyl

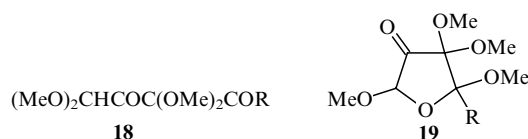
ketones (except for acetylpyridine) as well as to unsaturated, cycloaliphatic and, in certain cases, aliphatic methyl ketones. It is assumed that the process occurs through electrophilic attack of PhSe⁺ on the enol form of the ketone.⁴⁷

The same group of authors⁴⁸ expanded this oxidation method to β -diketones and β -oxo esters.



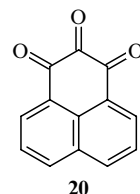
R¹ = Alk, Ph; R² = Alk, Ph, OAlk, OCH₂Ph.

In this case, only a catalytic amount of PhSeSePh was used, and the yields of oxo acetals **17** were considerably lower (10%–75%), especially for the diketones containing the acetyl fragment, which also undergoes partial oxidation. This reaction affords side products **18** and **19**.⁴⁸

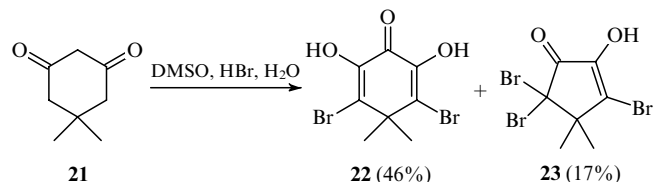


Since the discovery of a very simple method for the oxidation of activated alkyl halides, including phenacetyl bromides, with DMSO in the presence of bases (the Kornblum reaction),⁴⁹ a large number of studies have appeared in which DMSO is used as a convenient oxidant (for the relevant reviews, see Refs 5, 50–52). No wonder that DMSO plays an important role in the synthesis of α -dicarbonyl compounds as well.

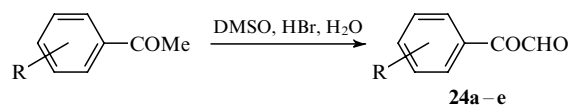
For example, DMSO in the presence of dry HBr oxidises the methylene groups in cyclic β -diketones to produce 1,2,3-triones **9** and **20** in 80% and 30% yields, respectively.^{53, 54}



It was found later that the oxidation of another cyclic diketone, dimedone (**21**), with DMSO in the presence of hydrogen bromide brings about not only oxidation of the methylene group but also ring bromination to give dibromotriketone **22**. In addition, a product of ring contraction, *viz.*, tribromocyclopentanedione **23**, is formed.⁵⁵



The DMSO–aqueous HBr system turned out to be very efficient in the transformation of acetylarenes to arylglyoxals **24a–e**.⁵⁶

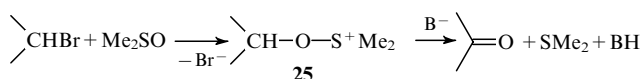


R = 4-Ph (a), 4-MeO (b), 4-NO₂ (c), 4-Br (d), 2-Ph (e).

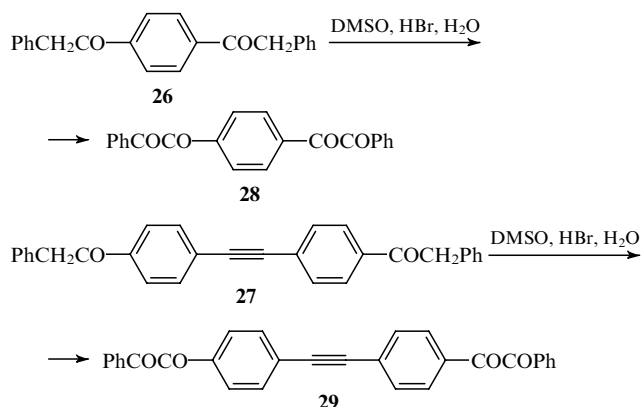
This is probably the most convenient reagent presently available for this transformation. The reaction is carried out at 55 °C for 1–24 h to give the corresponding arylglyoxals in high yields (42%–94%). Side processes have been noted in two cases only.

For example, the oxidation of 2-acetyl biphenyl results in oxidative cyclisation to give phenanthrenequinone in 47% yield. In the case of 4-acetyldiphenylamine, oxidation is accompanied by bromination of the unsubstituted phenyl ring to afford 4-(4-bromoanilino)phenylglyoxal (90%). Under the same conditions, 1,2-diphenylethanone affords quantitatively diphenylethanedione **7a** in 24 h, while 1,3-diphenylpropane-1,3-dione gives diphenyltriketone hydrate **12a**.⁵⁶

The following point related to the mechanism of this reaction is worthy of note. It is generally accepted that the Kornblum reaction occurs through the following pathway (without details of the decomposition step of the dimethylsulfoxonium intermediate **25**):^{50–52}



However, comparison of the results of oxidation of aryl methyl ketones in the DMSO–HBr–H₂O system and oxidation of α -bromoacetophenone in dry DMSO made it possible to suggest a different mechanism for oxidation with aqueous DMSO.⁵⁶ It was assumed that in this case the role of DMSO is reduced to the oxidative generation of a small amount of bromine followed by bromination and debromination of ketones with subsequent hydrolysis to arylglyoxal hydrates. Whatever the actual mechanism of this reaction, the DMSO–HBr–H₂O system is the most convenient for the preparative oxidation of acyclic ketones to α -dicarbonyl compounds and of acyclic β -diketones to triketones, provided that the substrates subject to oxidation are insensitive to bromine. A method has been patented for the synthesis of benzil **7a** using a concentrated HBr–DMSO system.⁵⁷ Other examples of smooth oxidation of methylene groups in bisdeoxybenzoins **26**, **27** to bis- α -diketones (**28**, **29**) are also known.^{58, 59}



The latter reaction, which serves as one of the steps in the synthesis of an aromatic tris- α -diketone⁵⁹ (see Section IV), demonstrates the high regioselectivity of the DMSO–HBr oxidising system with respect to the methyl groups in the acetylenic diketone **27**, since the triple bond remains unaffected. It is difficult or impossible to reach such a selectivity with other oxidants, e.g., SeO₂.

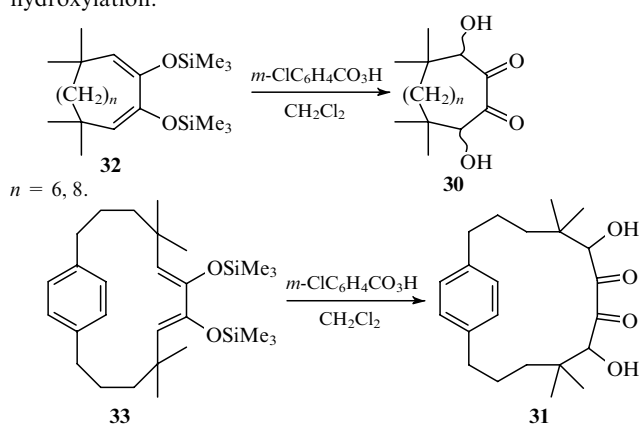
The methylene groups in 1,2-diphenylethanone and 1,3-diphenylpropane-1,3-dione are smoothly oxidised with a mixture of DMSO with concentrated H₂SO₄ in the presence of a catalytic amount of iodine.⁶⁰ However, the use of the same oxidative system for 1-phenylpropan-2-one and cyclohexanone gives very low yields of the diketones **7b** and **4a**. In this case, acetophenone gives a mixture of *Z*- and *E*-isomers of the enol form of 2-methylthio-1,4-diphenylbutane-1,4-dione, which are formed as products of phenylglyoxal transformation.⁶⁰

On prolonged action, *N*-bromosuccinimide in dry DMSO oxidises 1,2-diarylethanones at room temperature to give the corresponding diarylethanediones and oxidises indan-1-one, indan-2-one and indane-1,2-dione to indane-1,2,3-trione (**9**). The

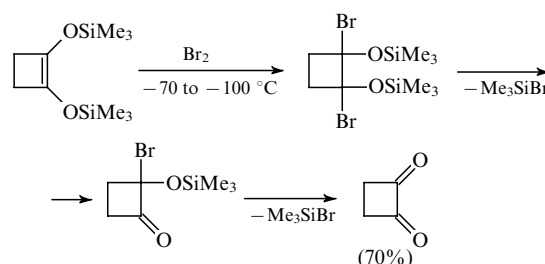
reaction with 1,3-diphenylpropane-1,3-dione under the same conditions affords diphenyl triketone **12a**.^{61, 62} It is assumed⁶² that *N*-bromosuccinimide acts as a brominating agent to give the intermediate 3-bromoindan-1-one, which is then oxidised with DMSO according to the Kornblum reaction.

The methyl groups of aryl methyl ketones are oxidised on treatment with DMSO and benzoyl chloride at room temperature. However, instead of arylglyoxals, the reaction gives acetals of their fully hydrated forms with formaldehyde, i.e. 1-aryl-2,4,6,8-tetraoxabicyclo[3.3.0]octanes.⁶³

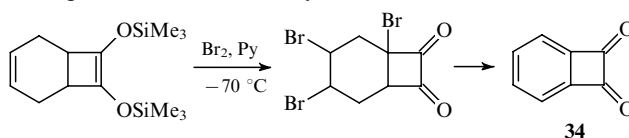
The vast variety of methods and reagents for the synthesis of α -hydroxycarbonyl compounds by hydroxylation of stable enol forms, e.g., of vinyl ethers/esters and thioethers/thioesters, enol silyl ethers and ketene silylacetals (for reviews, see Refs 5, 35, 64, 65) contrasts with the surprisingly small number of reagents known for their direct transformation to α -dicarbonyl derivatives. In fact, even the formation of α -dicarbonyl structures **30** and **31** in the oxidation of bisilyl ethers **32** and **33** with *m*-chloroperbenzoic acid (the Rubbotom method)^{46, 66, 67} actually occurs due to hydroxylation.



It is known that 1,2-bis(trimethylsilyloxy)alkenes, which are stable under non-hydrolytic conditions, can be oxidised with bromine in chloroform or CCl₄ to the corresponding cyclic diketones. This reaction occurs most successfully if it results in cyclobutanedione or non-enolizing diketones.^{68–71} In other cases, Me₃SiBr that is formed reacts with the enol forms of the resulting diketones, giving new silyl ethers of enols and, subsequently, various halogen-containing compounds.⁷⁰



A similar approach afforded 3,3,7,7-tetramethylcycloheptane-1,2-dione^{72, 73} and adamantylcyclobutanedione.⁷⁴ Likewise, the reaction of bromine with the bisilyl ether of bicyclo[4.2.0]octa-2,6-diene gives benzocyclobutanedione (**34**) through bromination and dehydrobromination.⁷³



2. Oxidation of α -hydroxycarbonyl compounds

Transformations of α -hydroxycarbonyl compounds to α -dicarbonyl compounds are well studied. Undoubtedly, the largest number of reagents for this kind of transformations have been

approved using the oxidation of benzoin as a very convenient model. Even 150 years ago, Laurent⁷⁵ and Zinin⁷⁶ showed that benzoin can be oxidised to benzil **7a** on treatment with chlorine or nitric acid. However, these reactions, unlike those developed later, did not become preparative methods.

Treatment of a solution of benzoin in pyridine with air in the presence of copper(II) sulfate at 100 °C for 2 h oxidises it to diketone **7a** in 86% yield.⁷⁷ Compound **7a** is obtained in quantitative yield by refluxing a solution of benzoin in acetic acid in the presence of a catalytic amount of copper acetate and ammonium nitrate.⁷⁸ Similar results are obtained if a catalytic amount of cobalt,^{78,79} iron or nickel salts⁷⁸ or complexes of Fe(II) with certain cysteine-containing peptides⁸⁰ are used. Complexes of Fe(II) with α,α' -xylenedithiolates catalyse the oxidation of benzoin to benzil **7a** in DMF at room temperature both by the atmospheric oxygen and *p*-benzoquinone; the latter oxidant was found to be more efficient in this reaction.⁸¹ It was suggested⁸² to prepare 4,4'-bis(carboxyphenyl)ethanedione ethers by oxidation of the appropriate benzoin with air in ethanol in the absence of catalysts at 60 °C for 13 h. 2-Hydroxy-1-phenyl-2-(2-quinolyl)ethanone (α -quinaldoin) is readily oxidised on passing air through its boiling solution in dioxane to give phenyl(2-quinolyl)ethanedione.⁵

The most commonly used oxidants are listed in Table 2 together with the relevant reaction conditions. These data make it possible to compare the reactivities of different reagents with respect to the oxidation of α -hydroxy ketones. Quinolinium fluorochromate, Bi(MnO₄)₂, AgBrO₃, AlCl₃, and *o*-iodylbenzoic acid can be regarded as the most efficient reagents.

In several studies,^{87–92} benzoin and other alcohols were oxidised with the same reagents under similar conditions. It turned out that such alcohols as benzyl alcohol, diphenylmethanol, and 1-phenylethanol were comparable with each other and

with benzoin with respect to the time required for their oxidation and the yields of the monoketones in the preparative experiments, *i.e.* the activity of these substrates is quite similar. However, oxidation of 4- and 4'-chloro-, bromo-, and methoxy-substituted benzoin with sodium or silver bromates in the presence of AlCl₃⁹⁰ or barium permanganate⁸⁸ is accompanied by an insignificant decrease in the yields of the corresponding diarylethanediones and an approximately twofold increase in the reaction time. The oxidation of 2-furoin with barium permanganate occurs much more slowly (4 h, yield 80%). These results of preparative experiments provide no more than a qualitative picture of the effect of the nature of α -hydroxy ketones and oxidants on the oxidation to 1,2-diketones. In order to reveal distinct regularities, one has to determine the rates of oxidation of different substrates under similar conditions. However, to our knowledge, there are no comparable kinetic experiments of this kind, although both the kinetics and the oxidation mechanism of α -hydroxy ketones have been studied rather thoroughly. For example, it follows from kinetic studies on the oxidation of benzoin with quinolinium dichromate to compound **7a** that the oxidation is 6 times slower than the substrate enolisation. Oxidation occurs through the initial coordination of the chromium atom with the carbonyl group of the substrate.⁹⁷

Many other reagents are known that oxidise benzoin to the diketone **7a**. For example, anhydrous Fe(NO₃)₃, which is normally unstable, is rather stable if impregnated in acidic montmorillonite. It affords benzil **7a** in a higher yield (85%–95%) than ytterbium nitrate.⁹⁸ On the other hand, K₂FeO₄ immobilised on the same support gives the diketone **7a** in only 36% yield, since this reagent cleaves the C–C bond of benzoin, producing benzaldehyde.⁹⁹ It was reported,¹⁰⁰ without specifying the conditions and yields of the reaction products, that catalytic amounts of tris(2,4-dibromophenyl)aminium hexachloroantimonate oxidise benzoin to the corresponding diarylethanediones. Benzoin can be oxidised with titanium isopropoxide,¹⁰¹ benzyltriethylammonium tribromide,¹⁰² triphenylstibine dibromide (Ph₃SbBr₂),¹⁰³ Ph₃PBr₂,¹⁰⁴ and PhMe₃N⁺Br₃[–]·NBS¹⁰⁵ to benzil **7a** in almost quantitative yield. Cobalt(III) acetate in acetic acid oxidises deoxybenzoins to benzoin and further to diphenylethanedione derivatives.¹⁰⁶

Copper sulfate and acetate have long been widely used for the oxidation of various benzoin structures. For instance, stoichiometric amounts of CuSO₄·5H₂O oxidise 1,2-difuryl-2-hydroxyethanone (2-furoin) and 2-phenyl-1-(2-pyrrolyl)-2-hydroxyethanone in aqueous pyridine at 100 °C in 2 h to give difurylethanedione (fural)¹⁰⁷ and phenyl(2-pyrrolyl)ethanedione¹⁰⁸ in 63% and 95% yields, respectively. Probably, copper acetate has an even higher oxidising activity. It oxidises 3-hydroxy-1,4-diphenylbutan-2-one to 1,4-diphenylbutane-2,3-dione in almost quantitative yield on refluxing for 7 min in 70% AcOH¹⁰⁹ and 2-hydroxycyclodecanone (sebacoine), also in aqueous AcOH,¹¹⁰ to cyclodecane-1,2-dione (sebacil) in 1 min. Copper acetate in AcOH was successfully used in the synthesis of cyclic diketones **35** and **36a,b**.^{46,65}

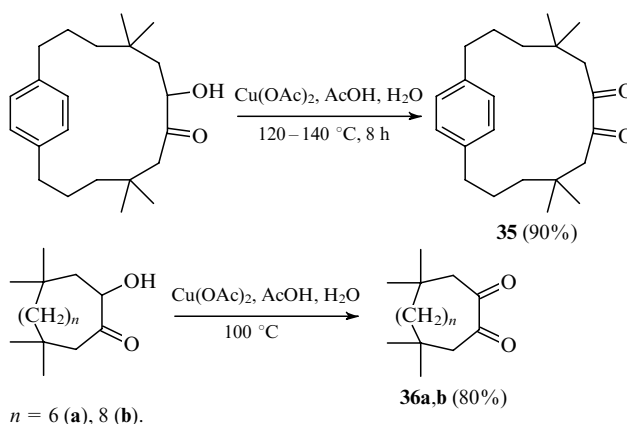
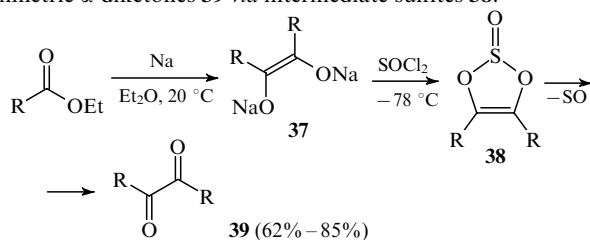


Table 2. Reagents and reaction conditions for the oxidation of 2-hydroxy-1,2-diphenylethanone (benzoin) to diphenylethanedione (benzil).

Reagent	Solvent	Temperature / °C	Time / h	Yield (%)	Ref.
O ₂ , CuSO ₄	C ₅ H ₅ N	100	2.0	86	77
Cu(OAc) ₂ , NH ₄ NO ₃	AcOH	reflux	1.5	90–100	78
PhSe(O)Se(O)Ph	THF	"	3.0	92	83
Quinolinium fluorochromate	CH ₂ Cl ₂	20	2.0	98	84
Trichloromelamine	CH ₂ Cl ₂	20	125.0	98	85
DMSO, HBr, H ₂ O	—	55	24.0	95	56
Bi ₂ O ₃	AcOH, EtO(CH ₂) ₂ OH	104	1.0	95	86
Zn(BiO ₃) ₂	Xylene	reflux	0.7	97	88
Ba(MnO ₄) ₂	MeCN	"	0.25	96	88
BaFeO ₄ ·H ₂ O	MeCN	"	6.0	95	89
AgBrO ₃ , AlCl ₃	MeCN	"	0.5	97	90
NaBrO ₃ , AlCl ₃	MeCN	"	0.75	97	90
Chromium bipyridylperoxide	MeCN	"	3.0	90	91
Bu ₄ N ⁺ IO ₄ [–]	CHCl ₃	"	2.5	85	92
FeCl ₃ ·6H ₂ O	AcOH, H ₂ O	"	0.8	90–95	93
<i>o</i> -Iodylbenzoic acid	THF, DMSO	20	6.0	> 90	94
	THF, DMSO	reflux	0.2	92	94
NaBrO ₃ , NaOH	H ₂ O	100	5–6	84–95 ^a	95
<i>N</i> -Chlorosuccinimide, Me ₂ Se, base	MeC ₆ H ₅	0	2.0	93	96

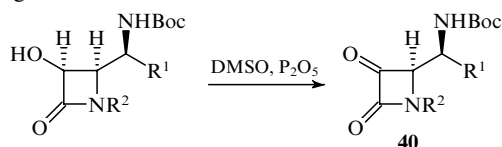
^a Benzylic acid is formed as a product of benzylic rearrangement of diphenylethanedione.

Sodium salts of enolic forms of hydroxy ketones that are formed in the acyloin condensation of esters (enedioxides **37**) are oxidised with thionyl chloride *in situ* at low temperature to symmetric α -diketones **39** via intermediate sulfites **38**.¹¹¹



$R = Me, Et, Bu^i, cyclo-C_3H_5, adamantyl, Ph$.

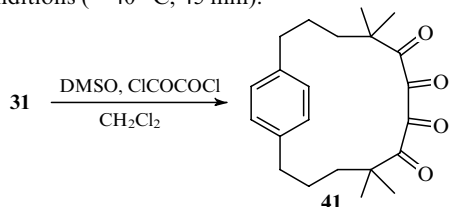
Reagents based on DMSO were successfully used for the oxidation of α -hydroxycarbonyl compounds. An aqueous solution of HBr in DMSO readily oxidises benzoin to benzil **7a** in high yield.⁵⁶ It is interesting that the same reagent also oxidises *o*-methylbenzoin to compound **7a**.¹¹² The reactivity of deoxybenzoin and its α -substituted derivatives in the oxidation to benzil **7a** was studied.¹¹³ The series of reactivities, benzoin > 2-bromo-1,2-diphenylethanone > 1,2-diphenylethanone, is a good confirmation of the suggested scheme of the oxidation of ketones with HBr in DMSO.⁵⁶ A combination of DMSO with P_2O_5 was used in the synthesis of azetidine-2,3-diones **40**, which were then oxidised to α -amino acid *N*-carboxyanhydrides according to Baeyer–Villiger.¹¹⁴



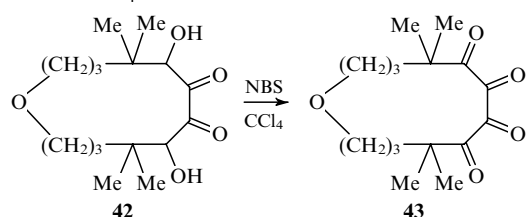
$R^1 = Me, Bu, Pr^i, Bu^i$; $R^2 = Ph, Ar, CH_2Ph$.

Such reagents as *N*-chlorosuccinimide with Me_2S and Et_3N , pyridinium chromate, pyridinium chlorochromate, the Jones reagent (CrO_3, H_2SO_4, H_2O), trifluoroacetic anhydride in DMSO, tetra-*n*-propylammonium perruthenate, RuO_4 , and $NaIO_4$ proved to be unsuitable for this purpose. The Corey reagent (Me_2SBr_2, Et_3N) was also inefficient,¹¹⁴ although it has been used successfully in the synthesis of various azetidine-2,3-diones from α -hydroxy- β -lactams.¹¹⁵ Treatment of hydroxy- β -lactams with sodium hypochlorite also leads to their oxidation according to Baeyer–Villiger.¹¹⁶

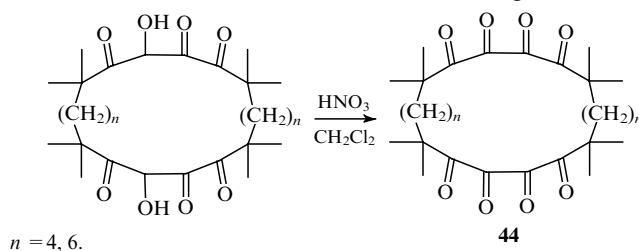
The Swern reagent ($DMSO-CICOCOCI$) oxidises dihydroxy[12]paracyclophanedione **31** to the tetraketone **41** under mild conditions ($-40^\circ C, 45\text{ min}$).⁶⁷



Oxidation of cyclotridecanedione **42** to the tetraketone **43** has been performed successfully by the same authors⁶⁸ with such a well-known reagent for the oxidation of alcohols as *N*-bromosuccinimide in CCl_4 .



However, bistetraketones **44** were obtained using nitric acid.⁴⁶

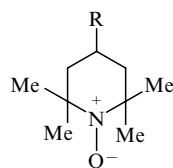


As a rule, aromatic derivatives of α -hydroxy ketones are readily oxidised with $DMSO-Ac_2O$, but the yields of α -diketones from aliphatic derivatives are low.¹¹⁷

α -Oxocarboxylic acids are important biologically active compounds and are of considerable interest for organic synthesis. It is not surprising that the development of methods for their synthesis draws much attention. Many reagents for the oxidation of alkyl α -hydroxycarboxylates to the corresponding oxo derivatives are known. These include $Pb(OAc)_4$, Ph_3SbBr_2 , tertiary amine oxides, sodium peroxodisulfate, 2-fluoro-1-methylpyridinium tosylate, DMSO with hexamethylenetetramine, $PhSOCl$, a complex of dimethyl selenide with *N*-chlorosuccinimide, sodium hypochlorite, diacetoxy- λ^3 -iodanylbenzene, $Co(II)$ compounds, bis(tetrabutylammonium) dichromate, $KMnO_4-CuSO_4$, ammonium vanadate, manganese pyrophosphate, immobilised chromic acid, chromyl chloride, vanadium(V) derivatives, periodinane (see *e.g.* Ref 118 and the references cited therein). A review published recently¹¹⁹ deals with the use of tetrapropylammonium perruthenate ($Pr_4N^+RuO_4^-$) as a mild catalytic reagent, particularly for the synthesis of α -keto acids. It was suggested to obtain esters of β, γ -unsaturated α -oxocarboxylic acids by the oxidation of the corresponding α -hydroxy derivatives according to the Swern procedure ($DMSO, CICOCOCI, CH_2Cl_2, -50^\circ C$).¹²⁰

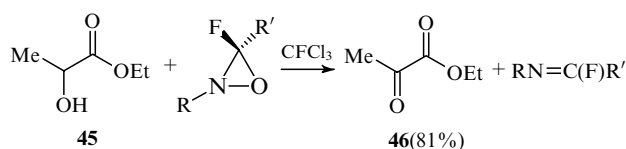
In view of the abundance of studies in this field, the detailed discussion of oxidative methods for the synthesis of α -oxocarboxylic acids is beyond the scope of our review. Therefore, we shall discuss here only relatively new and, in our opinion, versatile reagents applicable for the synthesis of other α -dicarbonyl compounds as well.

For example, the importance of tetramethyl-1-piperidinyloxy (TEMPO) has increased in recent years.

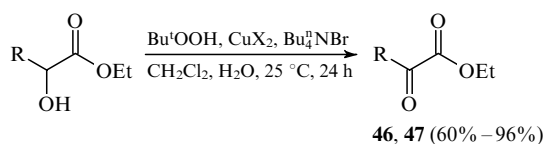


In particular, it was shown that various linear and cyclic primary and secondary alcohols are oxidised in high yields to high-purity aldehydes or ketones under mild conditions on treatment with 4-acetylamino-TEMPO ($R = AcNH$) in dichloromethane in the presence of *p*-TsOH.¹²¹ The reagent is readily generated in the reaction mixture. Phenylglyoxylic acid is formed under these conditions in 91% yield from phenylglycolic acid.¹²¹

Oxaziridines, particularly various 2-sulfonyloxaziridines, are powerful oxidants due to the high electrophilicity of the ring oxygen atom. They are used most widely for the α -hydroxylation of carbonyl compounds.^{64, 122} It was found that perfluoro-*cis*-2,3-dialkyloxaziridines also oxidise secondary alcohols to ketones at room temperature. In particular, they oxidise ethyl lactate (**45**) to ethyl pyruvate (**46**).¹²³



Finally, let us note a recently observed example of the oxidation of alkyl hydroxycarboxylates to α -oxo esters **46** and **47** on treatment with *tert*-butyl hydroperoxide in the presence of copper(I) and (II) salts and even metallic copper under phase-transfer catalysis conditions.¹²⁴



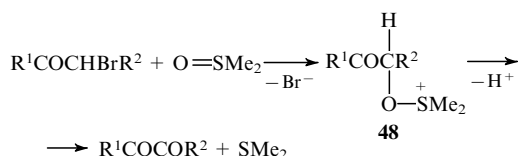
R = Me (**46**), Ph (**47**).

Dibismuth trioxide oxidises 12-hydroxy-11-ketosteroids to 11,12-diketosteroids in up to 70% yields.¹²⁵ This reagent can also be used for the synthesis of vicinal vinyl diketones from the corresponding vinyl α -hydroxy ketones.¹²⁶ Iodine combined with AcOH and MeOH oxidises D-(–)-ascorbic acid to D-(–)-dehydroascorbic acid in low yield.¹²⁷ Aliphatic α -hydroxy ketones are transformed to the corresponding α -diketones on treatment with *N*-bromosuccinimide in dry CCl₄ or aqueous dioxane.¹²⁸ Basic copper(II) carbonate [CuCO₃·Cu(OH)₂] acts in a similar way.¹²⁹ Acyloins of dioxepane structure were successfully oxidised to the corresponding α -diketones upon boiling with SeO₂ in a mixture of toluene and acetic acid.¹³⁰ The action of a solution of ferric chloride in HCl on 2-hydroxycyclohexanone results in a high yield of cyclohexanedione **4a**.¹³¹

3. Oxidation of α -halocarbonyl compounds

Oxidation of α -halocarbonyl compounds is one of the most convenient and popular methods for the synthesis of diketones.¹³²

A very simple and convenient method is the oxidation of halo ketones according to Kornblum with DMSO in the presence of bases.^{49–52, 133} In this case, α -bromocarbonyl compounds are oxidised more readily than alkyl or even benzyl bromides. The oxidation of α -bromo ketones with DMSO is commonly carried out at room temperature. This is explained by easier elimination of the proton from the intermediate dimethylsulfoxonium salt **48** due to the adjacent carbonyl group (see also Section II.1).^{134, 135}

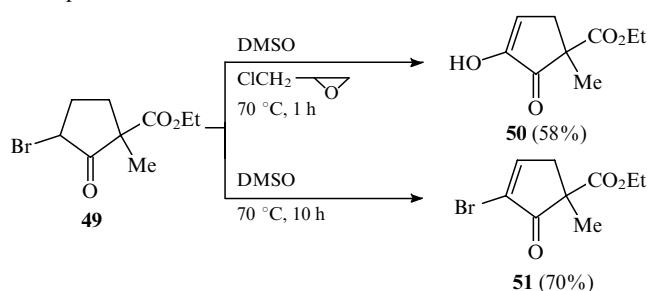


The method is particularly convenient for the oxidation of acyclic α -bromocarbonyl compounds. For example, phenylglyoxal (yield 71%) and diketone **7a** (yield 95%) were obtained by the oxidation of 2-bromo-1-phenylethanone and diphenylbromoethanone in dry DMSO at 25 and 45 °C, respectively.⁴⁹ The addition of sodium carbonate accelerates the process. However, the oxidation of *e.g.* ethyl bromoacetate with DMSO was also carried out without a base, using 2-phenoxyethyloxirane to bind the HBr evolved (the yield of ethyl glyoxylate was 70%).¹³⁶ However, it was noted¹³⁷ that *tert*-butyl bromoacetate could not be oxidised with DMSO. It was also shown that the addition of potassium iodide to a mixture of DMSO and Na₂CO₃ accelerates the oxidation of bromo ketones.¹³⁸

In the first studies by Kornblum and co-workers and in many subsequent studies, dry DMSO was used. Thorough dehydration of such a hygroscopic compound as DMSO is a difficult procedure. It was shown⁵⁶ that it is easier to oxidise aryl methyl ketones, α -hydroxy- and α -bromoacetophenone with aqueous HBr in DMSO. In this case, the oxidation mechanism differs considerably from that of the classical Kornblum reaction. The role of DMSO in an aqueous medium is reduced to the generation of Br₂ from HBr, while the dimethylsulfoxonium ion **48**, which is the key intermediate in the Kornblum reaction, is not formed in aqueous HBr (see Section II.1).

3-Bromocamphor is oxidised to camphoroquinone upon passing air through a solution of the substrate and NaI in DMSO.¹³⁹ However, despite the apparent similarity with the Kornblum reaction, its mechanism is different: DMSO serves as a solvent, while the process goes *via* free-radical intermediates.¹³⁹

Complications are observed in the oxidation of cyclic α -bromo ketones with DMSO. In this case, oxidation often competes with elimination of the DMSO molecule from the intermediate **48**. Instead of diketones, or along with them, this process produces α,β -unsaturated ketones and α -hydroxy ketones. This reaction pathway is particularly typical of steroid derivatives.¹⁴⁰ Heating of 2-bromocyclohexanone and 2-bromocyclopentanone in DMSO at 100 °C gives 3-bromocyclohexane-1,2-dione and 3-bromocyclopentane-1,2-dione rather than the corresponding diketones.^{141, 142} Under these conditions, the bromo ketone **49** gives the diketone **50**, which exists in the enol form, only in the presence of epichlorohydrin to bind the HBr that evolves. The reaction in the absence of epichlorohydrin results in the compound **51** as the main product.^{142, 143}

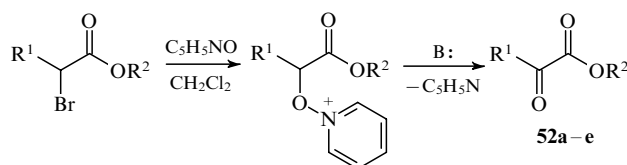


It was suggested^{142, 143} that this effect is due to the oxidation of the hydrogen bromide, which is formed in the primary oxidation act, with dimethyl sulfoxide to bromine, which brominates the intermediate diketone.

Nitrates formed in the reaction of α -bromo ketones and α -bromo acids with AgNO₃ undergo smooth transformations on treatment with a catalytic amount of sodium acetate in DMSO at room temperature to give high yields of α -dicarbonyl compounds or α -oxo acids.^{144–146}

The Kröhnke method (treatment of α -bromo ketones with pyridine and 4-nitrosodimethylaniline followed by hydrolysis) is of very limited use in the synthesis of 1,2-dicarbonyl compounds.¹³²

The oxidation of α -bromo acids and their esters with pyridine *N*-oxide is an efficient method for the synthesis of α -oxo acids and their esters.¹⁴⁷

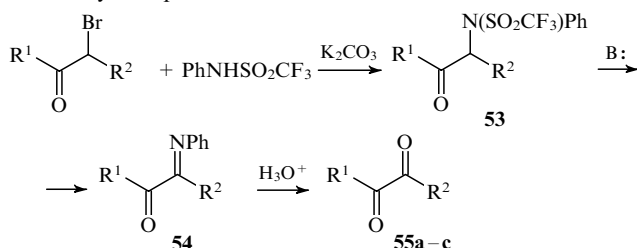


Compound 52	R ¹	R ²	Yield (%)
a	H	H	37
b	H	Bu ^t	97
c	H	CH ₂ Ph	89
d	Ph	H	70
e	Ph	Me	95

The addition of silver nitrate facilitates the formation of alkoxypyridinium salts. Their subsequent decomposition is carried out by heating in methanol or acetonitrile in the presence of Et₃N or in aqueous NaOH at room temperature.¹⁴⁷ A stronger nucleophile, 4-dimethylaminopyridine *N*-oxide, was also used in an oxidative transformation of this kind. However, in this case the intermediate salt was decomposed with the use of 1,8-diazabicyclo[5.4.0]undec-7-ene.¹⁴⁸

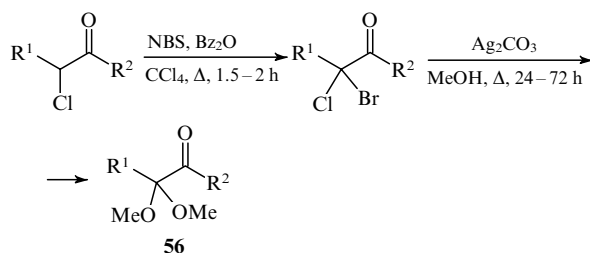
Similar oxidative properties are manifested by *N,N*-diethylhydroxylamine, which oxidises, readily and in high yields, various aromatic bromomethyl ketones to arylglyoxals in boiling methanol in the absence of bases.¹⁴⁹ The method is attractive due to its simplicity and serves as a rare example in which α -oxo aldehydes are formed more easily than aromatic α -diketones. The method is not applicable to 2-bromo-1,2-diphenylethanone, 2-chlorocyclohexanone and 2-bromo-1-phenylpropanone.

α -Bromocarbonyl compounds (as well as other activated alkyl halides) react with *N*-phenyltrifluoromethanesulfonamides under mild conditions. The resulting products **53** are readily decomposed with bases to anils **54**, which are, in turn, hydrolysed to α -dicarbonyl compounds **55**.¹⁵⁰



$\text{R}^1 = \text{C}_6\text{H}_{17}$, $\text{R}^2 = \text{Me}$ (79%); $\text{R}^1 = \text{OEt}$, $\text{R}^2 = \text{Pr}$ (67%), C_6H_{13} (62%).

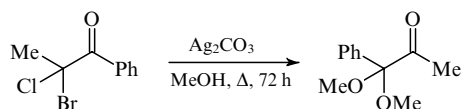
Monoketals of aliphatic diketones **56** were obtained in 43%–87% yields in two stages according to the following scheme:¹⁵¹



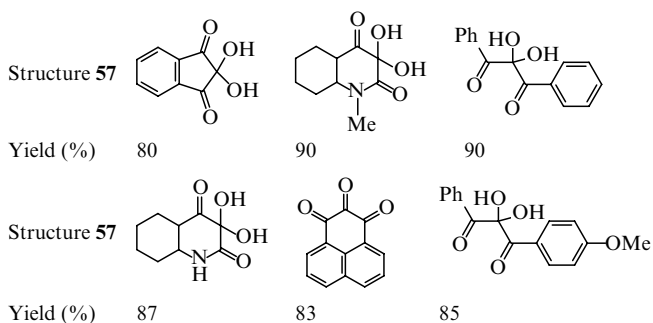
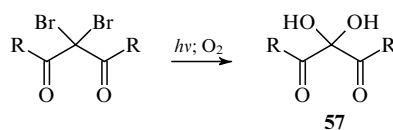
$\text{R}^1 = \text{R}^2 = \text{Me}$; $\text{R}^1 = \text{Et}$, $\text{R}^2 = \text{Me}$; $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{Et}$.

The method has the advantage that it provides the possibility of direct regiospecific synthesis of dimethyl ketals with involvement of only one carbonyl group of α -diketones that are difficult to obtain directly from the corresponding dicarbonyl compounds. The method is a good supplement to the synthesis of α -oxo acetals by the oxidation of methyl ketones with diphenyl diselenide as discussed in Section II.1.⁴⁷

It is interesting that the formation of an acetal from an aromatic bromo chloro ketone, namely, 2-bromo-2-chloro-1-phenylpropan-2-one, is accompanied by a rearrangement¹⁵¹ that gives 1,1-dimethoxy-1-phenylpropan-2-one.



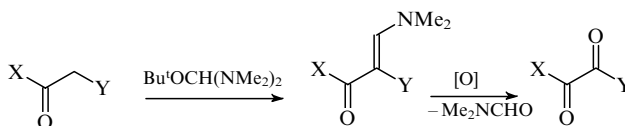
Cyclic and acyclic geminal dibromo diketones are transformed under conditions of photochemical oxidation at room temperature to hydrates of the corresponding vicinal triketones **57** in good yields.¹⁵²



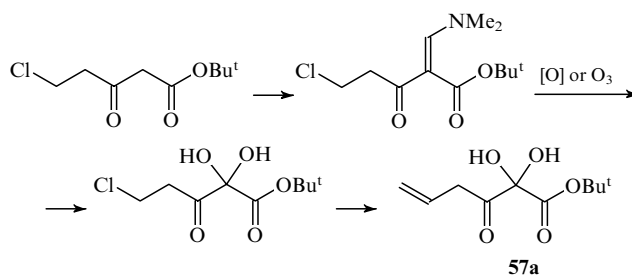
4. Oxidation of other classes of compounds with the CX–C=O function and oxidative rearrangements

In certain cases, carbonyl compounds containing nitrogen, sulfur or phosphorus in the α -position are rather accessible and can serve as good precursors in the synthesis of 1,2-dicarbonyl compounds.

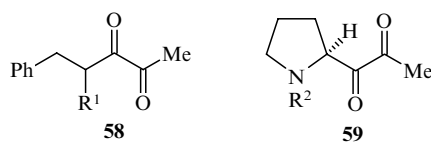
A general method for the insertion of an α -oxo group in ketones, esters, amides and lactams has been elaborated. This method is based on photooxidation of α -oxo enamines obtained from the corresponding carbonyl compounds according to the general scheme:



Dicarbonyl compounds obtained by this method are presented in Table 3. The photooxidation is carried out at -78°C with subsequent heating of the reaction mixture to 25°C . The method shows high selectivity. Using the same approach, the allylic vicinal tricarbonyl compound hydrate **57a**, which is a versatile di- and trielectrophilic synthon, was synthesised.¹⁵⁴



The same method was used to obtain polyfunctional α -diketones **58** and **59** from carboxylic acids.¹⁵⁵



$\text{R}^1 = \text{H}$, COOH , $\text{CH}_2\text{COOBu}^t$ (**58**); $\text{R}^2 = \text{H}$, COOBu^t (**59**).

It was shown that treatment of α -hydroxyimino ketones with N_2O_4 in THF or acetonitrile at -20°C gives diketones **7a,e** and triketone **12a** in over 60% yields.¹⁵⁶ Cyclohexane-1,2,3-trione hydrate was synthesised in an analogous way.¹⁵⁶ The reaction is assumed to occur *via* the intermediates **60**, since isotope-labelling experiments have shown¹⁵⁷ that the oxidation of oximes to ketones with NO^+ occurs *via* oxaziridine intermediates.

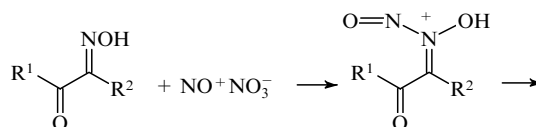
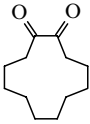
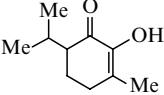
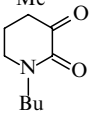
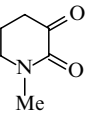
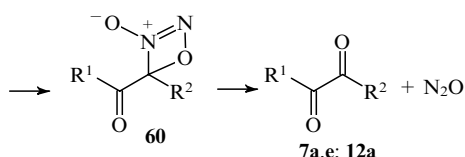


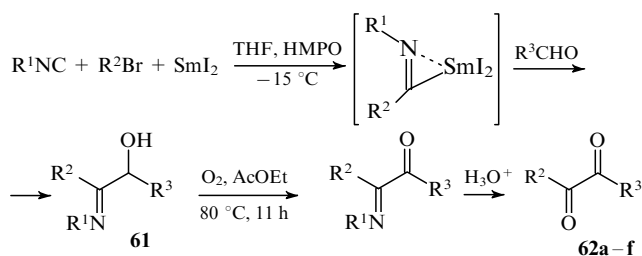
Table 3. Dicarbonyl compounds obtained by photooxidation of α -oxo enamines.¹⁵³

Compound	Yield (%)	Compound	Yield (%)
PhCOCOMe	68	PhCOCOPh	89
PrCOCOEt	74		82
	81	Cholestanedione (5)	87
PhCOCOOEt	91	4-MeOC ₆ H ₄ COCOOEt	92
EtCOCOOEt	81		74
Me(CH ₂) ₃ COCOOEt	75		58
	78		



R¹ = Ph; R² = Ph (**7a**), CH₂Ph (**7e**), CPh (**12a**).

Autooxidation of α -hydroxy imines **61** to diketones is rather a general method. Compounds **61** are obtained by the SmI₂-induced coupling of alkyl halides with xyllyl isocyanide and aldehydes.¹⁵⁸ The yields of diketones **62a–f** are higher than 90%.



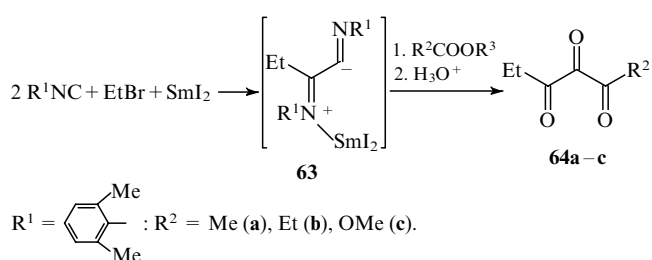
R¹ = ; R² = CH₂CH₂Ph; R³ = Et (**a**), Prⁱ (**b**);

R² = Prⁱ, R³ = CH₂CH₂Ph (**c**); R² = Et, R³ = Ph (**d**);

R² = (CH₂)₄OBu, R³ = 2-furyl (**e**);

R² = cyclo-C₆H₁₁, R³ = 2-pyridyl (**f**).

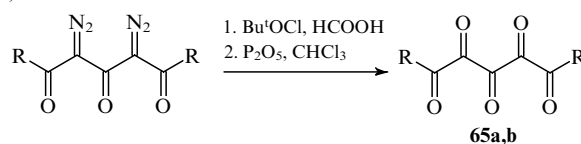
Organosamarium intermediates **63** obtained similarly are so nucleophilic that they readily react with esters and carbonates, thus providing a general way to vicinal triketones **64a–c**.¹⁵⁹



R¹ = ; R² = Me (**a**), Et (**b**), OMe (**c**).

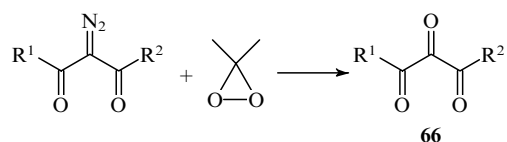
Aroylation of α -chloro imines in the presence of 1,3-dimethylimidazolinium iodide is rather a general method for the synthesis of aromatic 1,2-diketones. The oxo imines that are formed readily undergo hydrolysis to give the diketones ArCOCOPh (Ar = Ph, 3-ClC₆H₄, 4-ClC₆H₄, 4-MeOC₆H₄, 4-NO₂C₆H₄) in excellent yields.¹⁶⁰ The method was found to be applicable to the synthesis of heterocyclic diketones ArCOCOR (R = thienyl).¹⁶⁰

Examples of the oxidation of α -diazo ketones and diazo diketones are known.^{161,162} For instance, treatment of α -diazo ketones with triphenylphosphine gave phosphoranes, which were converted to α -oxo aldehydes with nitric acid. Phenylglyoxal was obtained by this method in 70% yield with respect to the starting benzoyl chloride.¹⁶¹ At present, there are reliable methods for direct oxidation of diazo ketones. For example, *tert*-butyl hypochlorite was used in one stage of the synthesis of pentaketones **65a,b**.¹⁶²



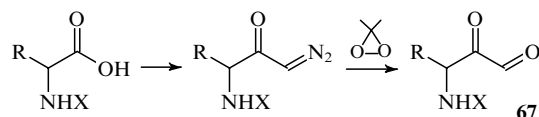
R = Bu^t (**a**), Ph (**b**).

Vicinal triketones **66** (in the form of monohydrates) were obtained in nearly quantitative yields by prolonged oxidation (10–30 h) of diazo diketones with dimethyldioxiranes (DMO, 'oxone') in acetone at room temperature.¹⁶³



R¹ = R² = Me, Ph, OEt; R¹ = Me, R² = Ph, OEt; R¹ = Ph, R² = OEt; R¹, R² = (CH₂)₃, CH₂CM₂CH₂, *o*-phenylene.

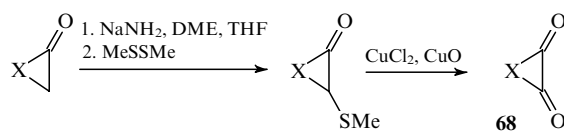
Oxidation of diazo ketones, that are obtained from substituted α -amino acids and dipeptides, with DMSO provides a general route for the synthesis of homochiral amino oxo aldehydes **67**, which exist as hydrates.¹⁶⁴



It was shown that phenylglycine undergoes oxidation with atmospheric oxygen in ethanol in the presence of an equimolar amount of VO(OEt)Cl₂ to give ethyl phenylglyoxylate.¹⁶⁵ The preparative value of this method is diminished by the side reaction of decarboxylation leading to the formation of a considerable amount of ethyl benzoate.

It is well known that the oxidation of bishydrazones of 1,2-diketones with mercury(II) oxide is one of general methods to synthesise disubstituted alkynes. In the case of diphenylethane-dione (benzil) monohydrazone, oxidation with Ag₂O results in benzil **7a**.¹⁶⁶ The use of some other oxidants mostly gives α -diazo ketones or ketazines, whereas diketones are only formed as by-products (see, *e.g.*, Ref. 167 and the references cited therein).

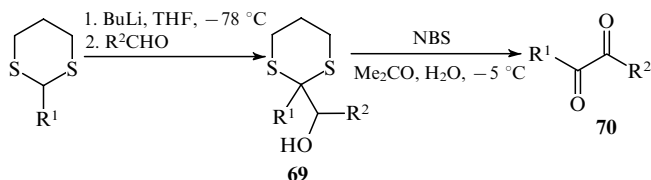
It was shown that cyclic ketones can be transformed to the corresponding α -diketones **68** by oxidation of their methylthio derivatives under mild conditions (acetone, 25–35 °C).¹⁶⁸ The overall yield of diketones over two stages is 42%–76%. Methylglyoxal was obtained in a similar way.¹⁶⁹



X = (CH₂)_n, n = 5–12.

(Biphenyl)phenylethanedione was isolated in ~90% yield after heating of ketone sulfur-containing derivatives 4-PhC₆H₄COCH(X)Ph (X = SMe, S⁺Me₂Br⁻) with aqueous HBr in DMSO at 55 °C.⁵⁶

It is known that derivatives of dithiane **69**, which are readily formed from aldehydes and 1,3-dithianyllithium, give α -hydroxy ketones in the presence of mercury(II) salts.¹⁷⁰ In another study,¹⁷¹ 1,3-dithiane was used as an acyclic synthon, but the intermediate product **69** was then oxidised with an excess of *N*-bromosuccinimide to give a series of α -diketones **70**, including fluorine-containing ones, in 54%–87% yields.

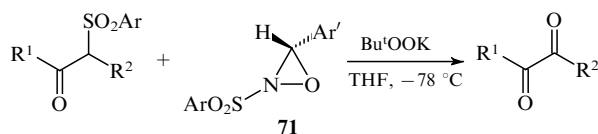


R¹ = Ph, R² = 2-FC₆H₄, 3-FC₆H₄, 4-FC₆H₄;
R¹ = 2-FC₆H₄, R² = 3-FC₆H₄, 4-FC₆H₄.

The oxidation of α -hydroxyalkyl-1,3-dithianes with NaNO₂ in trifluoroacetic acid to ketones was used¹⁷² for the synthesis of certain alkaloid analogues containing an α -diketone fragment.

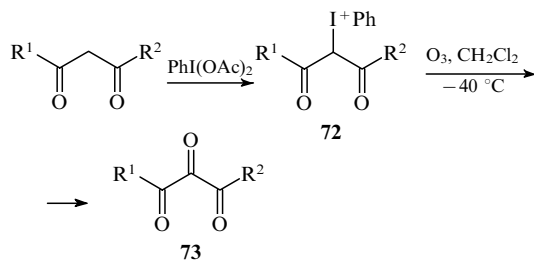
Iodine is yet another reagent for desulfurisation of α -oxo thioacetals. For instance, azetidine-2,3-diones were synthesised by refluxing diethyl dithioacetals of 2-oxo β -lactams with iodine in aqueous acetonitrile for 35–45 min.¹¹⁴

Very mild oxidative desulfonylation of α -sulfonyl ketones is carried out with oxaziridine **71**.¹⁷³



The method is unique due to its selectivity, as it makes it possible to obtain a wide range of complex cyclic and acyclic α -diketones containing such reactive functional groups as the azide, allenyl, acetal, furyl and other groups. Unfortunately, the more readily accessible (+)- and (–)-(camphorsulfonyl)oxaziridines turned out to be unsuitable for this reaction.¹⁷³

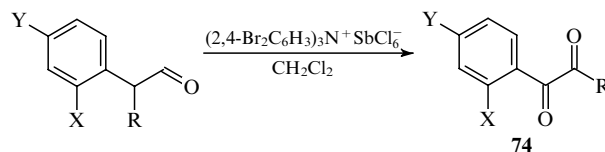
Various phosphorus and iodine ylides readily formed from β -diketones can serve as convenient precursors of vicinal tricarbonyl compounds.^{164, 174, 175} For example, oxidation of phosphorus ylides with singlet oxygen or ozone was used in the synthesis of allylic tricarbonyl compounds **57** and dioxo diester Bu^tOCOCO-COCH₂CH₂CO₂Et.^{164, 175} Potassium permanganate oxidises β -oxo(triphenylphosphoranylidene)s in a two-phase system to give substituted benzils or 1-arylpropane-1,2-diones in high yields.¹⁷⁶ Ozonolysis of α, α' -dioxoalkyl phenyliodonium **72** at low temperature made it possible to synthesise more than 20 cyclic and acyclic triketones **73** containing various fragments (alkyl, aryl, acetal, carbamido and other groups).¹⁷⁴



The important advantage of this method over the majority of others is that compounds **73** are formed and isolated on a preparative scale in the ketone rather than hydrate form.¹⁷⁴

A rearrangement of diarylactaldehydes that can be used for the synthesis of substituted benzils occurs at room temperature in

the presence of tris(2,4-dibromophenyl)aminium hexachloroantimonate as the oxidant.⁹⁹



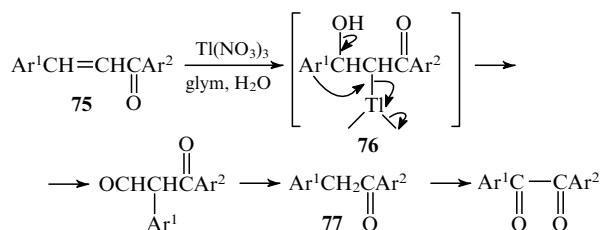
X = H; Y = Me, R = 4-MeC₆H₄;

Y = OMe, R = 4-MeOC₆H₄;

X = H, Y = Cl, R = 4-ClC₆H₄; X = Cl, Y = Me, R = 4-ClC₆H₄.

However, diphenylacetaldehyde and D,L-2-phenylpropionaldehyde do not enter into this reaction.⁹⁹

Oxidation of chalcones with thallium(III) nitrate¹⁷⁷ or PhIO¹⁷⁸ also results in benzils. For example, treatment of chalcones **75** with Tl(NO₃)₃ in aqueous solutions of glym in the presence of acids is a convenient way to synthesise benzils. The reaction scheme involves hydroxythallation of the double carbon–carbon bond, oxidative migration of an Ar group in the intermediate **76**, retro-Claisen condensation to give benzoin **77** and subsequent oxidation to diketones.

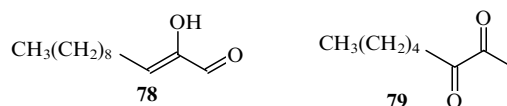


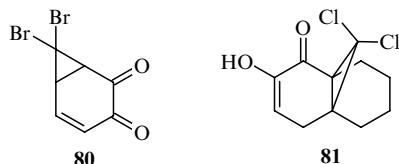
III. Oxidation of 1,2-diols, epoxides and other vicinally substituted compounds

The oxidation of glycols to α -dicarbonyl compounds can serve as a versatile method for the synthesis of the latter. However, these methods have been developed rather little, except for the industrial synthesis of glyoxal by gas-phase oxidation of ethylene glycol on copper or silver contacts. Various reactions leading to *o*-quinones are also known; these will not be considered in the present review. Much more commonly, syntheses of carbonyl compounds or carboxylic acids utilise the oxidative cleavage of the carbon–carbon bond in vicinal diols. The classic reagents of this type include lead tetraacetate, periodic acid and its salts (of which sodium periodate is particularly popular) (see, e.g., the reviews^{179, 180}). In addition, cleavage of glycols occurs on treatment with KMnO₄, MnO₂, NaBO₃, NaBiO₃ and organobismuth salts (Ph₃BiCO₃), Ce(IV) and Co(II) salts, hypochlorites, pyridinium chlorochromate, I₂ with AgOAc or iodine triacetate (ICl₃, AgOAc), *N*-iodosuccinimide in THF, VO(acac)₂, H₂O₂ in the presence of metal salts, *tert*-butyl peroxide with Al(O^{*t*}But)₃, upon anodic oxidation, etc.^{180–182} Considerable interest of researchers is attracted to the selective monooxidation of 1,2-diols aimed at the synthesis of chiral α -hydroxy ketones.

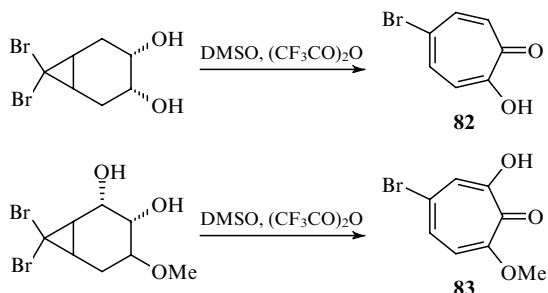
Probably, the most general reagents used for the oxidation of glycols to dicarbonyl compounds include DMSO, the H₂O₂–peroxytungstate system, *o*-iodylbenzoic acid and TEMPO-based reagents.

Dry DMSO in the presence of (CF₃CO)₂O and triethylamine oxidises acyclic and cyclic 1,2-diols to 1,2-diones at –60 °C.¹⁸³ Benzil **7a** and 1,2-dicarbonyl compounds **78–81** (some of these, in the enol form) were obtained by this method in 54%–98% yields with conservation of the carbon skeleton of the original diols.

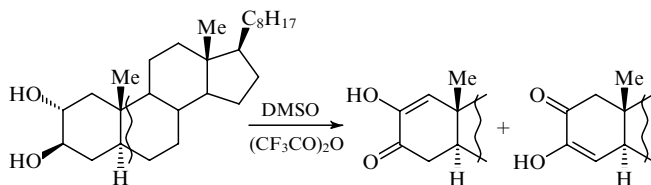




Treatment of diols containing the bicyclo[4.1.0]heptane skeleton with DMSO in trifluoroacetic acid results in tropolones **82** and **83**. It is assumed that the reaction occurs through ring expansion of the originally formed bicyclic diketones.



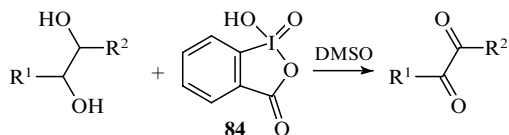
The oxidation of 5 α -cholestane-2 α ,3 β -diol affords a mixture of 2-hydroxy-5 α -cholest-1-en-3-one and 3-hydroxy-5 α -cholest-3-en-2-one in 84% overall yield.¹⁸³ The use of the Swern reagent in this reaction gives poorer results.¹⁸³



DMSO oxidises cyclohexane-1,2-diol and a number of acyclic vicinal diols to the corresponding 1,2-diketones at room temperature in the presence of dicyclohexylcarbodiimide in 60%–75% yields.¹⁸⁴

Diketone **7a** and its 4,4'-dibromo derivative are obtained smoothly and in high yields by oxidation of the corresponding 1,2-diarylethane-1,2-diols with DMSO in aqueous HBr at 110–115 °C.^{59,112}

It was found that *o*-iodylbenzoic acid **84** is a very mild oxidant for alcohols in DMSO at room temperature. It can also oxidise glycols without cleavage of the C–C bond giving the corresponding 1,2-diketones at room temperature in almost quantitative yields.¹⁸⁵



R¹, R² = Me, Ph, (CH₂)₄.

A method for the oxidation of primary and secondary alcohols and 1,2-diols with the reagent **84** has been patented.¹⁸⁶

Hydrogen peroxide usually cleaves glycols. However, it has recently been shown that acyclic vicinal diols are oxidised by H₂O₂ in a two-phase system in the presence of a catalytic amount of the [π-C₅H₅N(CH₂)₁₅Me]₃{PO₄[W(O)(O₂)₂]₄} complex to give diketones in 70%–93% yields.¹⁸⁷ The reaction occurs in a stepwise manner *via* intermediate α -hydroxy ketones. The results of the oxidation of cyclic diols are noticeably poorer: cyclooctane-1,2-dione was obtained in yields as low as 48%–58%, while cyclohexane-1,2-diol gives adipic acid rather than the diketone **4a**.¹⁸⁷

It is well known that such efficient oxidants as TEMPO transform vicinal diols to α -hydroxycarbonyl compounds (see,

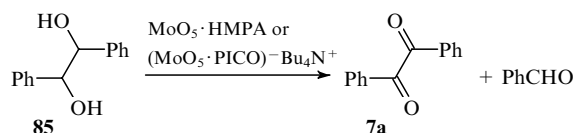
e.g., Refs 188 and 189) and oxidise 1,2-diphenylethane-1,2-diol **85** to benzil **7a**.¹⁹⁰ It was shown that the readily accessible 4-acetamido-TEMPO in combination with toluene-*p*-sulfonic acid in chloroform or CH₂Cl₂ can serve as a general reagent for the mild oxidation of linear and cyclic vicinal diols to α -diones.¹⁹¹

At present, the majority of other reagents for the oxidation of glycols are used less commonly. For example, it was shown that *cis*-cyclododecane-1,2-diol is oxidised to cyclododecane-1,2-dione on treatment with tris(triphenylphosphine)ruthenium dichloride [(Ph₃P)₃RuCl₂] in 53% yield.¹⁹² Later, an almost identical result was obtained using *tert*-butyl hydroperoxide in benzene in the presence of a phase-transfer catalyst, namely, PhCH₂N⁺Me₃–OMoBr₄.¹⁹³ Cyclohexane-1,2-diol undergoes oxidation to cyclohexane-1,2-dione **4a** in 51% yield at room temperature on treatment with a ruthenium complex (LPh₄)(RuO₂Cl₃), where L = P or As.¹⁹⁴

It was shown that KMnO₄ in the presence of nonionic tris[2-(2-methoxyethoxy)ethyl]amine, unlike other phase-transfer catalysts, oxidises phenylethane-1,2-diol and the diol **85** to phenylglyoxal and diketone **7a** in high yields.¹⁹⁵ Hydrogen peroxide applied onto the TS-1 zeolite converts one or both of the hydroxy groups in 1,2-diols to carbonyls, while cleavage of the C–C bond occurs only if an excess of the reagent is used.¹⁹⁶ Solvents affect strongly the reaction selectivity. For example, butane-2,3-diol is converted into 3-hydroxybutan-2-one in methanol and to butane-2,3-dione in acetone.

Unlike other periodates, tetrabutylammonium periodate in the presence of AlCl₃ in boiling chloroform oxidises the diol **85** to give mostly the diketone **7a** (yield 70%), and glycol cleavage occurs to a small extent (20% of benzaldehyde).⁸⁷ PhSe(O)Se(O)Ph is another reagent that enables the selective oxidation of the diol **85** to benzil **7a** (refluxing in THF for 3 h, yield 77%).⁸³ Quantitative yield of the compound **7a** in the oxidation of the diol **85** under very mild conditions is also provided by the system *N*-chlorosuccinimide–Me₂Se.⁹⁶ The catalytic system RuO₄[–]–BrO₃[–] cleaves the diol **85** to benzoic acid, whereas *trans*-RuO₃(OH)₂[–]–S₂O₈^{2–} affords benzil **7a** in 65% yield.¹⁹⁷

The mechanism of oxidation of *meso*- and *d,l*-diol **85** with peroxomolybdenum complexes, *viz.*, neutral MoO₅·HMPA and anionic (MoO₅·PICO)[–]–Bu₄N⁺ (PICO is picoline *N*-oxide) was studied.¹⁹⁸



In all cases, the oxidation of the diol **85** results in benzil **7a** and benzaldehyde. The latter is formed due to glycol cleavage of the diol **85**. The ratio of the reaction products is strongly affected by the nature of the substrates and oxidants. For example, the action of MoO₅·HMPA on both *meso*- and *d,l*-diol **85** results almost exclusively in benzaldehyde. However, the (MoO₅·PICO)[–]–Bu₄N⁺ oxidant mostly converts the *meso*-form of the diol **85** to the diketone **7a**, while the *d,l*-diol **85** is converted to benzaldehyde. Benzil **7a** is formed from a complex of the substrate with the oxidant in which the glycol is coordinated as a monodentate ligand, while benzaldehyde is formed from a complex in which the substrate plays the role of a chelating ligand. If the reaction is carried out in air, autooxidation takes place. There is evidence that the reaction occurs in the coordination sphere of the metal according to a homolytic mechanism.¹⁹⁸

A biochemical method was suggested for the transformation of ethylene glycol to glyoxal by treatment with oxidoreductase or microorganisms containing oxidoreductase, at 30 °C in aqueous solutions.¹⁹⁹

Ethylene glycol can also be oxidised to glyoxylic acid. Accessible oxidants based on nitric acid, namely, HNO₃–H₂SO₄–

V_2O_5 ²⁰⁰ and HNO_3 with Co, Al and Cu acetylacetonates,²⁰¹ have recently been suggested for this purpose.

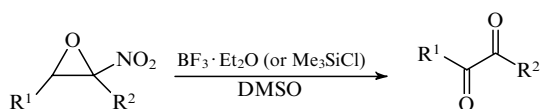
Such an efficient reagent as dimethyldioxirane can oxidise 1,2-diols without cleavage of the C–C bond of the glycol. However, the reaction stops at the step of the formation of hydroxy ketones, while diketones are found in the reaction mixture only as traces, since the carbonyl group that is formed deactivates the methine group as regards further oxidation.²⁰²

Glycol cleavage can be used for the synthesis of α -dicarbonyl compounds. Cleavage of methyl and ethyl D-tartrates in dry ether to the corresponding alkyl glyoxylates in 80%–85% yields on treatment with periodic acid²⁰³ can serve as an example.

Oxidation of epoxides usually results in α -hydroxy ketones. This was found for the first time in the treatment of epoxides with DMSO in the presence of a catalytic amount of BF_3 etherate.²⁰⁴ The same result was obtained on passing air through solutions of epoxides in DMSO. It was assumed²⁰⁵ that the oxidation follows a radical mechanism. It was shown subsequently that the reaction follows an ionic mechanism with epoxide ring opening on treatment with DMSO in the presence of various protic acids (CF_3COOH , H_2SO_4 , $MeSO_3H$, HBf_4 , HNO_3) resulting in the formation of an α -hydroxysulfoxonium salt. In turn, the latter decomposes to α -hydroxy ketones according to Kornblum.^{206, 207} Hydroxy ketones are also formed on treatment of epoxides with DMSO in the presence of molecular sieves²⁰⁸ or clay with microwave heating.²⁰⁹ Epoxysilanes are also oxidised in DMSO in the presence of triflates and tertiary amines to give α -hydroxyacylsilanes.²¹⁰

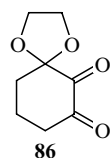
Unlike the reagents indicated above, the aqueous HBr –DMSO system smoothly converts diphenyloxirane to benzil **7a** in 71% yield; however, bis(α -diketone) **28** is formed from the corresponding bis(epoxide) in 31% yield only.²¹¹

1,2-Diones are formed upon oxidation of α -nitro epoxides.^{212–214} This process occurs in the presence of tetrakis(triphenylphosphine)palladium and triethylamine in boiling benzene and gives satisfactory yields of α -diketones.^{212, 214} The oxidation of nitro epoxides with the $BF_3 \cdot Et_2O$ (or Me_3SiCl)–DMSO system in CH_2Cl_2 at 0 °C followed by the addition of triethylamine gives the corresponding diketones in somewhat higher yields (54%–87%).^{213, 214}



$R^1, R^2 = Ph, Pr, Me, (CH_2)_4Me, (CH_2)_3, (CH_2)_4$.

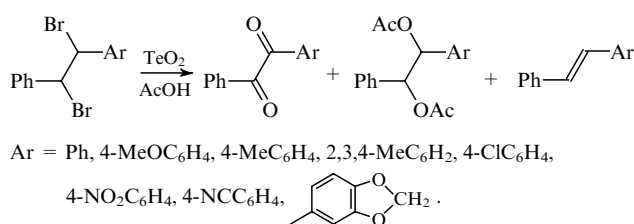
The same method afforded the triketone ketal **86**.^{213, 214}



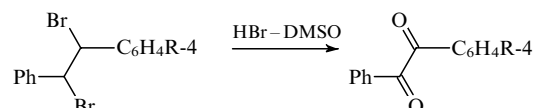
The reaction of α -nitro epoxides with $BF_3 \cdot Et_2O$ in acetonitrile in the presence of NaI gave good yields of α -iodo ketones.^{213, 214}

Transformations of vicinal dihalides (or halohydrins) to α -dicarbonyl compounds are not typical in organic synthesis, although dibromination of alkanes or bromination of alkenes followed by transformation to α -diketones can serve as an alternative to hydrocarbon oxidation. These transformations can be performed efficiently with a number of reagents that have appeared in the last few years.

Refluxing of 2-aryl-1,2-dibromo-1-phenylethanes in acetic acid in the presence of tellurium dioxide gives benzil **7a** and its derivatives (yields 19%–82%) as well as the diacetates of the corresponding 1,2-diols and stilbenes.²¹⁵ The diacetates and stilbenes predominate among the products in the case of substrates with electron-withdrawing substituents.



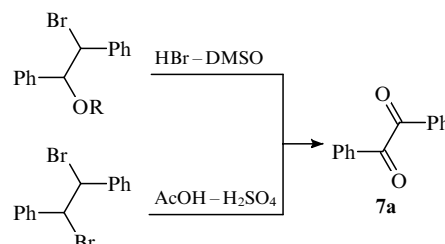
DMSO is a more convenient and accessible reagent for this kind of transformation.²¹⁶ For example, it was found that heating of *meso*- and *d,l*-2-aryl-1,2-dibromo-1-phenylethanes in the aqueous HBr –DMSO system at 110 °C for 4–8 h readily gives benzil **7a** and its derivatives in 70%–80% yields.



$R = H, Me, MeO, Cl, NO_2$.

This transformation occurs also without HBr but requires a longer time.¹¹² Later, this reaction was carried out with many acyclic and cyclic vicinal dibromides under microwave irradiation and gave α -diketones in 51%–75% yields.²¹⁷

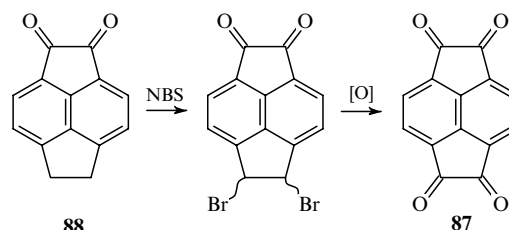
2-Bromo-1,2-diphenylethanol and even its methyl ether and formate undergo oxidation to diphenylethanedione in aqueous HBr –DMSO even more readily than 1,2-dibromo-1,2-diphenylethane.¹¹² If the oxidation is carried out without HBr , it follows the same direction but occurs more slowly.¹¹²



$R = H, Me, CHO$.

The cheapest way to oxidise 1,2-dibromo-1,2-diphenylethane to benzil (yield 80%) is heating the substrate in acetic acid in the presence of sulfuric acid.²¹⁸ It was found later that the addition of such compounds as iodine, potassium iodide or sodium sulfite to the reaction mixture accelerates considerably the oxidation of vicinal dibromides.²¹⁹

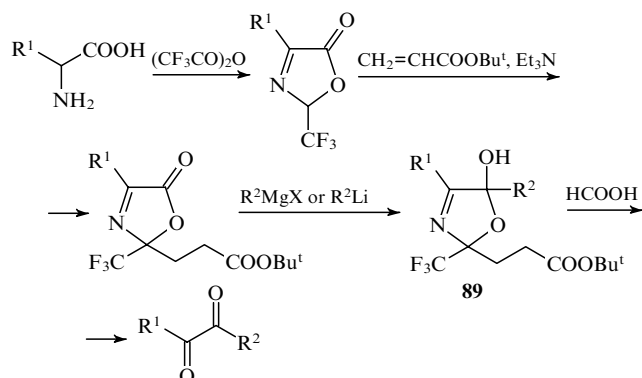
The possibility of the synthesis of 1,2,5,6-tetraketopyracene (**87**), a structural element of buckminsterfullerene, according to the following scheme was studied:^{220, 221}



Oxidation of the starting 1,2-dioxopyracene (**88**) with sodium dichromate resulted in the cleavage of the diketone carbon–carbon bond. However, the target tetraketone **87** could be obtained by the oxidation of the dibromide prepared by bromination of the diketone **88** with *N*-bromosuccinimide according to the reported procedure.²²² The oxidation of the dibromide was carried out by treatment with the $AgNO_3$ – $MeCN$ system and then with $NaOAc \cdot 3H_2O$ –DMSO.²²⁰ The yield of the tetraketone **87** reached 80% but was irreproducible. Later, the same research

group found that the dioxopyracene **88** could be directly oxidised to the tetraketone **87** by treatment with benzeneseleninic anhydride²²¹ (see Section IV).

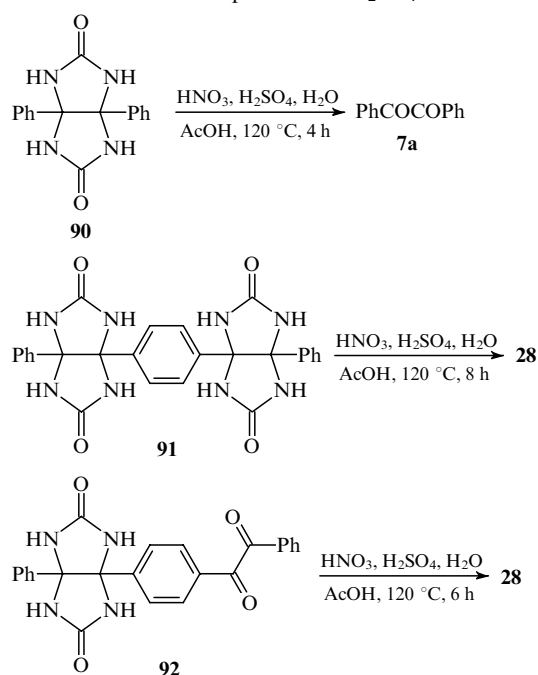
Methods are known for the transformation of five-membered heterocycles to α -diketones. Certain 5-hydroxyoxazolines of the type **89** decompose in formic acid at room temperature to give the corresponding α -diketones in good yields. A method based on this reaction was elaborated for the synthesis of α -diketones from α -amino acids, as shown below.²²³



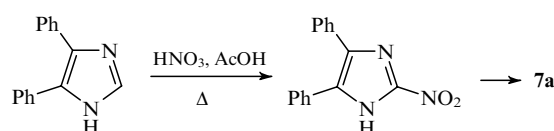
$R^1 = \text{Pr}^i$; $R^2 = \text{Ph}$, $\text{C}\equiv\text{CPh}$; $R^1 = \text{Bu}^s$, $R^2 = \text{Bu}^n$; $R^1 = \text{Ph}$, $R^2 = \text{Bu}^n$;
 $R^1 = \text{CH}_2\text{CH}_2\text{SMe}$, $R^2 = \text{Me}$; $R^1 = (\text{CH}_2)_3\text{NHCOCF}_3$; $R^2 = \text{Bu}^n$, Ph .

A number of acetylenic α -diketones used in the synthesis of tetrasubstituted furans were obtained according to the same scheme.²²⁴

Diaryl-substituted glycolurils **90–92** are oxidised to benzil **7a** and diketone **28** (yield 80%–90%) on heating with nitric acid in aqueous acetic acid in the presence of H_2SO_4 .²²⁵



The oxidation of 4,5-diphenylimidazole to the benzil **7a** occurs at milder conditions than that for glycolurils. It does not require the presence of sulfuric acid and water and affords the products in 80%–85% yield. The reaction involves the intermediate formation of 2-nitro-4,5-diphenylimidazole.²²⁵



IV. Oxidation of alkanes, alkenes, alkynes and their derivatives

Of the classes of compounds listed above, alkynes can be converted to α -dicarbonyl compounds most easily (followed by alkenes and finally alkanes). Table 4 lists the reagents used for the preparative oxidation.

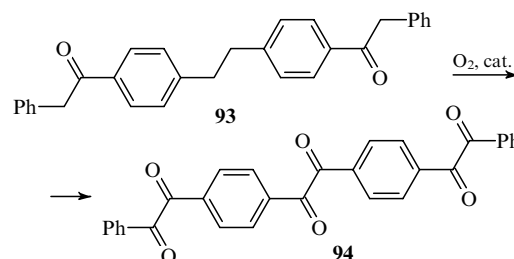
Table 4. Reagents used for the preparative oxidation of alkanes, alkenes, alkynes and their derivatives to α -dicarbonyl compounds $R^1\text{COCOR}^2$.

Substrate	Reagent
$R^1\text{CH}_2\text{CH}_2\text{R}^2$	$\text{Na}_2\text{Cr}_2\text{O}_7 - \text{AcOH} - \text{Ce}(\text{OAc})_3$, $(\text{PhSeO})_2\text{O}$, $\text{O}_2 - (\text{Co}(\text{OAc})_2, \text{Mn}(\text{OAc})_2, \text{NaBr})$; Gif-system: $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O} - \text{Bu}^t\text{OOH} - \text{MeCOCH}=\text{CH}_2$
$R^1\text{CH}=\text{CHR}^2$	SeO_2 , KMnO_4 , $\text{CrO}_3 - \text{AcOH}$, $\text{O}_2 - (\text{Co}(\text{OAc})_2, \text{Mn}(\text{OAc})_2, \text{NaBr})$, OsO_4 , $\text{HBr} - \text{DMSO}$, $\text{I}_2 - \text{DMSO}$, $\text{NaBr} - \text{HCl} - \text{DMSO}$, $\text{Bu}_4\text{NBr} - \text{HCl} - \text{DMSO}$, $\text{Br}_2 - \text{H}_2\text{SO}_4$, $\text{I}_2 - \text{H}_2\text{SO}_4$, $\text{HBr} - \text{H}_2\text{SO}_4$, $\text{NaBr} - \text{H}_2\text{SO}_4$
$R^1 - \text{C}\equiv\text{C} - \text{R}^2$	O_3 , KMnO_4 , NH_4MnO_4 , $\text{Zn}(\text{MnO}_4)_2$, RuO_4 , OsO_4 , $\text{Ti}(\text{NO}_3)_3$, SeO_2 , O_2 , $\text{PhSeSePh} - (\text{NH}_4)_2\text{S}_2\text{O}_8 - \text{MeOH}$, $\text{MoO}(\text{O}_2)_2 - \text{Hg}(\text{OAc})_2$, $\text{H}_2\text{O}_2 - \text{H}_3\text{PMO}_{12}\text{O}_{40}$, $\text{H}_2\text{O}_2 - \text{H}_3\text{PW}_{12}\text{O}_{40}$, $\text{H}_2\text{O}_2 - \text{MeReO}_3$, CF_3COOOH , $\text{HNO}_3 - \text{NaNO}_2 - \text{PdCl}_2$, $\text{Cr}(\text{V}) - N, N' - \text{ethylenebissalicylidene imine}$, H_3PO_5 , dialkyldioxiranes, $\text{PhIO} - \text{RuCl}_2(\text{PPh}_3)_3$, $\text{PhI}(\text{OCOCF}_3)_2$, H_5IO_6 , I_2O_5 , $\text{HgO} - \text{I}_2$, $\text{NBS} - \text{DMSO}$, $\text{I}_2 - \text{DMSO}$, anodic oxidation

For many reasons, direct oxidation of alkanes to α -dicarbonyl compounds is a difficult technical problem, and only a few examples of this kind of oxidation are known.

For example, in view of the great practical importance of acenaphthenequinone, processes for its synthesis by direct oxidation of acenaphthene were studied. Such oxidants as H_2O_2 , HNO_3 , permanganates and oxygen under pressure or in the presence of various catalysts were used.²²⁶ None of these methods gave good yields of acenaphthenequinone. The oxidation of acenaphthene with $\text{Na}_2\text{Cr}_2\text{O}_7$ in AcOH with addition of cerium acetate at 40°C does not provide high yield of acenaphthenequinone either (38%–60%). On the other hand, as noted above, sodium dichromate does not oxidise dioxopyracene **88** to the tetraketone **87**. However, this was performed with the use of benzeneseleninic anhydride $(\text{PhSeO})_2\text{O}$, which oxidises compound **88** to the tetraketone **87** in 82% yield on heating in chlorobenzene at 125°C .²²¹

1,2-Diphenylethane and its derivatives undergo oxidation with oxygen in the liquid phase in the presence of $\text{Co} - \text{Mn} - \text{MBr}$ catalysts to give the corresponding diphenylethanediones.^{228–230} If oxygen is passed through a solution of compound **93** in glacial acetic acid containing the tetrahydrates of manganese and cobalt acetates and NaBr , not only the α -ketomethylene groups but also the ethane fragment are oxidised at 110°C , leading to the formation of the hexaketone **94** in 70% yield.²²⁸

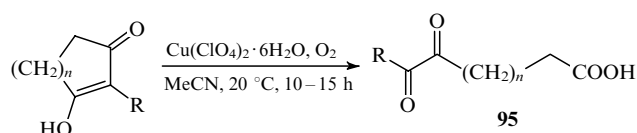


A study of the oxidation of 1,2-diphenylethane with oxygen in the presence of Co–Mn–MBr catalysts showed that this process follows the radical mechanism. In the first step, it gives 1,2-diphenylethane-1,2-diol, which is then oxidised to 1,2-diphenylethanone. The latter is transformed to benzil **7a**. The overall selectivity reaches 80%.^{229,230} The selectivity of oxidation is affected only by the reaction temperature and the concentration of $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$.²³⁰

Oxidation of pentane and hexane with the $\text{Ph}_3\text{Bi}-\text{Bu}^t\text{OOH}$ system at room temperature initially gives α -diketones, which are then oxidised to carboxylic acid anhydrides.²³¹ In this case, it is the oxygen formed from the hydroperoxide in the coordination sphere of the metal that serves as the actual oxidant.²³¹

Dicarbonyl compounds are also obtained upon oxidative formation or cleavage of the C–C bonds. Oxidation of cyclohexane, cyclooctane and cyclododecane in Gif-systems under the action of $\text{Fe}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}-\text{Bu}^t\text{OOH}$ in the presence of methyl vinyl ketone results in the corresponding 1-cycloalkylbutane-2,3-diones as the main products.²³² The reaction occurs through the Michael-type addition of the cycloalkane to methyl vinyl ketone followed by the insertion of the *tert*-butylperoxy group at the α -position to the carbonyl group of the adduct, which then slowly eliminates Bu^tOH to give α -diketones.²³²

Oxidative cleavage of the C–C bonds can also result in dioxo carboxylic acids. For instance, the oxidation of the enol forms of cyclic 1,3-diketones with copper(II) salts and oxygen results in acids **95**.²³³



$n = 0$, $R = \text{Me}$; $n = 1$: $R = \text{Me}$, $\text{CH}=\text{CH}_2$, $\text{CH}_2\text{CH}=\text{CH}_2$, Ph .

Over ten years ago, Haines²³⁴ noted that there are probably few reliable methods for the transformation of alkenes to 1,2-dicarbonyl compounds. This statement is no longer wholly true since the late 80's when new oxidising DMSO-based reagents appeared.

Selenium dioxide was among the first reagents that oxidise alkenes to α -dicarbonyl compounds. It oxidises alkenes containing no allylic hydrogen atoms rather successfully on heating them in acetic acid, trichlorobenzene or without a solvent. For example, ethylene and stilbene are oxidised to glyoxal and benzil **7a** in up to 70% yields;^{35,234} styrene is converted to phenylglyoxal along with hydroxylation products,²³⁵ while propene, a representative of allylic alkenes, gives methylglyoxal in only 19% yield.²³⁴

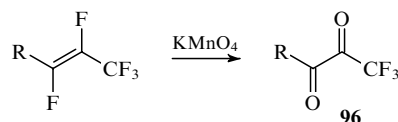
The direction of the oxidation of alkenes with potassium permanganate strongly depends on the reaction conditions. In alkaline media, internal alkenes mostly form 1,2-diols, while in nearly neutral or weakly alkaline media (pH 9–9.5) α -hydroxy ketones are formed.²³⁴ Symmetric cyclic and acyclic alkenes are oxidised with potassium permanganate in cold acetic anhydride (not above 10 °C) to give the corresponding α -diketones in moderate yields.^{236,237} The selectivity of the process is not high as noticeable amounts of 2-acetoxy ketones and dicarboxylic acids are formed. It was noted that the reaction may be hazardous.²³⁷ In addition, attempts to synthesise diketones from cyclohexene and norbornene failed.²³⁴ The oxidation of *E*-alkenes gives somewhat higher yields of diketones than the oxidation of the *Z*-isomers.^{234,236} Styrene can be converted to phenylglyoxylic acid by oxidation with potassium permanganate under alkaline conditions.²³⁸

Oxidation of nonterminal alkenes with permanganate under conditions of phase-transfer catalysis gives α -diols, α -diketones and α -hydroxy ketones along with carboxylic acids. The ratio of the oxidation products can be controlled by varying the conditions.²³⁴ For example, cyclododecane-1,2-dione and decane-5,6-dione were obtained in 69% and 53% yields from the correspond-

ing alkenes in the $\text{KMnO}_4-\text{CH}_2\text{Cl}_2-\text{H}_2\text{O}$ system containing acetic acid and Adogen 464.²³⁹

Such a heterogeneous reagent as $\text{KMnO}_4-\text{CuSO}_4 \cdot 5\text{H}_2\text{O}-\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in CH_2Cl_2 oxidises cyclooctene and cyclododecene to the corresponding diketones in moderate yields.²⁴⁰ In the absence of copper acetate, the reaction stops in the step of formation of α -hydroxy ketones.²⁴⁰

Oxidation of nonterminal fluoroalkenes with permanganate under strictly controlled conditions (the ratio alkene : $\text{KMnO}_4 = 1 : 0.3-0.7$, acetone : water = 24 : 1; -30 to -20 °C) affords diketones **96** in 30%–80% yields.^{241,242}

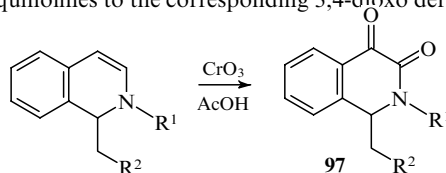


$R = \text{CF}_3, \text{Ph}$.

It is assumed that this reaction occurs *via* an intermediate product of hydroxylation of the C=C bond, which undergoes dehydrofluorination to give the target products. Although satisfactory yields are obtained, cleavage of the C–C bond cannot be avoided completely, even at 50% conversion of the starting olefin.²⁴²

Perfluoroalkenes can also be converted to dicarbonyl compounds by catalytic or stoichiometric oxidation with osmium tetroxide. In this case, tetrafluoroethylene is converted to glyoxylic acid in good yield, while perfluorocyclohexene gives perfluorocyclohexane-1,2-dione.^{243,244}

Chromium(VI) compounds are mostly known as oxidants that cleave the C=C bonds. However, a few cases have been reported in which dicarbonyl compounds were obtained upon oxidation of the double bonds with chromium trioxide. For example, CrO_3 in acetic acid was used for the oxidation of a series of 1,2-dihydroisoquinolines to the corresponding 3,4-dioxo derivatives **97**.²⁴⁵



$R^1 = 2,4,6-(\text{NO}_2)_3\text{C}_6\text{H}_2\text{CH}_2$, $R^2 = \text{PhCO}$;

$R^1 = 2,4-(\text{NO}_2)_2\text{C}_6\text{H}_3\text{CH}_2$, $R^2 = \text{PhSO}_2$, $4-\text{NO}_2\text{C}_6\text{H}_4\text{CO}$.

Both stilbene isomers are converted on treatment with a catalytic amount of CrO_3 and an excess of aqueous *tert*-butyl hydroperoxide to give mixtures of oxidation products, *trans*-stilbene oxide being the major component. In this case, approximately equal amounts of benzil **7a**, benzophenone and benzoin benzoate are formed.²⁴⁶ Norbornene was found to be inert under these conditions.²⁴⁶

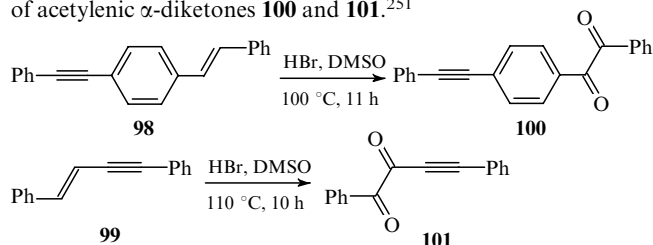
A study of the liquid-phase oxidation of (*E*)-stilbene with oxygen in acetic acid at 105 °C in the presence of a Co–Mn–bromide catalyst showed that rapid and total conversion of the substrate results in a complex mixture of products [PhCOOH , Ph_2CO , Ph_2CHCHO , PhCOCOPh , PhCH_2COPh , $\text{PhCH}(\text{OAc})\text{COPh}$, $\text{PhCH}(\text{OAc})\text{CH}(\text{OAc})\text{Ph}$, *etc.*] with up to 46% content of benzil **7a**.²⁴⁷ These products are formed from the primary oxidation product, *i.e.* 1,2-diphenyloxirane.²⁴⁷

Peracetic acid oxidises *trans*-1-acetoxy-2-iodo-1,2-diphenylethylene to diketone **7a** in low yield.²⁴⁸

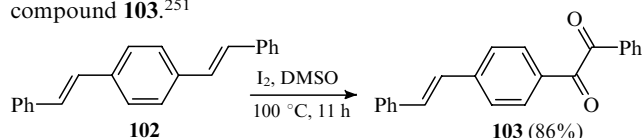
DMSO-based oxidants are much more versatile and convenient reagents for the synthesis of α -dicarbonyl compounds from alkenes. This was first discovered in 1989 for stilbene, which was oxidised readily and in high yield to benzil **7a** in the $\text{HBr}-\text{H}_2\text{O}_2-\text{DMSO}$ system.²⁴⁹ It was found subsequently that hydrogen peroxide accelerates the reaction but does not act as an oxidant. A solution of aqueous HBr in DMSO successfully oxidises stilbenes with both donor and acceptor substituents to

give the corresponding diarylethanediones in 56%–86% yields. It turned out that the first act of the process involves the electrophilic addition of bromine, which is formed *in situ* from HBr and DMSO, to the double bond, but it is the intermediate 1,2-diaryl-1,2-dibromoethanes that undergo oxidation. In this case, DMSO plays a dual role, specifically, it generates a microscopic amount of bromine from HBr (it is this reaction that is accelerated by hydrogen peroxide) and oxidises dibromides by a mechanism resembling that of the Kornblum reaction.^{112, 157} Since the first act of the reaction is the electrophilic addition of bromine to the double bond, it becomes clear why the oxidation of 4-nitrostilbene requires much longer time than that of stilbene, while 4,4'-dinitrostilbene does not undergo oxidation at all.¹¹² Compounds other than hydrogen bromide can be successfully utilised as the bromine sources. For instance, good results were achieved in the NaBr–H₂SO₄–DMSO, NaBr–HCl–DMSO, and Bu₄NBr–HCl–DMSO systems.¹¹⁴ In some cases, passage of air through a solution of HBr in DMSO increases the oxidation efficiency.²⁵⁰

Triple bonds are practically inert with respect to HBr in DMSO. This fact was successfully used to perform selective oxidation of double bonds in the enynes **98** and **99** in the synthesis of acetylenic α -diketones **100** and **101**.²⁵¹

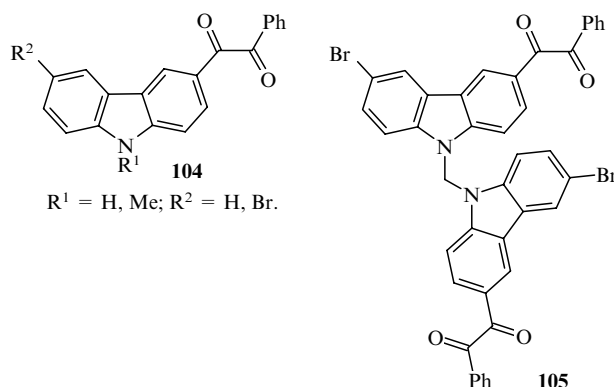


Iodine in DMSO can also oxidise alkenes to dicarbonyl compounds, but it is much less reactive than HBr–DMSO.^{251–254} This reagent oxidises only stilbene and its derivatives containing electron-donating or weak electron-withdrawing substituents (Me, OMe, Cl) at position 4.^{252, 253} The decrease in the reaction rate caused by electron-withdrawing substituents made it possible for the first time to perform selective oxidation of only one bond in 1,4-(*E,E*)-distyrylbenzene (**102**) to give compound **103**.²⁵¹



Styrene, being an alkene with a terminal double bond, is oxidised both with bromine and HBr in DMSO to give phenylglyoxal. This results in a much larger amount of side products than in the oxidation of stilbenes.²⁵⁵

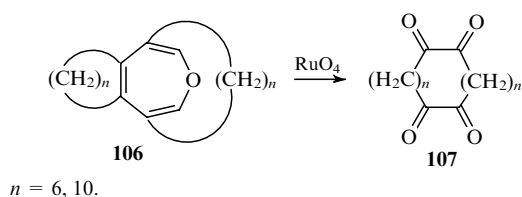
In the oxidation of 3-styryl- and 3,6-distyrylcarbazoles with the HBr–DMSO system, oxidation of the double bonds is accompanied by side processes such as bromination of the carbazole moiety and methylenation of the free NH groups to give dioxo- and tetraoxocarbazole derivatives **104** and **105**.²⁵⁶



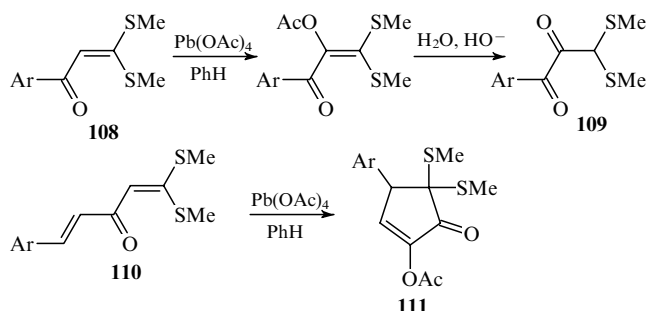
These side processes that are beneficial in this case occur due to the reaction of the carbazole moiety with bromine and formaldehyde generated upon the reaction of HBr with DMSO at 120 °C.²⁵⁶

The most efficient method for the oxidation of stilbenes to diketones (yields 50%–81%) is probably refluxing the substrates in acetic acid in the presence of H₂SO₄ containing admixtures of bromine, iodine, HBr, NaBr or sodium sulfite.^{218, 219} As mentioned above, the reaction involves intermediate electrophilic halogenation of double bonds if halogens, hydrogen halides or their salts are used.^{218, 219}

In addition, examples of the specific oxidation of double bonds with the formation of specific types of dicarbonyl compounds are worth noting. Oxidation of compounds **106** with RuO₄ (formed from RuCl₃·3H₂O and NaIO₄) in a mixture of CCl₄ and aqueous MeCN affords macrocyclic bis- α -diketones **107** in yields up to 40%.²⁵⁷



Aroylketene dithioacetals **108** are oxidised with Pb(OAc)₄ in boiling benzene to give acetoxy dithioacetals, which are hydrolysed under mild conditions to compounds **109**. Under similar conditions, their vinylogues **110** undergo oxidative cyclisation according to Nazarov, giving 2-acetoxycyclopentenone derivatives **111**, which are precursors of di- and tri-ketones.²⁵⁸



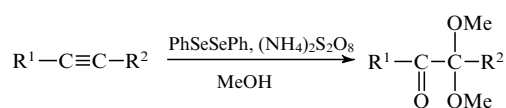
Oxidation of alkynes to α -dicarbonyl compounds, unlike that of alkanes and alkenes, is one of reliable methods to obtain compounds of this class. Numerous reagents are known to perform this type of transformation successfully, although there is always a danger of cleavage of the carbon–carbon bond both in substrates and in products. The oxidation of alkynes has been covered in reviews and books rather thoroughly,^{4, 5, 40, 234} and in most cases we are going to refer to the newer studies or those not included in these sources.

Alkynes are comparatively resistant against oxygen, and only few examples of their oxidation with oxygen to diketones are known. Passage of air through a solution of diphenylacetylene in acetic acid containing a Co–Mn–MBr catalyst for 3 h at 110 °C gives benzil **7a** in up to 90% yield.²⁵⁹ Oxidation of cyclooctyne with air at low temperatures to give the corresponding α -dione was also reported.²⁶⁰

Ozonisation of both terminal and internal alkynes in alcohols at low temperatures serves as a method for the synthesis of oxo aldehydes and α -diketones. The ozonisation of 1-ethoxypent-1-yne in hexane gave ethyl 2-oxopentanoate.²³⁴

Oxidation of alkynes that do not contain methylene groups adjacent to the triple bond to α -dicarbonyl compounds is carried out with selenium dioxide.^{40, 234} The oxidation is facilitated upon addition of catalytic amounts of sulfuric acid. For example, refluxing diphenylacetylene with SeO₂ in AcOH containing sulfuric acid gives diketone **7a**. The reaction with phenylacetylene

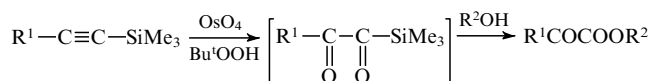
under the same conditions gives phenylglyoxylic acid.²³⁴ Diphenyl diselenide is another selenium-containing reagent that oxidises the triple bond. It converts alkynes to diketone and oxo aldehyde monoacetals in high yields in boiling methanol in the presence of ammonium peroxodisulfate.²⁶¹



$\text{R}^1 = \text{Ph}; \text{R}^2 = \text{H, Ph, 3-Bu}^t\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 2\text{-BrC}_6\text{H}_4;$
 $\text{R}^2 = \text{H}; \text{R}^1 = \text{PhCH}_2, \text{Bu}^n, \text{C}_6\text{H}_{13}, \text{HOOCCH}_2; \text{R}^1 = \text{R}^2 = \text{Pr}^n.$

Potassium, zinc and ammonium permanganates are widely used to oxidise alkynes (for the reviews, see Refs 4, 234, 262). To our knowledge, in these reactions terminal alkynes undergo only oxidative cleavage with the formation of carboxylic acids and loss of one carbon atom, whereas α -diketones can be obtained only from internal alkynes. A particularly efficient general method for the synthesis of α -dicarbonyl compounds from alkynes involves the oxidation of the latter with potassium permanganate in aqueous acetone or dioxane under nearly neutral conditions provided by the addition of sodium hydrogen carbonate and magnesium sulfate.²³⁴ Of potassium, magnesium and zinc permanganates, the latter is the most efficient reagent for the oxidation of alkynes in dichloromethane.²⁶³ Potassium permanganate in aqueous acetone proved to be a convenient oxidant of 3,6-di(phenylethynyl)carbazoles to the corresponding 3,6-bis(phenylglyoxylyl)carbazoles.^{264, 265} The mechanism of the oxidation of alkynes with KMnO_4 and the effect of the substrate structure on the process were studied.²⁶⁶ It was shown that the oxidation rate depends on electronic rather than on steric factors.

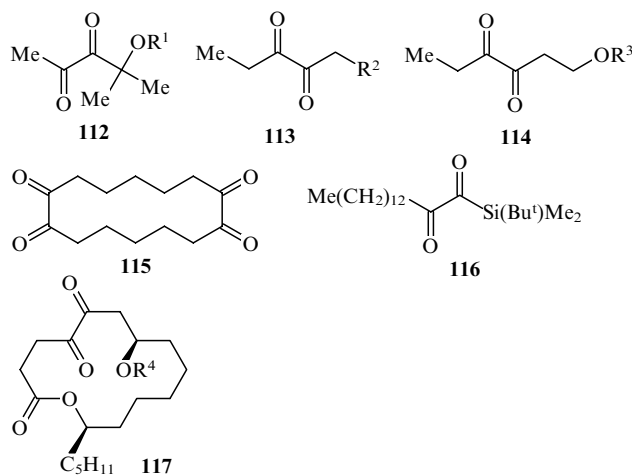
Certain similarity is observed between the oxidation of alkynes with osmium and ruthenium tetroxides. Terminal alkynes are oxidised with OsO_4 to carboxylic acids. On the other hand, alkynes with an internal triple bond can be oxidised to α -diketones using this reagent.^{234, 267} It was found that OsO_4 forms complexes with alkynes in the presence of pyridine or isoquinoline, $2\text{OsO}_4\text{L}_4\text{R}^1\text{C}\equiv\text{CR}^2$ (where L is pyridine or isoquinoline); these complexes are hydrolysed in the presence of sodium sulfite to the corresponding diketones, R^1COCOR^2 . However, phenylacetylene is converted to benzoic acid under these conditions.²⁶⁸ There are methods for the transformation of alkynes to dicarbonyl derivatives with a catalytic amount of OsO_4 in the presence of co-oxidants, such as potassium chlorate, hydrogen peroxide, *tert*-butyl hydroperoxide and morpholine *N*-oxide.²³⁴ It is believed that OsO_4 is the actual oxidant, while a co-oxidant, for example, potassium chlorate, regenerates OsO_4 from the osmium dioxide formed in the first step.²⁶⁹ Acetylene is oxidised with the $\text{OsO}_4-\text{KClO}_3$ system to give glyoxylic acid,²⁶⁷ and alkoxyalkynes form α -oxo esters in high yields under similar conditions.²⁶⁹ Trimethylsilylalkynes are oxidised to methyl or butyl phenyl(-alkyl)glyoxylates on treatment with a catalytic amount of OsO_4 in the presence of BuOOH in methanol or *tert*-butyl alcohol at 0°C .²⁷⁰ It is believed that α -oxo esters are formed from the primary oxidation products, *i.e.* silylated diketones, on decomposition with an alcohol.²⁷⁰



$\text{R}^1 = \text{Ph, C}_5\text{H}_{11}, \text{C}_6\text{H}_{13}; \text{R}^2 = \text{Me, Bu}^t.$

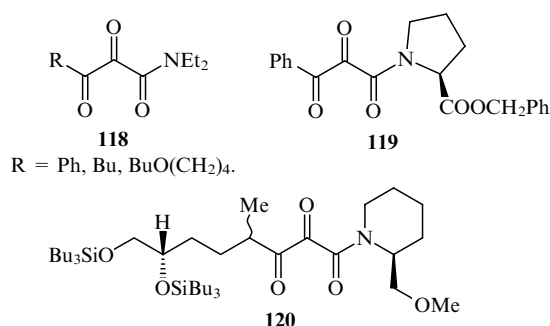
Ruthenium tetroxide, which is generated *in situ* from RuO_2 dihydrate, RuCl_3 or tris(triphenylphosphine)ruthenium dichloride and such oxidants as NaIO_4 , NaOCl or PhIO or by electrochemical oxidation, serves as an efficient reagent for the transformation of internal alkynes to α -diketones under mild conditions.^{234, 271} Probably, the main advantage of RuO_4 is that it reacts under mild conditions (often at, or below, room temper-

ature) and its high selectivity. For example, benzil **7a** and α -diketones **112–117** with various functional groups are obtained in 27%–95% yields from the corresponding internal alkynes and ruthenium dichloride with NaIO_4 .²⁷²



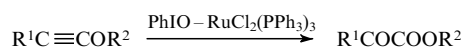
$\text{R}^1 = \text{Ac, tetrahydropyran-2-yl}; \text{R}^2 = \text{COOMe, OCOBu}^t;$
 $\text{R}^3 = \text{CH}_2\text{Ph, tetrahydropyran-2-yl}; \text{R}^4 = \text{Si}(\text{Bu}^t)\text{Me}_2.$

The same method was used in the synthesis of dioxo amides **118–120** from the corresponding acetylenic carboxamides.²⁷³

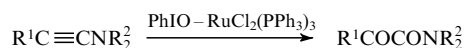


Terminal alkynes are converted to carboxylic acids upon oxidation with a catalytic amount of ruthenium tetroxide generated electrochemically from ruthenium dioxide.²⁷¹ On the other hand, dialkyl- and phenylalkylalkynes are oxidised with RuO_4 to give α -diketones in high yields in a two-phase system CCl_4 –saturated aqueous NaCl .²⁷¹

Iodosylbenzene combined with $\text{RuCl}_2(\text{PPh}_3)_3$ in CCl_4 readily oxidises internal alkynes to the corresponding α -diketones.²⁷⁴ The same reagent oxidises alkoxy- and aminoalkynes to α -oxo esters and α -oxo carboxamides in 44%–84% yields.²⁷⁵



$\text{R}^1 = \text{Me, R}^2 = \text{Et}; \text{R}^1 = \text{Pr}^i, \text{R}^2 = \text{Me}; \text{R}^1 = n\text{-C}_6\text{H}_{13}, \text{R}^2 = \text{Me};$
 $\text{R}^1 = \text{Bu, R}^2 = \text{Pr}^i; \text{R}^1 = \text{Ph, R}^2 = \text{Et}.$

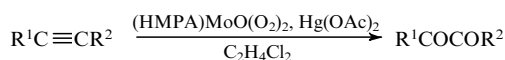


$\text{R}^1 = \text{Me, R}^2 = \text{Et}; \text{R}^1 = \text{Pr}^i, \text{R}^2 = \text{Me}; \text{R}^1 = \text{Ph, R}^2 = \text{Me, Et}.$

Thallium nitrate is one more reagent that readily oxidises triple bonds. However, its use in the synthesis of α -dicarbonyl compounds is rather limited. Symmetric dialkylalkynes are converted with $\text{Tl}(\text{NO}_3)_3$ in acidic methanolic medium to give α -hydroxy or α -methoxy ketones, whereas alkylarylalkynes undergo oxidation with 1,2-alkyl shift to give α -branched carboxylic acids.⁵ It is only diphenylacetylene and its substituted derivatives that undergo oxidation on refluxing with $\text{Tl}(\text{NO}_3)_3$ in glym containing HClO_4 to give benzils in 45%–97% yields.²⁷⁶

In recent years, molybdenum and tungsten peroxocomplexes have been extensively studied as oxidants of alkynes.^{277–282} It was

shown that both terminal and internal alkynes undergo oxidation to the corresponding α -oxo aldehydes and α -diketones in rather good yields (55%–90%) on treatment with a $\text{MoO}(\text{O}_2)_2$ –hexamethylphosphoramide complex in the presence of mercuric acetate in a dichloroethane–methanol mixture.²⁷⁷



$\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{H}$, Ph ; $\text{R}^1 = \text{R}^2 = \text{C}_6\text{H}_{13}$; $\text{R}^1 = \text{Bu}$, $\text{R}^2 = \text{H}$, Ph .

No oxidation occurs in the absence of $\text{Hg}(\text{OAc})_2$. It is known that the action of hydrogen peroxide on Na_2MoO_4 salts [wherein $\text{M} = \text{Mo}(\text{VI})$ or $\text{W}(\text{VI})$] results in oxodiperoxo complexes with the composition $\text{MoO}(\text{O}_2)_2$, which possess strong oxidative properties. It turned out that dilute H_2O_2 oxidises phenylacetylene and hex-1-yne rather readily in the presence of a catalytic amount of molybdates or tungstates (Na_2MoO_4), phase-transfer catalysts, and mercuric acetate. However, the yields of the resulting oxo aldehydes are low, while carboxylic acids are the main products.²⁷⁸ Diphenylacetylene was inert under these conditions. Heteropolyacids, such as $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ and $\text{H}_3\text{PW}_{12}\text{O}_{40}$, manifest higher catalytic activity in the oxidation of alkynes with hydrogen peroxide;^{280–282} these catalysts convert acetylene to glyoxal (yields up to 63%).²⁸⁰ However, phenylacetylene and certain dialkyl- and alkylphenylalkynes are oxidised under these conditions mostly to give carboxylic acids, unsaturated ketones and α -oxo epoxides.^{279, 281, 282} Generally, this type of catalytic oxidation of the triple bond to α -dicarbonyl compounds is no more selective than the oxidation with hydrogen peroxide or peroxy acids. For instance, it is known that trifluoroperacetic acid oxidises diphenylacetylene to afford a mixture of benzil **7a** and benzoic acid.²⁸³ Mixtures of products are also formed upon oxidation of alkynes with hydrogen peroxide in the presence of methylrhodium trioxide MeReO_3 .²⁸⁴ The reaction in the two-phase system CH_2Cl_2 – H_2O converts diphenyl-, dipropyl-, and *tert*-butyl(methyl)alkynes to the corresponding α -diketones (yields 38%–67%), and terminal alkynes (phenylacetylene and non-1-yne) are oxidised to phenyl- and heptyl glyoxalic acids (yields 68% and 47%).²⁸⁴

Nitrogen oxides catalyse the oxidation of acetylene to glyoxal at temperatures from 170 to 250 °C,²⁸⁵ and $\text{Pd}(\text{II})$ catalyses its oxidation in 30%–60% HNO_3 to oxalic acid.²⁸⁶ It was shown that acetylene is not oxidised in HNO_3 at 25 °C or in the HNO_3 – NaNO_2 system, but PdCl_2 – NaNO_2 in nitric acid at 15 °C favours the formation of glyoxal in 40%–50% yield with respect to the acetylene consumed.²⁸⁷ $\text{Hg}(\text{NO}_3)_2$ is less reactive. Methylacetylene was found to be more reactive than acetylene with respect to oxidation, while phenylacetylene gives stable organopalladium compounds that do not undergo further oxidation under the reaction conditions.²⁸⁷

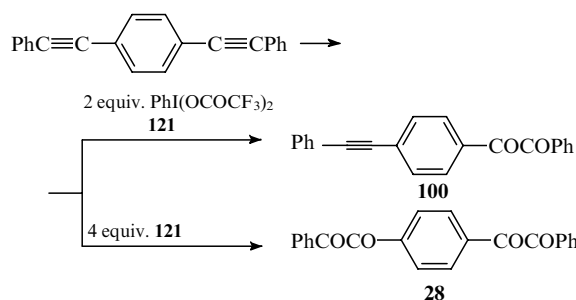
Diphenylacetylene is oxidised in high yield to benzil **7a** under the action of complexes of $\text{Cr}(\text{V})$ with *N,N'*-ethylenebis(salicylideneimine) (salen-complexes). However, phenylacetylene is mostly converted to benzoic acid under these conditions, while only a small amount of phenylglyoxal is formed.^{288, 289}

Phenylacetylene and certain internal alkynes are efficiently oxidised with monoperoxyphosphoric acid (H_3PO_5). However, this reaction produces mixtures of the corresponding α -dicarbonyl compounds with benzoic acid and rearrangement products. The reaction involves α -oxo carbenes as intermediates.²⁹⁰

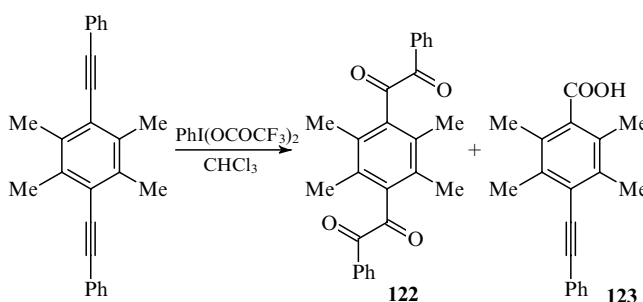
The oxidation of alkynes with dimethyl- and methyl(trifluoromethyl)dioxiranes also occurs *via* α -oxo carbene intermediates. The reaction results in mixtures of oxidation products, including α -diketones and α -oxo acids.^{291, 292}

Bis(trifluoroacetoxy)- λ^3 -iodanylbenzene **121** smoothly oxidises internal alkynes to α -diketones and terminal alkynes to α -hydroxy ketones.^{293–296} Two equivalents of the reagent **121** selectively oxidise one triple bond in bisphenylethynylbenzene to give acetylenic diketone **100**, while four equivalents of the reagent

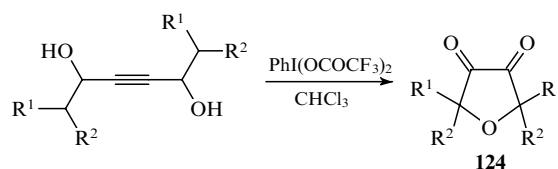
oxidise the substrate completely, converting it to the tetraketone **28**.²⁹³



Compound **121** oxidises only one triple bond in diphenylbutadiyne to produce a mixture of diphenyl-1,4-dioxobutene (40%) and acetylenic diketone **101** (30%).²⁹⁶ Compound **121** oxidises diphenylacetylene and its derivatives with electron-donating or moderate electron-withdrawing groups to the corresponding benzils in yields above 70%. However, (4-nitrophenyl)phenylacetylene is converted to 4-nitrobenzil in only 28% yield.²⁹⁴ Despite the high selectivity of the reagent **121** as the oxidant, cleavage of the triple bond cannot be avoided completely. For example, the oxidation of bisphenylethynylidurene gives the acid **123** in addition to the tetraketone **122**.²⁹⁴



The action of compound **121** on 1,4-dihydroxybutynes results, as expected, in the oxidation of the triple bond along with the intramolecular dehydration to give substituted tetrahydrofuran-diones **124** in one step and in high yields.²⁹⁷



$\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^1, \text{R}^2 = (\text{CH}_2)_4$.

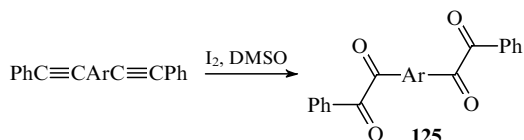
Like compound **121**, iodosylbenzene oxidises diphenylacetylene to benzil **7a**. The mechanism of its action is somewhat analogous to the mechanism of oxidation of alkynes with ozone.²⁹⁸

Periodic acid (H_5IO_6) is yet another iodine-based oxidant, which converts diphenylacetylene to benzil **7a** in almost quantitative yield on heating in acetic acid.²⁹⁹ Like I_2O_5 , this oxidant has the advantage that treatment of diphenylacetylene in boiling methanol or ethylene glycol affords mono- and diketals of benzil **7a**, which are difficult to obtain by other methods.²⁹⁹ It is believed that I^+ rather than I^{7+} or I^{5+} is the actual oxidising particle in this case. This opinion is supported by the conversion of diphenylacetylene to mono- and dimethyl ketals of benzil **7a** on heating in methanol with $\text{HgO}-\text{I}_2$.²⁹⁹

N-Bromosuccinimide in dry DMSO is an efficient oxidant of triple bonds in phenylacetylene, diphenyl-, dimethyl- and methylphenylacetylene.³⁰⁰ The reaction can occur even at room temperature. The yield of benzil **7a** reaches 98%, but other alkynes mentioned above form α -dicarbonyl derivatives in lower yields. Diphenylbutadiyne is oxidised to diphenyl tetraketone ($\text{PhCO}-\text{COCOCOPh}$) isolated as the dioxime.³⁰⁰ A certain drawback of

this oxidising system is that DMSO has to be dried thoroughly, as the oxidation of diphenylacetylene does not occur even in the presence of 0.5% water.³⁰⁰ Oxidative reagents based on commercial, non-dried DMSO, *viz.*, HBr, I₂ or PdCl₂ in DMSO,^{253, 254} do not have this drawback. Heating of diarylalkynes in DMSO containing iodine at 115–155 °C provides high yields of benzils.^{253, 254} High reactivity and selectivity of the reagent are confirmed by the fact that it oxidises (4-nitrophenyl)phenylacetylene in 90% yield and does not affect the formyl group in (4-formylphenyl)phenylacetylene, which is very reactive and liable to oxidation.

Various bisphenylethynylarennes are oxidised to the tetraketone **28**, as well as tetraketones **125**, on heating in DMSO with an equimolar amount of iodine (yields 71%–90%).^{253, 254}



Ar = 1,4-C₆H₄, 4,4'-C₆H₄C₆H₄, 4,4'-C₆H₄OC₆H₄, dibenzofuran-3,8-diyl, 4,4'-C₆H₄CH₂C₆H₄, 4,4'-C₆H₄COC₆H₄, fluorene-2,7-diyl, fluorenone-2,7-diyl.

The same reagent was successfully used in the synthesis of 4,4'-bis(arylglyoxylyl)benzophenones from 4,4'-bis(arylethynyl)benzophenones³⁰¹ and a series of fluoro-derivatives of bis- α -diketones, FC₆H₅COCOC₆H₅XC₆H₅COCOC₆H₅F (X = CO, COCO, Het).³⁰²

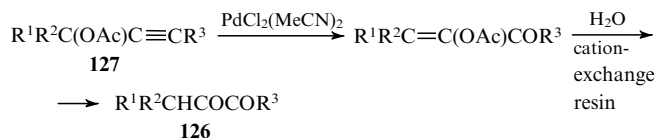
By decreasing the quantity of iodine to a catalytic amount, it was possible to oxidise only one triple bond in bis(phenylethynyl)benzene and to obtain the diketone **100**.²⁵² It was noted above that the reactivity of iodine in DMSO as an oxidant of the double bonds in stilbenes is low. This enables selective oxidation of only the triple bond in compound **98** giving (*E*)-styrylbenzil **103**.²⁵¹ The acetylene-containing tetraketone **29** is readily converted on treatment with the I₂–DMSO system to the hexaketone **94** in 90% yield.⁵⁹ Thus, the use of a combination of two oxidants, HBr–DMSO and I₂–DMSO, opens for the first time the possibility of the selective oxidation of either triple or double bonds in enynes.

The reactivity of iodine in DMSO decreases abruptly in the oxidation of a sterically hindered acetylenic substrate, *viz.*, mesitylacetylene, although the direction of the oxidation does not change.^{253, 254} A new oxidative process has been discovered recently.³⁰³ Prolonged heating of sterically hindered bis(phenylethynyl)durene with iodine in DMSO gave duroquinone, 2,3,5,6-tetramethyl-4-hydroxybenzil and benzoic acid as the main products, instead of the expected tetraketone **122**. This reaction is a rare example in which iodine in DMSO causes the cleavage of the carbon–carbon bonds. A similar process was observed in the oxidation of the enyne **99**, which resulted in benzil **7a** and benzoic acid instead of the expected diphenylbutenedione.²⁵¹ The I₂–DMSO system also proved to be inefficient in the oxidation of a terminal alkyne, *viz.*, phenylacetylene. In this case, a complex mixture of oxidation products with a content of phenylglyoxal no more than 20% is formed even if the conversion of the substrate is incomplete.²⁵⁵

It was shown^{251, 253, 254, 304} that internal alkynes [diarylalkynes and bis(phenylethynyl)benzenes] are readily oxidised to benzil **7a** and tetraketones **28** and **125** on heating in DMSO in the presence of a catalytic amount of PdCl₂. This reagent proved to be even more selective with respect to the triple bonds than I₂–DMSO. It is totally inert to alkenes. This enables its efficient use in the oxidation of acetylenic compounds containing double bonds.²⁵¹ On the other hand, PdCl₂–DMSO is more sensitive to steric factors in substrates than I₂–DMSO.^{253, 254}

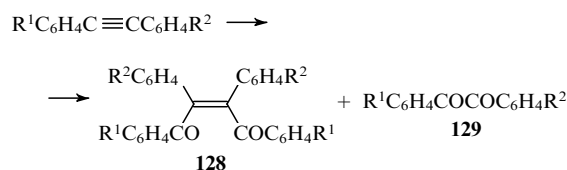
A method for the synthesis of α -diketones **126** from α -acetoxalkynes **127** in high yields was suggested.³⁰⁵ In the first step, substrates **127** are oxidised with complexes of PdCl₂ with acetoni-

trile or benzonitrile under very mild conditions at room temperature. The resulting enol acetates are readily hydrolysed to diketones **126** in the presence of cation-exchange resins.



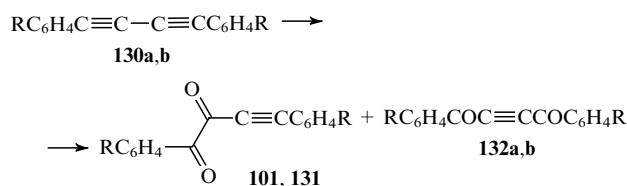
R¹, R², R³ = H, Alk, cyclo-Alk, Ar.

Anodic oxidation of diarylalkynes in acetonitrile on a graphite electrode gives mixtures of products, of which 1,2,3,4-tetraaryl-but-2-ene-1,4-diones **128** are the main components.³⁰⁶ The corresponding benzils **129** are formed in only 12%–35% yields.



R¹, R² = H, OMe.

Anodic oxidation of diarylbutadiynes **130a,b** under similar conditions results in the respective 1,2-diketones **101** (5%) and **131** (28%) and butyne-1,4-diones **132a,b** (60% and 12%).³⁰⁶



R = H (**101**, **130a**, **132a**), OMe (**130b**, **131**, **132b**).

As shown previously, a mixture of the same products, *viz.*, **101** and **132a**, results from the oxidation of diphenylbutadiyne with bis(trifluoroacetoxy)- λ -3-iodanylbenzene **121**.²⁹⁶

V. Conclusion

Despite the great diversity of oxidative methods for the synthesis of vicinal di- and polycarbonyl compounds (most often, α -diketones), extensive studies in this field are being continued. In our opinion, several most topical problems can be distinguished.

For example, now there are many reliable and general reagents for the oxidation of such substrates as ketones, their α -hydroxy and α -halogeno derivatives and β -diketones. On the other hand, methods for the oxidation of alkenes, vicinal dihalides and especially alkanes have been developed insufficiently. There are almost no versatile reagents for the oxidation of these classes of compounds, except for the recently suggested DMSO-based oxidants suitable for the oxidation of alkenes and substituted 1,2-dibromoethanes. Only after such reagents as HBr–DMSO, I₂–DMSO and PdCl₂–DMSO had appeared, did selective oxidation of either the triple or the double bond in enynes become possible. The results presented in Section IV show convincingly that alkynes rather than alkenes, and even more so alkanes, are the most suitable as substrates in the synthesis of α -dicarbonyl compounds. Thus, the traditional belief that 'alkynes are more difficult to oxidise than alkenes' has to be reconsidered.³⁰⁷

Yet another problem is the obvious lack of reliably proven mechanisms for the oxidation reactions presented in this review. Although a great deal of studies have been carried out, the mechanisms of action of even such well-studied oxidants as SeO₂ and KMnO₄ remain debatable. There are relatively few systematic studies on the quantitative estimation of the effect of the structure of substrates and oxidants on the reactivity. Because of the insufficiency of the theoretical basis, new reagents in this branch

of synthetic chemistry mostly appear incidentally, and the majority of publications are of preparative character.

Finally, it is to be noted that general approaches to the synthesis of compounds with more than three contiguous carbonyl groups have not been developed so far, and only a few syntheses of acyclic pentaketones have been reported. On the other hand, recent non-empirical quantum-chemical calculations show that hypothetical polyketones $R(CO)_nR$ ($n = 6-11$) can be rather stable.³ Synthesis of such compounds is one of the urgent problems of organic synthesis.

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Reactions of phosphorus acid halides with *N*-silylated organic compounds[†]

A B Ouryupin, I A Rakhov, T A Mastryukova

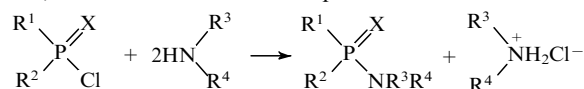
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Abstract. Data on reactions of *N*-silylated amines, carboxamides, amino acids, and their derivatives with trivalent and pentavalent phosphorus acid halides are summarised. The effect of structural factors on the direction of phosphorylation is discussed. The bibliography includes 133 references.

I. Introduction

The necessity of development of new methods for the synthesis of phosphorus acid amides is associated with the fact that some of these compounds are widely used as bioregulators and key reagents in the synthesis of new medicinal preparations.¹ The phosphoramidite method for the formation of internucleotide bonds remains so far the most efficient in the automated synthesis of oligonucleotides.² However, analysis of literature data on the methods for the preparation of compounds with the P–N bond allows one to reveal certain drawbacks in the popular methods for the synthesis of amides of phosphorus acids.^{3,4} The vast majority of the methods is based on low-selective reactions of phosphorylating reagents with amines or their salts. The use of a large excess of bases (sometimes toxic) hinders purification of the target amides, which creates additional experimental difficulties.



The use of *N*-silylated nitrogen-containing compounds may appear to be the solution of the problem. At present, serious attention has been drawn to the studies on the reactivity of these compounds.^{5,6} The reaction of these silylated compounds with phosphorus acid halides is very attractive for the synthesis of phosphoramidites and phosphoramidates, as it produces volatile halogenosilanes, which can be easily removed from the reaction mixture and repeatedly used in the reaction cycle. Other advantages of the use of silylamines instead of amines have been reviewed.⁵ The ultimate result of this type of reactions definitely depends both on the structural features of the electrophilic phosphorylating agent and on the nature of the silicon–nitrogen

bond that affects the nucleophilicity and configuration of the nitrogen atom.^{7,8}

Since there is no universal scale of nucleophilicity and electrophilicity,⁹ this review compares the reactivity of *N*-silylated nitrogen-containing compounds, which are combined into different groups according to formal structural features, with respect to phosphorus acid halides. In each case, the reaction features that can be attributed to the contribution of the phosphorus component are discussed additionally.

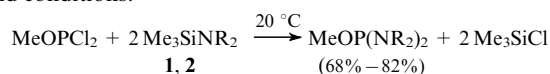
II. Reactions with *N*-silylamines

A characteristic feature of *N*-silylamines is their rather high reactivity with respect to phosphorus acid halides, particularly those of trivalent phosphorus. This may result from changes in hybridisation of the nitrogen atom and, as a consequence, from changes in its nucleophilicity due to the introduction of the silyl group.^{5,7}

The steric factor also exerts a significant effect on the reactivity of silylamines. Generally speaking, the N–Si bond in silylamines is so labile that the latter may act as silylating agents, for example, diethyl(trimethylsilyl)amine (**1**). However, the ability of the Si–N bond to undergo cleavage decreases dramatically with an increase in the volume of the alkyl groups at the silicon atom (*e.g.*, in the case of triisopropyl and *tert*-butyldimethylsilyl groups).¹⁰ A similar effect was also noted in acid hydrolysis of *N-tert*-butyldimethylsilyl- and *N*-triisopropylsilyl-β-lactams.¹¹ Methods for the synthesis of *N*-triisopropylsilylated compounds and their stability have been reviewed.¹² *tert*-Butyldipropylsilylated primary amines appeared to be inert to acylation.¹³ Therefore, this review deals exclusively with the replacement of the trimethylsilyl group at the nitrogen atom by a phosphorus-containing fragment.

1. Reactions with trivalent phosphorus acid halides

It has been shown^{14–21} that reactions of silylamines, mainly amine **1**, with a series of trivalent phosphorus acid chlorides occur under mild conditions.



R₂N = Et₂N (**1**), Me₂N (**2**), .

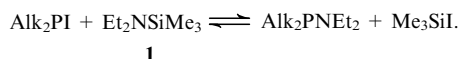
A B Ouryupin, I A Rakhov, T A Mastryukova A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 85. Tel. (7-095) 135 92 49 (T A Mastryukova)

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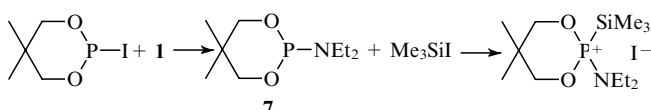
Uspekhi Khimii 67 (9) 827–838 (1998); translated by S S Veselyi

[†] The review is devoted to the memory of academician M I Kabachnik (1908–1997).

Finally, the reversibility of the reaction of dialkylphosphinous diiodides with the amine **1** in dichloromethane at room temperature has been demonstrated recently.³⁴

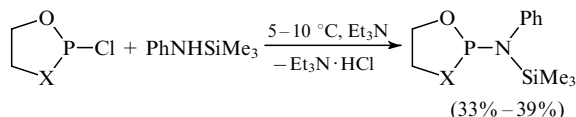


Studies of this kind of reactions are complicated by side reactions of phosphoramidites that are formed with organoiodine compounds.^{29, 32, 34} For example, the reaction of the amine **1** with 2-iodo-5,5-dimethyl-1,3,2-dioxaphosphorinane results in the phosphoramidite **7**, which immediately reacts with the product of this reaction, viz., iodotrimethylsilane.²⁹



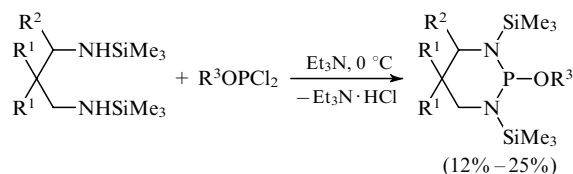
Unlike acyl fluorides,³⁵ trivalent phosphorus acid fluorides do not react with silylamines. All attempts to carry out such transformations failed.^{29, 36, 37} Thus, the reaction of silylamines with P(III) acid chlorides remains the most suitable for the synthesis of phosphoramidites.

It should be noted that phosphorylation of silylamines in the presence of a base may occur with the preservation of the N—Si bond. For example, the reaction of 2-chloro-1,3,2-diheterophospholanes with *N*-trimethylsilylaniline under mild conditions afforded the corresponding 2-(*N*-trimethylsilyl-*N*-phenylamino)-1,3,2-diheterophospholanes.³⁸



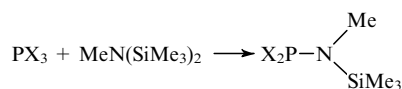
X = O, NPh.

Similarly, Menshutkin's chlorides can react, though partly, at the N—H bond of *N,N'*-bis(trimethylsilyl)trimethylenediamines.^{39, 40}



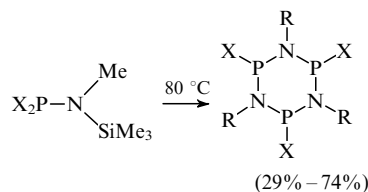
R¹, R² = H, Me; R³ = Me, Et, Ph.

With disilazanes, it becomes possible to obtain products of substitution of one or two trialkylsilyl groups, depending on the reaction conditions. Monosubstitution occurs with equimolar amounts of the reagents and at low temperature.^{41, 42}



X = Cl, Br.

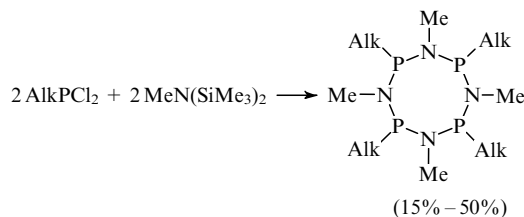
The resulting *N*-silylamidophosphorodihalidites are thermally unstable and can be transformed to cyclotriphosphazanes on heating of the reaction mixture.^{42, 43}



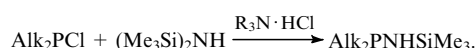
X = Cl, Br; R = Me, Et.

The reaction of alkylphosphonous dichlorides with methylbis(trimethylsilyl)amine also affords mono- and diphosphoryla-

tion products, depending on the ratio of the reagents,⁴⁴ and boiling of equimolar amounts of the reagents in acetonitrile leads to cyclotetraphosphazanes.^{45, 46}

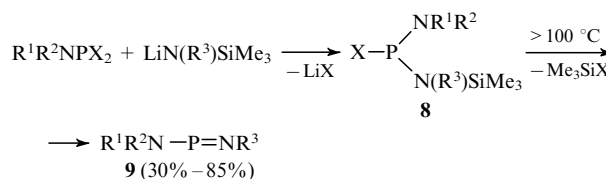


The synthesis of *N*-trimethylsilyldialkylphosphinamidites by boiling dialkylphosphinous chlorides with an excess of hexamethyldisilazane in the presence of a catalyst was also described.⁴⁷



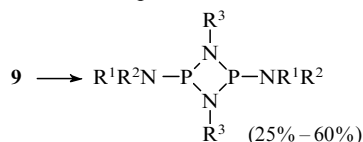
Trivalent phosphorus acid fluorides are inert with respect to disilazanes.⁴⁸ The Si—N bond remains unchanged after heating a mixture of F₂PCl with (Me₃Si)₂NPF₂ or Me₃Si(Bu^t)NPF₂. This is explained⁴⁹ by *p*_π–*d*_π overlapping of orbitals of the Si, N, and P atoms resulting in a corresponding decrease in the nucleophilicity of nitrogen.

A method for the synthesis of a series of compounds of two-coordinated phosphorus **9** from *N,N,N'*-trisubstituted *N*-(trimethylsilyl)phosphorodiamidohalidites **8**, which had been synthesised from R¹R²NPX₂ and LiN(R³)SiMe₃, was developed.^{50–56}



X = Cl, Br; R¹ or R² are bulky substituents, R³ = Prⁱ, Bu^t, R₃Si, C₆H₂Bu₃¹, adamant-1-yl.

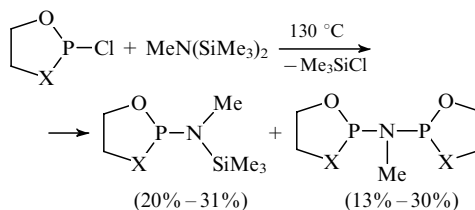
In this case, it was possible to isolate only compounds with bulky substituents at both nitrogen atoms. Otherwise, dimerisation of the imidophosphorous amides **9** to 1,3-diaza-2,4-diphosphetidines takes place.^{52–55}



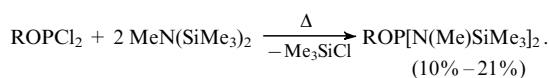
R¹, R² = Me, Et, Pr.

The nature of the halogen at the phosphorus atom has no significant influence on the elimination of the halosilane.^{50–56} The same method was used for the preparation of the less stable *P,N*-dialkyl(aryl)-^{57, 58} and *P*-aryloxy-*N*-aryliminophosphines.⁵⁹

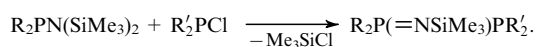
Reactions of phosphorochloridites with hexa- and heptamethyldisilazanes were studied.^{60, 61} The attractiveness of these reactions is explained by the fact that they allow the syntheses of functionally substituted amides of trivalent phosphorus acids. Unfortunately, phosphorylation of disilazanes occurs under more drastic conditions than phosphorylation of monosilylamines.



X = O, NPh;



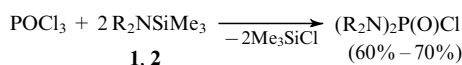
Phosphorylation of phosphorus-substituted disilazanes can be accompanied by rearrangement to give compounds containing phosphorus in different coordination states.⁶²



2. Reactions with pentavalent phosphorus acid halides

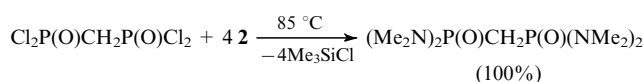
Since pentavalent phosphorus has lower electrophilicity than trivalent phosphorus, a general decrease in the rates of phosphorylation of silylamines with the corresponding phosphorus(V) acid halides is observed.

The replacement of the chlorine atoms in pentavalent phosphorus acid chlorides by the amino groups in reactions of acid chlorides with amines **1** and **2** is incomplete even on heating.¹⁴

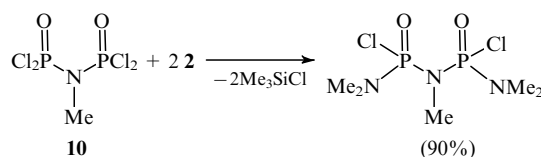


R = Et (**1**), Me (**2**).

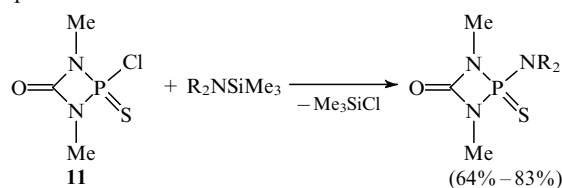
Complete replacement of the chlorine atoms in methylenebis(phosphonic dichloride) in its reaction with the amine **2** is possible only on heating.²²



The phosphorylating ability of *N*-methyliminodiphosphonic tetrachloride (**10**) is even lower.⁶³



Nucleophilic substitution of the chlorine atom at a less electrophilic thiophosphoryl centre occurs more readily when the latter is incorporated into a strained four-membered ring, as in compound **11**.⁶⁴

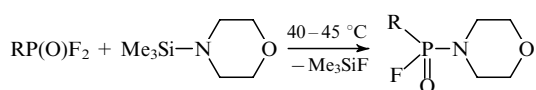


R = Me, Et.

However, the presence of electron-withdrawing and bulky phenyl groups at the nitrogen atom of the silylamine prevents the cleavage of the Si–N bond in this reaction.

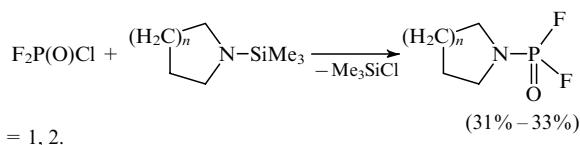
Chlorocyclotriphosphazenes also belong to pentavalent phosphorus acid chlorides, but we considered that there is little sense in repeating in this review the previously published data^{65, 66} on their reactions with silylamines.

Unlike trivalent phosphorus acid fluorides, P(V) fluoro-derivatives react with silylamines in some cases. For example, the reaction of *N*-trimethylsilylmorpholine with the mixture of isobutenyl- and 2-chloroisobutylphosphonic difluorides affords products of replacement of one of the fluorine atoms.⁶⁷

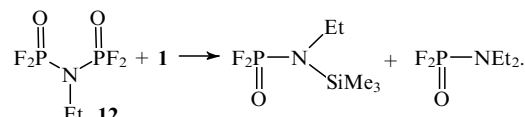


R = Me₂C=CH, Me₂CClCH₂.

N-Silylated pyrrolidine and piperidine react rather smoothly with phosphorus oxofluoride POF₃. However, in their reaction with phosphorus oxochloridodifluoride, substitution of the chlorine atom is the first to occur.⁶⁸

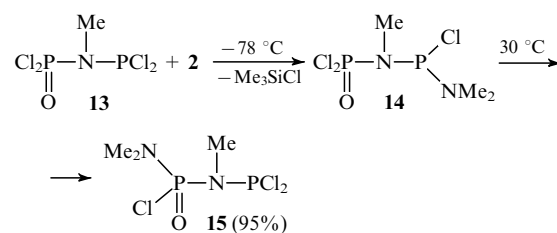


Unlike *N*-methyliminodiphosphonic tetrachloride (**10**), *N*-ethyliminodiphosphonic tetrafluoride (**12**) reacts with the amine **1** with the cleavage of the P–N bond.⁶⁹

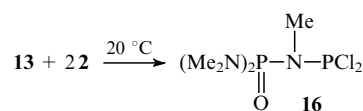


Although reactions of silylamines with phosphorus acid fluorides are rather interesting from the synthetic point of view, they are little studied. Undoubtedly, this can be explained by the high toxicity of the latter compounds. Phosphorylation of silylamines with phosphorous acid bromides and iodides has not been described in literature.

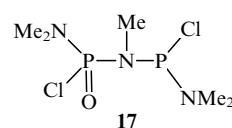
The reaction of the amine **2** with mixed amidotetrachloride **13** can serve as a characteristic of the relative ability of the halogen atoms in trivalent and pentavalent phosphorus acid halides to be replaced by the amino groups of silylamines.^{70, 71} At –78 °C and with an equimolar ratio of the reagents, the product of the replacement of one chlorine atom at the trivalent phosphorus atom by the dimethylamino group (compound **14**) is formed selectively. The structure of compound **14** is confirmed by ¹H and ³¹P NMR spectroscopic data. An increase in the reaction temperature to 30 °C and exposure of the reaction mixture at this temperature for 1 h result in migration of the dimethylamino group from the trivalent phosphorus atom to the pentavalent one to give compound **15**.



The reaction of the tetrachloride **13** with 2 equivalents of the amine **2** at room temperature affords the product of replacement of both chlorine atoms at the pentavalent phosphorus atom by the dimethylamino groups (compound **16**).

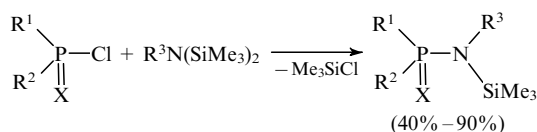


In the authors' opinion, compound **17** is formed as an intermediate in this reaction.



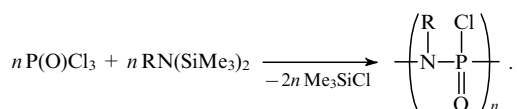
This assumption is supported by the fact that compound **17**, synthesised independently, undergoes rearrangement at room temperature to form compound **16**.

As in the case of P(III) derivatives, the reaction of P(V) acid chlorides with disilazanes can be used for the preparation of *N*-silylated amides.^{72,73}

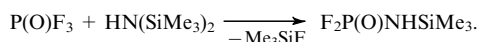


$\text{R}^1, \text{R}^2 = \text{Alk}, \text{Ar}, \text{AlkO}, \text{ArO}; \text{X} = \text{O}, \text{S}, \text{NR}^4$.

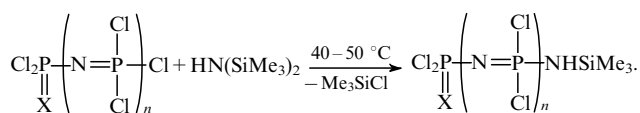
Successful synthesis of these amides requires that appropriate reaction conditions are selected depending on the structure of the phosphorylating agent used. Reactions at room temperature mainly involve more electrophilic MePOCl_2 and 1-chloro-1-oxophosphol-3-ene,⁷² whereas diphenyl phosphorochloridate reacts at 60 °C,⁷³ and phosphinothioic chlorides react only at 130–150 °C.⁷⁴ *N,N*-Bis(trimethylsilyl)-*P*-phenylphosphonothioic diamide is obtained under even more drastic conditions (in the presence of aluminium chloride).⁷⁵ As a rule, reactions of this type afford a monophosphorylation product, except for the reaction of disilazanes with POCl_3 .⁷⁶



The reaction of hexamethyldisilazane with POF_3 afforded the corresponding *N*-silylmonoamide in moderate yield.⁷⁶



Monosubstitution of the chlorine atoms in mixed imidochlorides can be used for the preparation of acyclic oligophosphazenes.⁷⁷



$\text{X} = \text{O}, \text{S}$.

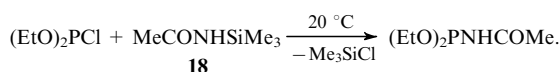
Thus, reactions of both trivalent and pentavalent phosphorus acid chlorides with silylamines are of significant interest for the synthesis of phosphoramidites and phosphoramidates.

III. Reactions with *N*-silylamides

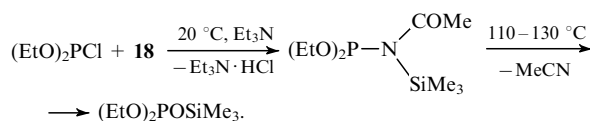
Many *N*-phosphorylated amides and lactams are known to be physiologically active substances with a broad spectrum of action.^{1,78} In addition, certain *N*-phosphorylated amides are used as condensation agents in the synthesis of carboxamides and esters.⁷⁹ The development of convenient methods for their synthesis is therefore of large practical importance.

The introduction of an acyl group into a silylamine molecule changes substantially both the nucleophilic properties of the nitrogen atom and the geometry of the molecule. Studies of the reactivity of silylamides performed by representatives of the Kazan' school of chemists allowed them to elucidate the regularities of the reaction of silylamides with trivalent and pentavalent phosphorus acid chlorides.^{80–87}

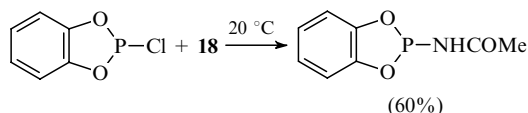
Reaction conditions have a significant effect on the direction of the reaction of diethyl phosphorochloridites with *N*-trimethylsilylacetamide (**18**).^{8,80} For example, cleavage of the Si–N bond with the formation of *N*-diethoxyphosphinetriylacetamide takes place at room temperature.



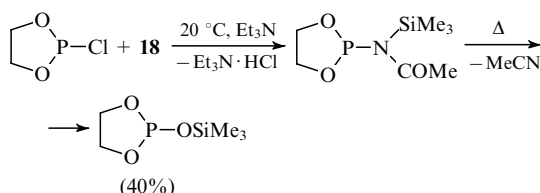
The Si–N bond remains unchanged in the presence of triethylamine; in this case, the reaction product is *N*-trimethylsilyl-*N*-(diethoxyphosphinetriyl), and only heating of the reaction mixture to 110–130 °C brings about the elimination of the acetonitrile molecule and the formation of a Si–O–P bond.



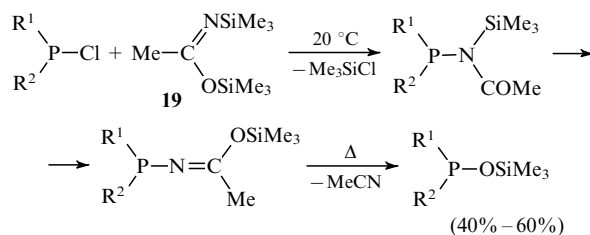
Under similar conditions (room temperature, inert solvent), 2-chlorobenzo-1,3,2-dioxaphospholene reacts with amide **18** to give 2-acetylaminobenzo-1,3,2-dioxaphospholene.⁸¹



Similarly, but in the presence of triethylamine, the reaction of 2-chloro-1,3,2-dioxaphospholane with amide **18** afforded 2-(*N*-acetyl-*N*-trimethylsilylamino)-1,3,2-dioxaphospholane, which is transformed to 2-trimethylsilyloxy-1,3,2-dioxaphospholane on heating.⁸²

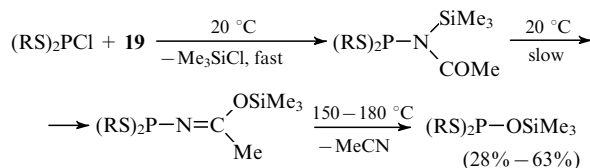


The product of disilylation of acetamide, compound **19**, has the structure of an imide in which one of the trimethylsilyl groups is linked with the nitrogen atom, and the second group, with the oxygen atom.^{8,88} Phosphorylation of this compound with phosphorochloridites at room temperature affords *N*-trimethylsilyl-*N*-dialkoxy- or alkoxy(amino)phosphinetriylacetamides. Their structures were confirmed by IR and ¹H and ³¹P NMR spectra.^{82–86} Their conversion into the corresponding trimethylsilyl phosphites was explained by the possible presence of isomeric *N*-(1-trimethylsilyloxyethylidene)phosphoramidites in the reaction mixture.

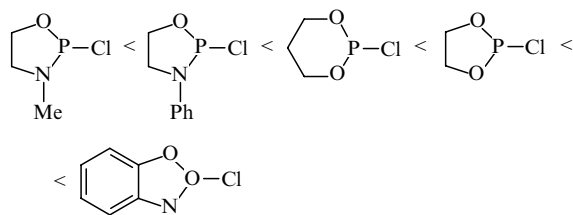


$\text{R}^1 = \text{R}^2 = \text{OAlk}, \text{R}^1 = \text{OAlk}, \text{R}^2 = \text{NHR}^3$.

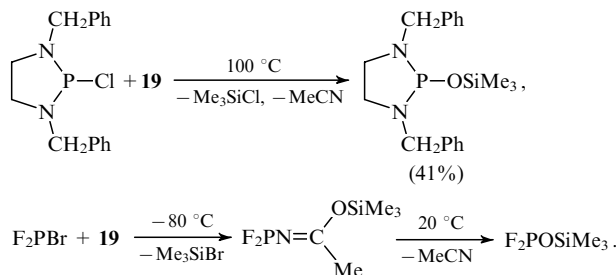
The *O*-silylated isomer appeared to be more stable than the *N*-silylated one and was isolated after phosphorylation of compound **19** with dialkyl phosphorochloridithioite.⁸⁵



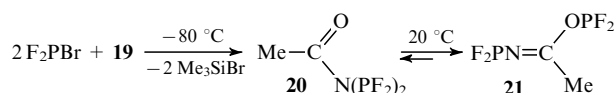
The reaction under discussion also proceeds in a similar way with other phosphorochloridites. In this case, the ease of the formation of silyl phosphites increases in the following series:⁸³



Isomerisation of the phosphorylation intermediate followed by its decomposition is also observed in some cases.^{86, 89}



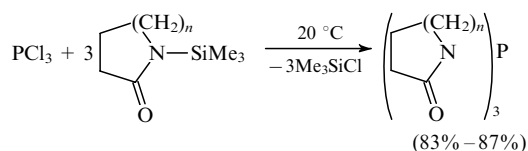
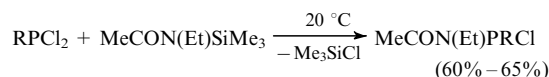
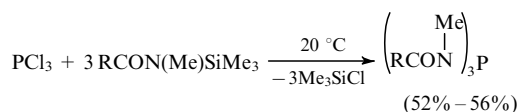
If the latter reaction is carried out with an excess of F_2PBr , bisphosphorylated acetamide is obtained. It is formed as a mixture of *N,N*- (**20**) and *N,O*-isomers (**21**), the isomer **20** undergoing rearrangement into the isomer **21**.⁸⁹



Thus, the reaction of trivalent phosphorus acid chlorides with *N,O*-bis(trimethylsilyl)acetamide is a convenient general method for the synthesis of highly reactive trivalent phosphorus acid silyl esters.

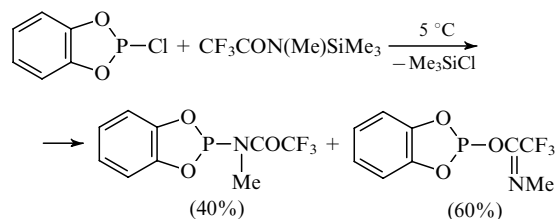
The reactivity of disilylamides with respect to phosphorochloridites decreases upon introduction of electron-withdrawing substituents at the carbonyl carbon atom, for example, when methyl group of acetamide is substituted by a phenyl or methoxy group. Methyl *N,N*-bis(trimethylsilyl)carbamate does not react with diethyl phosphorochloridite and 2-chlorobenzo-1,3,2-dioxaphospholene,^{86, 89} and *N,O*-bis(trimethylsilyl)trifluoroacetamide does not react with PF_2Br .⁸⁹

Contrary to silylated primary amides, *N*-silylated secondary amides and lactams can be selectively phosphorylated at the nitrogen atom with phosphorus trichloride and alkylphosphonous dichlorides.^{90, 91}

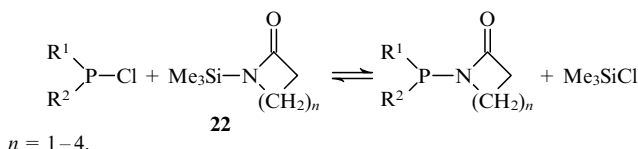


$n = 1, 2$.

Nevertheless, there is an example of the formation of a mixture of *N*- and *O*-phosphorylation products in the reaction of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide with 2-chlorobenzo-1,3,2-dioxaphospholene.⁹²

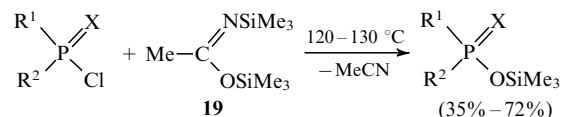


It was found recently that the reaction of some trivalent phosphorus acid chlorides with silyllactams **22** may be reversible, and the position of equilibrium is determined by the structure of the phosphorylating agent.⁹³

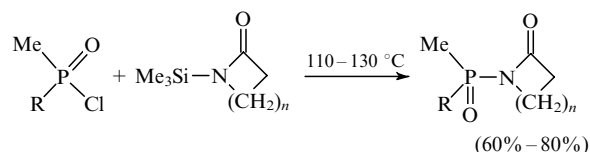


The reversibility of the process was proved by mixing equimolar amounts of *N*-phosphoryllactams and chlorotrimethylsilane. In this case, the compositions of the reaction mixtures were the same as those in the reactions of phosphorochloridites with silyllactams. The reversibility of the reaction of *N*-trimethylsilyl- β -lactams with trivalent phosphorus acid chlorides was postulated on the basis of indirect data.

Reactions of silylated amides with pentavalent phosphorus acid chlorides are insufficiently studied. It was shown that, as in the case of phosphorochloridites, the reaction of *N,O*-bis(trimethylsilyl)acetamide **19** with phosphorus oxochloride, methylphosphonic dichloride, diethyl phosphorochloridate, diethyl and dimethyl phosphorothiochloridate is accompanied by the formation of silyl phosphates.⁸⁷



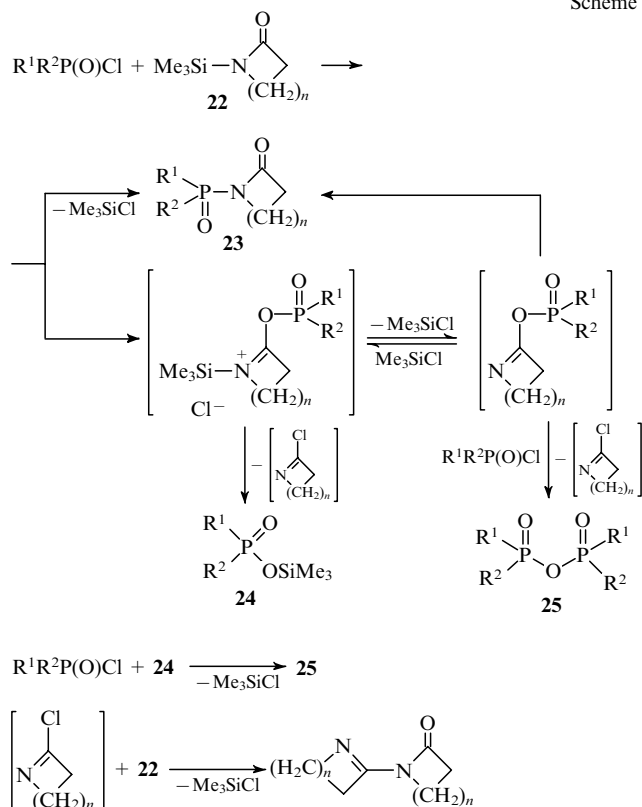
Previously, it was found that *N*-silylated lactams react, although under drastic conditions, with alkyl(aryl) methylphosphonochloridates and *N,N*-diethyl-*P*-methylphosphonamidochloridate to form the products of substitution at the nitrogen atom, as in the reaction with phosphorus trichloride.⁹⁴



$\text{R} = \text{OEt}, \text{OPh}, \text{NEt}_2; n = 2, 3$.

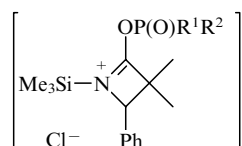
A scheme was proposed recently, according to which pentavalent phosphorus acid chlorides $\text{R}^1\text{R}^2\text{P}(\text{O})\text{Cl}$ react with silyllactams **22** both at the nitrogen atom and the oxygen atom of the carbonyl group (Scheme 1).⁹⁵ Strictly speaking, the possibility of silylotropy should be taken into account when estimating the reactivity of *N*-silyllactams; however, under the conditions used,⁹⁵ the trimethylsilyl group had to be bound to the nitrogen atom. Therefore, the nature of the products obtained was explained by the authors from the viewpoint of dual reactivity of the silyllactam system. The formation of *N*-phosphoryllactams **23** may result from both the direct attack at the nitrogen atom and the $\text{O} \rightarrow \text{N}$ isomerisation of the *O*-phosphorylated intermediates which are also the sources of side products, namely, silyl phosphates **24** and pyrophosphates **25**. The predominance of one or another pathway of decomposition of the intermediates depends on different factors including the nature of the organophosphorus fragment. Successive replacement of the alkyl groups in the chloride by

Scheme 1



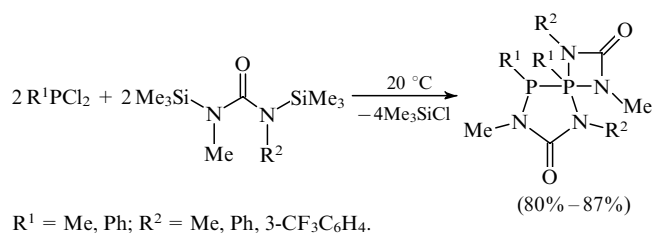
alkoxy groups decreases the yield of *N*-phosphorylated derivatives **23**. The authors explain this fact by a decrease in the rate of nucleophilic attack by the nitrogen atom on the phosphorus atom in the intermediate and by a larger contribution of other directions of its transformation.

It should be noted that attack on the oxygen atom of *N*-trimethylsilyl- β -lactams by pentavalent phosphorus acid chlorides is hindered by severe steric requirements to the assumed transition state.

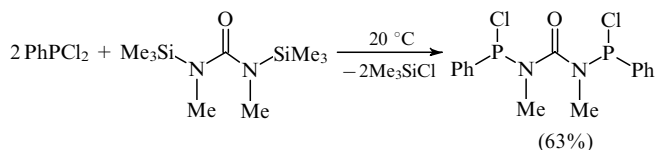


The structure of the products formed in the reaction of *N,N'*-bis(trimethylsilyl)ureas with trivalent phosphorus acid chlorides is determined by the nature of substituents at the phosphorus atom.^{96–100}

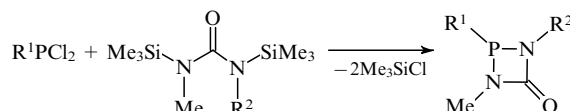
The attack of phenyl- and methylphosphonous dichloride on the nitrogen atom of the Si–N bond in urea is accompanied by subsequent cleavage of one of the P–N bonds, probably due to the high strain of the corresponding diazaphosphetidine ring.^{96,97}



In the presence of an excess of phenylphosphonous dichloride, the reaction stops at the usual step of replacement of the trimethylsilyl group.⁹⁹

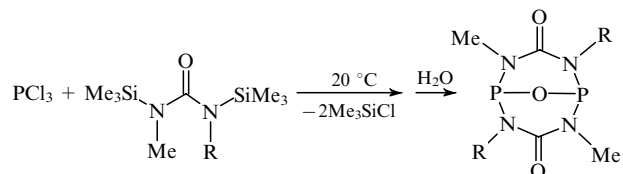


Replacement of the alkyl groups in the starting alkylphosphonous dichlorides by electron-withdrawing groups (CCl₃ or C₂F₅) changes the direction of this reaction resulting in the formation of 1,3,2-diazaphosphetidin-4-ones.^{97,98}



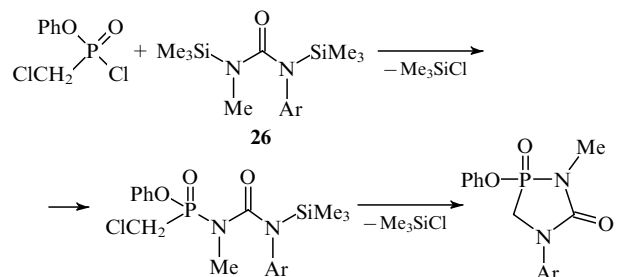
$R^1 = \text{CCl}_3, \text{C}_2\text{F}_5; R^2 = \text{Me, 3-CF}_3\text{C}_6\text{H}_4.$

On the contrary, replacement of the alkyl group in alkylphosphonous dichlorides by a chlorine atom⁹⁷ or a dialkylamino group⁹⁹ favours the formation of bicyclic compounds.



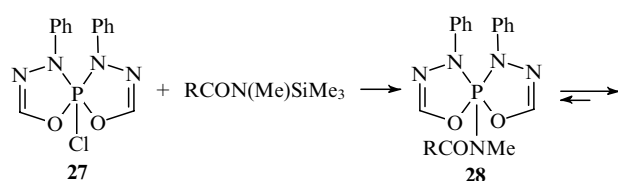
$R = 3\text{-CF}_3\text{C}_6\text{H}_4.$

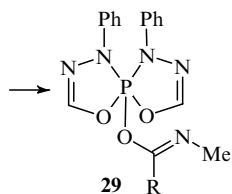
Phosphorylation of unsymmetrical *N,N'*-bis(trimethylsilyl)ureas **26** with phenyl (chloromethyl)phosphonochloridate is complicated by the attack by the second silylamide group of urea on the carbon atom of the chloromethyl group to give 1,4,2-diazaphospholane-2,5-diones.¹⁰¹



It is interesting that the nucleophilicity of the nitrogen atom in *N,N*-bissilylated sulfamides is so much lower than that in *N*-silyl-carboxamides that the former do not react with phosphonous dichlorides.¹⁰⁰

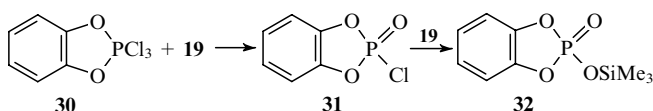
Reactions of halophosphoranes with silylamides are also ambiguous. The reaction of *N*-methyl-*N*-(trimethylsilyl)trifluoro- and -trichloroacetamides with the chlorophosphorane **27** affords a mixture of *N*- (**28**) and *O*-phosphorylated (**29**) trihaloacetamides. It is noteworthy that, like the product of the reaction of the silylamide **19** with dialkyl phosphorochloridodithioites, the *N*-phosphorylated isomer is less stable and is converted on storage into the *O*-phosphorylated isomer.¹⁰²



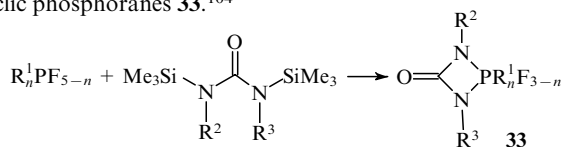


R = CCl₃, CF₃.

It is assumed that the reaction of 2,2,2-trichlorobenzo-1,3,2-dioxaphospholene (**30**) with disilylamide **19** occurs through the step of *O*-phosphorylation of silylamide. With the ratio of the reagents 1 : 1, 2-chloro-2-oxobenzo-1,3,2-dioxaphospholene (**31**) is formed. With an excess of silylamide, the reaction affords the silyl phosphate **32**.¹⁰³



N,N'-Disilylated ureas react with fluorophosphoranes to give cyclic phosphoranes **33**.¹⁰⁴



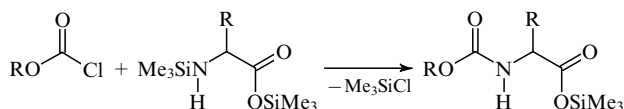
n = 1–3.

Thus, practical application of silylamides requires additional studies on the optimisation of conditions for the synthesis of *N*-phosphorylated amides.

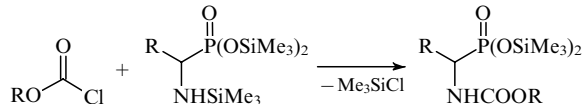
IV. Reactions with *N*-silylated amino acids and other *N*-silylated compounds

N-Silylated amino acids can be regarded as *N*-silylamines that contain a functional group in their alkyl part.

Reactions of *N,O*-bis(trimethylsilyl) derivatives of natural α -amino acids with acyl chlorides were used for the protection of the amino group.¹⁰⁵

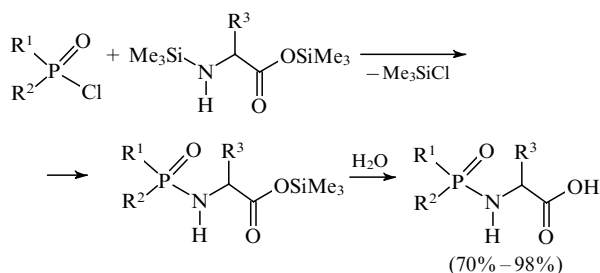


N-Acyl derivatives of α -aminoalkylphosphonic acids were synthesised in a similar way.¹⁰⁶



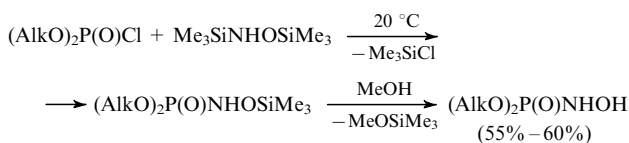
No other examples of this type of reaction have been documented.

However, it turned out that *N*-phosphorylated amino acids can be obtained by the reaction of *N,O*-bis(trimethylsilylated) amino acids with pentavalent phosphorus acid halides.^{107–109}

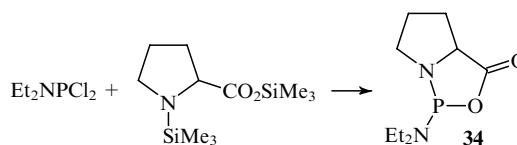


N-Phosphorylated acids are formed in high yields. Intermediate silyl esters of *N*-phosphorylated amino acids were isolated in the case of glycine derivatives.¹⁰⁷

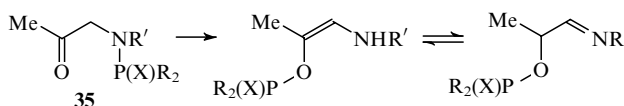
This type of selective *N*-phosphorylation of *N,O*-bissilylated compounds was also used in the synthesis of *N*-(dialkoxyphosphoryl)hydroxylamines.¹¹⁰



Both silyl groups participate in the reaction of bis(trimethylsilyl)proline with diethylphosphoramidodichloridite, which results in the formation of a bicyclic product (**34**).¹¹¹

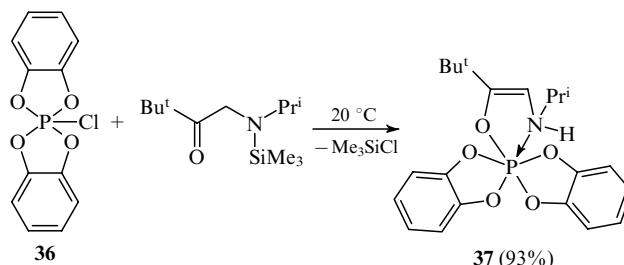


Phosphorylation of silylated α -amino ketones occurs at the nitrogen atom. Phosphoro- and prototropic transformations of primary phosphorylation products **35** are observed in this case.¹¹²



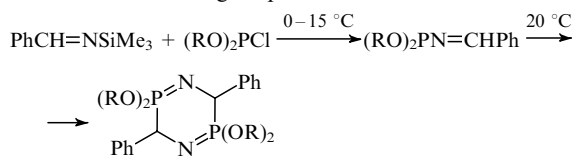
X = O, S or unshared electron pair.

The reaction of 1-(*N*-isopropyl-*N*-trimethylsilylamino)-3,3-dimethylbutan-2-one with spiroposphorane **36** was complicated by the formation of an N→P donor-acceptor bond. As a result, the tricyclic compound **37** with the hexacoordinated phosphorus atom was formed.¹¹³

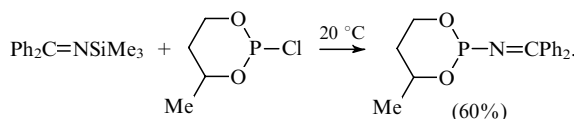


The peculiarities of the reactions of phosphorus acid chlorides with such amino acid derivatives as *N*-silyllactams, which may be also attributed to *N*-silylamides, have been discussed in Section III.

In the studies of the reactivity of compounds containing a silyl group at the imine nitrogen atom,^{114,115} it was found that phosphorochloridites react with aldimines¹¹⁴ and ketimines¹¹⁵ under mild conditions and the *N*-(dialkoxyphosphinetriyl)aldimines that formed undergo rapid dimerisation.

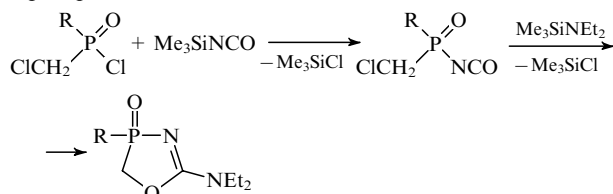


RO = EtO; (RO)₂ = O(CH₂)₂O, 1,2-OC₆H₄O.

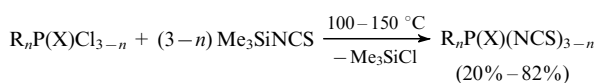


Among other *N*-silylated compounds containing a C=N bond, isocyanates and isothiocyanates are worth noting.

Phosphorylation of isocyanatosilanes has been studied very little. Only the syntheses of diethylphosphoramidobisisocyanatide¹¹⁶ and phosphorisocyanatidic difluoride¹¹⁷ have been reported. Recently, the reaction of isocyanatotrimethylsilane with phosphinic chlorides was used in the synthesis of 1,3,4-oxazaphosphol-2-enes.¹⁰¹

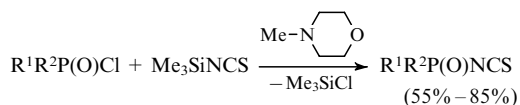


Trimethylsilyl isothiocyanate reacts with trivalent and pentavalent phosphorus acid chlorides only on strong heating.^{118, 119}

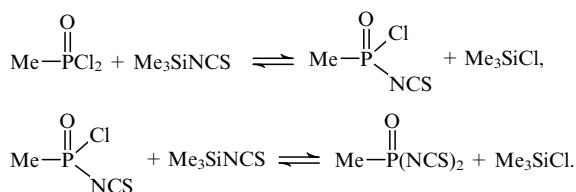


R = Ph, Me, EtO; X = O, S or unshared electron pair; $n = 0-2$.

Because of the large practical importance of phosphoryl isothiocyanates, which are the products of this reaction and which are widely used as intermediates in the synthesis of pesticides and complexones, attempts were made to decrease the reaction temperature by adding catalysts. The use of tin and titanium tetrachlorides for this purpose was unsuccessful.^{118, 120} On the contrary, when the reaction was carried out in the presence of *N*-methylmorpholine, it became possible to obtain thermally unstable phosphoryl isothiocyanates at 20 °C in high yields.¹²¹

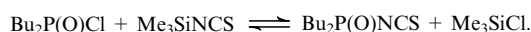


In some cases, the reaction of isothiocyanatotrimethylsilane with pentavalent phosphorus acid chlorides is reversible.¹²² Using the ³¹P NMR method, it was found that the compositions of the reaction mixtures prepared from methylphosphonic dichloride and 2 equivalents of isothiocyanatotrimethylsilane and from methylphosphonic diisothiocyanate and 2 equivalents of chlorotrimethylsilane were identical.



The yield of phosphonic diisothiocyanate may be increased by distilling off the chlorotrimethylsilane that formed in the reaction.

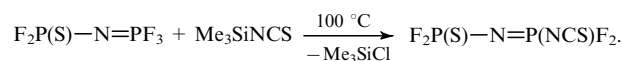
The low yield of dibutylphosphinic isothiocyanate in comparison with those of the corresponding phosphoric and phosphonic isothiocyanates is also explained by the reversibility of the reaction under study.



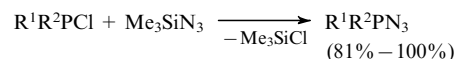
The use of isothiocyanatoalkoxydimethylsilane instead of isothiocyanatotrimethylsilane increases the reactivity of the Si-N bond in reactions with trivalent and pentavalent phosphorus acid chlorides;¹²³ however, the Si-O bond is cleaved even at low temperatures (20–60 °C) to afford a mixture of products.

Phosphoric acid fluorides are rather low-reactive with respect to Me₃SiNCS even on heating, and the fluorine atom of the

phosphorimide moiety is more reactive than that of the thiophosphoramidate moiety.¹²⁴

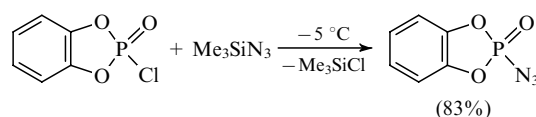


The increased reactivity of the Si-N bond in azidotrimethylsilane and the commercial availability of this compound allow one to consider it as a convenient reagent for the synthesis of thermally labile phosphorus acid azides. For example, phosphorochloridites react with Me₃SiN₃ to give high yields of the product even at 0 °C.^{125–130}



R¹, R² = Cl, Cl₃CCMe₂O, Et₂N, Pr₂N; R¹ + R² = O(CH₂)₂O, 1,2-OC₆H₄O.

Pentavalent phosphorus acid chlorides¹²⁷ and chlorophosphoranes¹³¹ behave similarly.



V. Conclusions

Reactions of phosphorus acid halides, particularly chlorides, with *N*-silylated organic compounds are undoubtedly of interest for synthetic chemists, since they can serve as the basis for the development of methods for the synthesis of both new types of compounds and reactive intermediates. However, no strict quantitative analysis of the regularities of this reaction has been carried out so far, which inhibits practical recommendations regarding optimum conditions of this reaction in particular cases in order to reach the required selectivity.

In the recently published special issues of the 'Chemical Reviews' devoted to current problems of the chemistry of silicon¹³² and phosphorus,¹³³ the problems concerning the application of compounds with a nitrogen-silicon bond in the organophosphorus synthesis were not properly taken into account. We hope that the present review fills this gap.

Based on the literature data and their own experience, the authors have the courage to state that the potential of the reactions under discussion has not been totally exploited. In particular, this refers to phosphorylation of biopolymer fragments under mild conditions, for which methods of silylation have been largely developed. In this case, the result of the reaction may be controlled by varying substituents at the silicon and phosphorus reaction centres. Such studies may be carried out in the near future.

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The influence of the carrier gas on the retention parameters and the height equivalent to the theoretical plate in gas–solid chromatography

V G Berezkin, I V Malyukova

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Abstract. The influence of the nature of the carrier gas and of its pressure on the retention and the height equivalent to the theoretical plate in gas–solid chromatography is analysed. The physicochemical processes responsible for this influence are examined. It is shown that the carrier gas is an active participant in the chromatographic process. The bibliography includes 145 references.

I. Introduction

Gas–solid chromatography is one of the principal versions of gas chromatography and its significance in the solution of important analytical and preparative problems has been increasing continuously.^{1,2}

The compounds being chromatographed, the adsorbent (solid), and the carrier gas as a rule participate in the separation process in gas–solid chromatography. The solid may also play the role of a volumetric adsorbent (for example, palladium may chemisorb hydrogen reversibly³), but few such absorption systems are known and we shall not consider them in the present review. It is noteworthy that inadequate attention has been paid currently to the carrier gas as a participant in the chromatographic process and as a factor capable of improving the separation significantly.

The retention of chromatographed compounds is a result of the adsorption of the analyte compounds/sorbate on a solid with a relatively high specific surface (the adsorbent).¹ In gas–solid chromatography, the retention is determined by the nature of the sorbate, the nature of the adsorbent surface and its structure, and also the nature and pressure of the carrier gas employed.

The first experimental data concerning the influence of the nature of the carrier gas and the retention of the analyte were obtained already in the initial stage of the development of gas–

solid chromatography. Thus, as early as 1962, Zhukhovitskii and Turkel'taub noted that in gas–solid chromatography account must be taken primarily of the influence of the carrier gas on the sorbability of the components of the mixture being separated, because a change in the nature of the carrier gas may alter significantly the separation criteria.⁴ However, in routine chromatography, this fact has not always been taken into account. This can probably be accounted for by the fact that, firstly, permanent gases, the influence of which on the retention parameters is insignificant, were usually employed as carrier gases and, secondly, the accuracy of the measurement of the retention parameters on packed columns, especially in the initial period of the development of gas–solid chromatography, was insufficiently high.

The influence of the nature of the carrier gas on the retention may be predicted by analysing the general relations describing the adsorption equilibria and the relation between these equilibria and the retention volume (see, for example, Refs 1, 2 and 6–9). The equilibrium is characterised by the following functional relations.

1. The equation of the adsorption isotherm for the compounds participating in the chromatographic process:

$$a_i = f(c_i, c_m, a_m), \quad (1a)$$

$$a_m = \psi(c_m, a_i, c_i), \quad (1b)$$

where a_i is the concentration of the adsorbed compound i on the surface of the adsorbent, c_i is the concentration of compound i in the gas phase, c_m the concentration of the carrier gas in the mobile phase (proportional to its partial pressure), and a_m is the concentration of compound m (the carrier gas) on the surface of the adsorbent.

2. The equations for the effective partition coefficient $K_{im\text{ef}}$ (see, for example, Berezkin and de Zeeuw²):

$$K_{im\text{ef}} = \left(\frac{\partial a_i}{\partial c_i} \right)_{c_m} = \left[\frac{\partial f(c_i, c_m, a_m)}{\partial c_i} \right]_{c_m},$$

$$K_{im\text{ef}} = \left(\frac{\partial a_i}{\partial c_i} \right)_{c_m} = \frac{V_{Ni}(c_i, c_m)}{S} = V_s(c_i, c_m), \quad (2)$$

where V_{Ni} is the retention volume for compound i , S the overall surface area of the adsorbent employed, and $V_s(c_i, c_m)$ the specific

V G Berezkin, I V Malyukova A V Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Leninskii prosp. 29, 117912 Moscow, Russian Federation. Fax (7-095) 230 22 24. E-mail: berezkin@ips.ac.ru (V G Berezkin), malyuk@ips.ac.ru (I V Malyukova)

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retention volume calculated per unit surface of the adsorbent employed.

We may note that the nonideality of the gas phase and its adsorption on the surface of the adsorbent influence the retention. However, as noted in the above monograph,² the role of the second factor is frequently more important.

3. The equation for the retention volume:

$$V_{Ni} = \left(\frac{\partial a_i}{\partial c_i} \right)_{c_m} S = K_{im\text{ef}} S. \quad (3)$$

We may note that the functions a_i and a_m [Eqns (1a) and (1b)] are functions of several variables and their derivatives are therefore expressed as partial derivatives.

Taking into account the general ideas concerning the adsorption of a mixture of gases on the surface of a solid adsorbent (see, for example, monograph by Kiselev and Yashin¹), it follows from Eqn (3) that in the general case V_{Ni} also depends on the nature of the carrier gas, its partial pressure, and its adsorption in the chromatographic system.

If it is assumed that the adsorption of the carrier gas may be neglected, Kiselev's equation follows from Eqn (3) as a special case:^{1,6}

$$V_{Ni} = K_i S. \quad (4)$$

In it, Henry's constant K_i may be expressed by the following equations:

$$K_{im\text{ef}} = K_i,$$

$$K_i = \frac{\partial a_i}{\partial c_i} = \frac{a_i}{c_i}. \quad (5)$$

It follows from the relations quoted above that the partition coefficient depends in the general case on the partial pressure (concentration) of the carrier gas and its nature. Analysis of this relation is of theoretical and practical interest.

We believe that studies on the influence of the nature of the carrier gas on the retention are important because they make it possible, firstly, to refine the real picture of the chromatographic process, secondly, to establish the corresponding general relations, and, thirdly, to assess the carrier gas as a factor actively influencing the principal parameters of the chromatographic separation. Certain examples of the practical use of gas–solid chromatography, reflecting the role of the carrier gas, are presented in Table 1. Evidently, many carrier gases have found an application in gas–solid chromatography — ranging from the inert helium to the vapours of water and organic compounds, but helium, nitrogen, and hydrogen are mainly employed in chromatographic practice.²⁰

Table 1. Examples of the chromatographic systems used in gas-solid chromatography.

Carrier	Sorbent	Sorbate	Temperature /°C	Detector	Ref.
Helium	activated charcoal	methane	20–170	TCD	10
	graphitised carbon black	argon, cyclohexane, benzene	100–400	—	11
	ditto	benzene, n-pentane	20	FID	12
	Porapak S	methane	0	"	13
	Chromosorb 101,	alkanes, aromatic hydrocarbons,	100	"	14
	Chromosorb 104	n-alcohols, acids			
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	10–250	"	15
	Al ₂ O ₃	n-butane	100	—	16
	13X molecular sieve	H ₂ , HD, and D ₂	–195, –183	TCD	17
	NaY molecular sieve	C ₁ –C ₄ hydrocarbons	20–200	"	18
	Al ₂ O ₃ /KCl ^a	buta-1,3-diene	130	FID	19
	Al ₂ O ₃ /KCl ^a	propane, isobutane, n-butane	100	"	20
Nitrogen	activated charcoal	benzene, cyclohexane, volatile organic compounds	20, 30, 77, 100	TCD	21–23
	ditto	methane	20–170	"	10
	"	H ₂ , CO, CH ₄ , C ₂ H ₄ , C ₂ H ₆ , C ₂ H ₂	20–40	TCD	15
	graphitised carbon black	argon, cyclohexane, benzene	100–400	"	11
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	16
	Al ₂ O ₃	n-butane	100	—	19
	NaY molecular sieve	C ₁ –C ₄ hydrocarbons	20–200	TCD	18
	silica gel, activated charcoal, Al ₂ O ₃	mixture of hydrocarbon gases	60–180	"	25
	Al ₂ O ₃ /KCl ^a	buta-1,3-diene	130	FID	19
	Al ₂ O ₃ /KCl ^a	propane, isobutane, n-butane	100	"	20
Hydrogen	graphitised carbon black	argon, benzene, cyclohexane	100–400	—	11
	Porapak Q	Kr, CO ₂ , H ₂ O, C ₂ H ₆ , C ₂ H ₄ , C ₂ H ₂ , C ₃ H ₈ , C ₃ H ₆	70	TCD	25
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	15
	Al ₂ O ₃	n-butane	100	—	16
	13X molecular sieve	H ₂ , HD, D ₂	–195, –183	TCD	17
	NaA molecular sieve	hydrogen isotopes	(–221)–(–161)	"	27
	silica gel, activated charcoal, Al ₂ O ₃	mixture of hydrocarbon gases	60–180	"	25
	Al ₂ O ₃ /KCl ^a	buta-1,3-diene	130	FID	19
	5A molecular sieve ^a	CO, N ₂ , CH ₄ , C ₂ H ₂ , He, Ne, Ar, Kr, Xe	60, 100, 120	TCD	28

Table 1 (continued).

Carrier	Sorbent	Sorbate	Temperature /°C	Detector	Ref.
Hydrogen	5A molecular sieve ^a	He, O ₂ , N ₂ , CH ₄ , CO	25	TCD	29
	13X molecular sieve ^a	naphthene and paraffin fractions of petroleum	150	FID	30
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	15
D ₂	5A molecular sieve	hydrogen isotopes	(–221)–(–161)	TCD	27
HD	ditto	ditto	(–221)–(–161)	"	27
Argon	activated charcoal	methane	20–170	"	10
	graphitised carbon black	cyclohexane, benzene	(–263)–127	–	11
	Porapak S	methane	0	FID	13
	Porapak Q	Kr, CO ₂ , N ₂ O, C ₂ H ₆ , C ₂ H ₄ , C ₂ H ₂ , C ₃ H ₈ , C ₃ H ₆	70	TCD	26
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	15
	Al ₂ O ₃	n-butane	100	–	16
	molecular sieves	air	–	TCD	31
	activated charcoal	He + N ₂ + Ar + H ₂ + CO mixture	45–63	"	32
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	15
Krypton	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	"	15
Carbon dioxide	Porapak S	methane	0	"	13
	Porapak Q	Cr, CO ₂ , N ₂ O, C ₂ H ₆ , C ₂ H ₄ , C ₂ H ₂ , C ₃ H ₈ , C ₃ H ₆	70	TCD	26
	Chromosorb 101, Chromosorb 104	alkanes, aromatic hydrocarbons, n-alcohols, organic acids	–	FID	14
	Al ₂ O ₃	C ₁ –C ₁₀ hydrocarbons	100–250	FID	15
	NaY molecular sieve	C ₁ –C ₁₀ hydrocarbons	20–200	TCD	18
	molecular sieves	air	–	"	31
	activated charcoal, silica gel, Al ₂ O ₃	mixture of hydrocarbon gases	60–180	"	25
	Al ₂ O ₃ /KCl ^a	propane, isobutane, butane	100	FID	20
	Al ₂ O ₃ ^a	light organic compounds	50–150	"	33
	Chromosorb	butane-2,3-diol, propane-1,2-diol, ethane-1,2-diol	85	FID	34
Steam	Al ₂ O ₃	alcohols, ethers, ketones	–	–	35
	Polysorb	C ₅ –C ₁₀ alcohols and acids	230	FID	36
	type Y potassium–barium zeolite	<i>m</i> - and <i>p</i> -xylenes	–	"	37
	Chromosorb P, AW, Al ₂ O ₃	hydrocarbons	125–260	"	38
	silica gel	C ₁ –C ₄ hydrocarbons	–	TCD	39
Nitrogen + steam	graphitised carbon black	methane, propane, isobutane, n-butane	60	FID	40
	teflon	ethene, ethylene glycol, propylene glycol, diethylene glycol	110–150	"	41
Helium + steam	KY zeolite	organic oxygen- and nitrogen-containing gases	40–300	TCD	42
	Al ₂ O ₃	C ₈ –C ₁₂ n-paraffins, aromatic hydrocarbons	170	FID	43
Steam + ammonia	porous glass beads, diatomaceous brick	organic acids and amines	125–200	"	44
Ethyne	activated charcoal	methane	20–170	TCD	10
Ethyne, propene	Porapak Q	Kr, CO ₂ , N ₂ O, C ₂ H ₆ , C ₂ H ₄	70	"	27
Methane	silica gel	nitrogen, ethene, propane	75	"	45
Propene, <i>trans</i> -but-2-ene	Polysorb 1	silicon tetrachloride	130, 150, 170	"	46

Table 1 (continued).

Carrier	Sorbent	Sorbate	Temperature /°C	Detector	Ref.
Freon 116	silica gel	nitrogen, argon, carbon dioxide, sulfur dioxide	—	FID	47
Tetrachloro-methane, chloroform, dichloro-methane, ethanol	Porapak Q, Porapak S	ethane, n-butane	90–130	TCD	48
Dichloromethane	Polysorb 1	silicon tetrachloride	130, 150, 170	TCD	46
n-Hexane, n-butyl chloride, ethyl acetate, ethanol	silica gel	α - and β -naphthols, phenols, and ethers	190	UVD	49
Ethanol, methanol, propanol	Al ₂ O ₃	anthracene, phenanthrene, <i>o</i> -, <i>m</i> -, and <i>p</i> -dinitrobenzene	140, 160, 210	—	50
Ethanol with added ethylene-cyclohexane	silica gel, Al ₂ O ₃ , Spherosil	<i>o</i> -, <i>m</i> -, and <i>p</i> -phenylenediamines, <i>N</i> -alkylanilines, isomeric <i>N</i> -phenylnaphthylamines	150, 180, 190	UVD	49
n-Hexane, ethanol	chromaton	alkanes, aromatic hydrocarbons, n-alcohols, ketones	75–250	TCD	51
Nitrogen + isopentane vapour	5A molecular sieve	oxygen, argon, neon, helium	—	FID	52

Note. The following designations have been adopted: TCD = thermal conductivity detector; FID = flame-ionisation detector; UVD = ultraviolet detector. ^a On capillary columns.

In this review, the authors attempted to survey and analyse the experimental data concerning the dependence of the retention of the compounds chromatographed on the nature and pressure of the carrier gas employed and to assess the possibility of using the carrier gas to increase the selectivity of the separation of the analyte. The physicochemical foundations of the influence of the nature of the carrier gas on the principal characteristics of the chromatographic process are examined for this purpose.

II. The role of the carrier gas in gas–solid chromatography

In the initial period of the development of gas–solid chromatography, nitrogen and air were used as the mobile phase.^{21–23, 53–56} Subsequently, hydrogen²⁵ and helium^{57, 58} also began to be used, which made it possible to improve the characteristics of the chromatographic process by increasing the sensitivity of the thermal conductivity detector. During this period, the principal chromatographic detector was the thermal conductivity detector (TCD). Subsequently individual communications appeared concerning the application of neon,^{32, 59} xenon, and krypton⁶⁰ as carrier gases, but in the main this was associated not so much with the study of the influence of the nature of the carrier gas on the chromatographic process as with the need to employ highly sensitive ionisation detectors.

The first publications about the systematic investigation of organic and water vapours as carrier gases appeared at the end of the 1950s.^{61, 62} However, the saturation of the inert carrier gas with steam had also been used earlier. Thus Turkel'taub *et al.*³⁹ described the chromatographic analysis of a C₁–C₄ hydrocarbon mixture and other gases on silica gel with addition of steam (1 vol.%–8 vol.%) to the usual carrier gas. As the content of steam in the mobile phase increased, a decrease in the retention volumes of the components of the mixture analysed and a change in the shape of the peaks were observed. Similar results were obtained by Booker⁶³ in a study of the chromatographic separation of gaseous hydrocarbons on alumina; he confirmed that the

symmetry of the chromatographic zones was significantly improved after the addition of steam to the carrier gas.

Wiseman⁵⁸ drew attention to the fact that the width of the elution curves for ethyl acetate and isobutyl alcohol was greater when nitrogen was used as the carrier gas. However, a theoretical justification of this phenomenon was not achieved.

Green and Roy¹⁰ are the authors of the first communication in which a significant change in the retention time of the chromatographed compound was noted after the replacement of one carrier gas by another. The investigators presented the following data concerning the separation of a low-boiling gas mixture (H₂, O₂, N₂, CO, CH₄, CO₂, C₂H₄, and C₂H₆) on activated charcoal at 25 °C for five carrier gases: He, Ar, N₂, air, and ethyne. For example, the retention time of methane assumed the following values (min) other conditions being equal: 34 in helium, 22 in argon, 16 in nitrogen, 15 in air, and 5 in ethyne. Thus the retention increased by a factor of ~7 when ethyne was replaced by helium. Satisfactory results in the separation of a complex mixture have been obtained¹⁰ using programmed temperatures (Fig. 1).

A change in the retention volumes when different carrier gases were employed (H₂, He, Ne, and Ar) was noted also in a study of the separation of mixtures of permanent gases on columns with activated charcoals and molecular sieves.⁵⁹

It is known that the sorption of light gases (including carrier gases) in gas–solid chromatography on solid adsorbents may be significant. Thus, carbon dioxide is strongly adsorbed by molecular sieves. Karmen *et al.*³¹ pointed out the possibility of using it as the carrier gas, which made it possible to separate nitrogen and oxygen on molecular sieves. When carbon dioxide was replaced by the inert helium, there was virtually no separation.

Further investigations demonstrated that the nature of the carrier gas influences the retention of the chromatographed compounds and this is characteristic of adsorbents of different types. Thus it has been shown that²⁶ the retention times (retention volumes) of various gases on porous organic polymeric adsorbents of the Porapak Q type diminish appreciably when the heavy

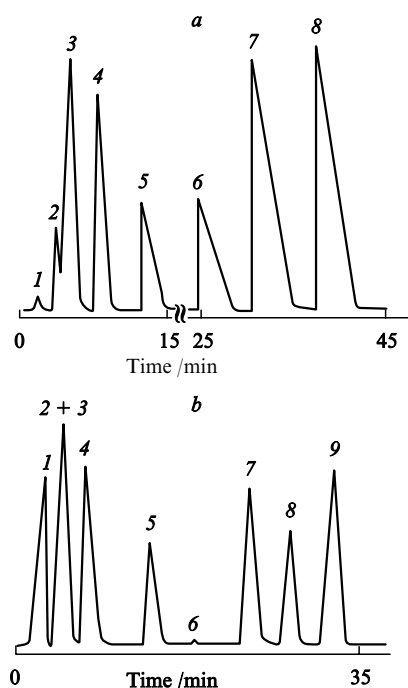


Figure 1. Chromatogram of a gas mixture of organic and inorganic compounds with helium (a) and argon (b) as the carrier gases;¹⁰ (1) hydrogen; (2) oxygen; (3) nitrogen; (4) carbon monoxide; (5) methane; (6) carbon dioxide; (7) ethyne; (8) ethene; (9) ethane. Experimental conditions: column length 3 m, sorbent — activated charcoal (40–60 mesh), temperature programming from 25 °C to 170 °C at 3 K min⁻¹ (a) and to 160 °C (b).

carbon dioxide or gaseous hydrocarbons (ethene and propene) are used as the carrier gas (Table 2).

Vyakhirev and Bruk⁶⁴ investigated the influence of the nature of the carrier gas on the chromatographic separation of mixtures of gaseous hydrocarbons on a silica gel column using hydrogen, nitrogen, and carbon dioxide as the carrier gases. The adsorption isotherms and the Henry adsorption coefficients for various carrier gases calculated from them indicate that the degree of

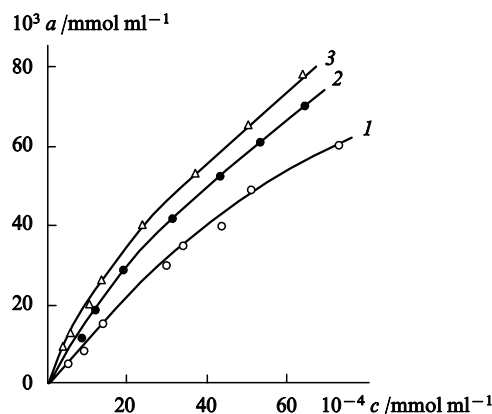


Figure 2. Adsorption isotherms of n-butane on silica gel at 40 °C.⁶⁴ Carrier gases: (1) carbon dioxide; (2) nitrogen; (3) hydrogen.

adsorption of n-butane in a flow of CO₂ is lower (Fig. 2) than in N₂ and H₂, which can be explained by the stronger adsorption of CO₂ on silica gel. Accordingly the retention of the components in the separation of a mixture of hydrocarbons is smaller in a flow of carbon dioxide than in a flow of nitrogen and hydrogen. The nature of the carrier gas also influences the shape of the adsorption isotherm (Fig. 2). The isotherms for n-butane in N₂ and H₂ have a more convex form (relative to the abscissa axis), while those in CO₂ are less convex. A certain degree of linearisation of the n-butane isotherm in a flow of CO₂ can undoubtedly be accounted for by the stronger adsorption of carbon dioxide on silica gel compared with the adsorption of nitrogen and hydrogen, i.e. by the dynamic modification of the silica gel surface by the adsorbed carbon dioxide molecules.

Turkel'taub and Zhukhovitskii⁶⁵ were some of the first investigators to note that the nature of the carrier gas plays a significant role in gas–solid chromatography. This is manifested by a change in the shape of the recorded peaks and in retention when one carrier gas is replaced by another. The adsorption coefficient of the component decreases sharply if its adsorption characteristics are close to those of the carrier gas, and at the same time the carrier gas exerts a significantly smaller influence on the effectively adsorbed component. Modification of the adsorbent surface by molecules of a heavy carrier gas improves the symmetry of the zones of the chromatographed compounds.

The characteristics of the influence of the carrier gas can be explained qualitatively (and in a number of instances also quantitatively) by competitive adsorption and by the employment of the Langmuir equation for binary mixtures in order to interpret the observed phenomena (see, for example, Kel'tsev's monograph⁶⁶).

Thus the first investigations already showed that the mobile phase plays a more important role in gas–solid chromatography than in gas–liquid chromatography.

Subsequent studies were devoted mainly to the establishment of the general quantitative and semiquantitative characteristics of the influence of the nature of the carrier gas and of its pressure on the retention of the chromatographed compounds and also to the theoretical justification of such influence.

III. Gas–solid chromatography on packed columns

1. Gases as the mobile phase

Hoffman and Evans¹⁵ established a linear relation between the retention times of normal hydrocarbons and the reciprocal of the square of the radius of the atom of an inert monatomic carrier gas. However, this relation is doubtful for the following reasons: firstly, the characteristic quantity (chromatographic constant) for the chromatographed substance is not the retention time but

Table 2. Retention volumes (V_R /ml) of certain gases on a packed column with Porapak Q as the adsorbent and different carrier gases.²⁶

Sorbate	Carrier gas					
	H ₂	N ₂	Ar	CO ₂	C ₂ H ₄	C ₃ H ₆
Temperature 20 °C						
Kr	24	20	18	17	13	8
CO ₂	70	61	53	—	41	23
N ₂ O	67	88	78	69	57	32
C ₂ H ₆	265	—	—	154	—	—
Temperature 52 °C						
Kr	12	12	11	10	10	7
CO ₂	28	27	25	—	23	16
N ₂ O	38	38	35	32	32	21
C ₂ H ₆	88	84	86	65	61	—
C ₃ H ₈	435	430	425	305	260	—
Temperature 70 °C						
Kr	8	8	8	8	7	5
CO ₂	20	19	17	—	16	13
N ₂ O	24	23	23	22	18	—
C ₂ H ₆	50	50	50	46	42	—
C ₃ H ₈	220	220	220	180	155	—

the retention volume^{67–69} and, secondly, according to the results obtained by Hoffman and Evans,¹⁵ helium exerts a stronger modifying effect than argon, which conflicts with known data from other investigations.

Brokman *et al.*¹⁶ investigated the influence of the nature of the carrier gas on the interphase equilibrium distribution of the volatile sorbate. The specific retention volume (V_g^T) was selected as the parameter sensitive to the alteration of the nature of the distribution for the given sorbate–sorbent pair at the given temperature. The results obtained, presented in Table 3, enabled the authors to conclude that the distribution constants hardly change on passing from one carrier gas to another. This should imply that the nature of the carrier gas hardly affects the distribution process and that the change in the retention time of n-butane can be explained solely by the different inlet pressures of the carrier gases (two parameters are actually altered — the viscosity and pressure of the carrier gas). It is noteworthy that this is the only study in which it was concluded that the nature of the carrier gas does not influence the retention of the analyte.

Table 3. The specific retention volume of n-butane on a column with activated alumina at a temperature of 100 °C with various carrier gases.¹⁶

Carrier gas	<i>t</i> /min	<i>P</i> ₀ /Torr	James–Martin correction	V_g^T /ml g ^{−1}
H ₂	4.29	1025	0.830	16.8 ± 0.1
N ₂	4.96	1290	0.710	16.6 ± 0.1
He	5.14	1320	0.695	16.9 ± 0.1
Ar	5.24	1420	0.660	16.3 ± 0.1

However, in our view the authors of the above study¹⁶ treated their results incorrectly. The carrier gases arranged in order of decreasing retention volumes (ml g^{−1}) of the chromatographed compounds (*i.e.* in order of increasing influence on the retention volume) form the following series: He (16.9) > H₂ (16.8) > N₂ (16.6) > Ar (16.3). We may note that the accuracy of measurement of the retention volumes in the study under discussion was not less than to within 0.1 ml g^{−1}, so that the sequence presented above ('the influence series') may be regarded as experimentally rigorously established; it confirms the dependence of the equilibrium retention volume on the nature of the carrier gas employed. This sequence is consistent with the adopted idea that the adsorbability of the carrier gas increases in the same series. Thus the conclusion reached by the authors¹⁶ that the retention is independent of the nature of the carrier gas conflicts with their own experimental data.

Gvozdoch *et al.*¹⁴ confirmed the influence of the nature of the carrier gas on the retention of the chromatographed compounds on porous organic polymers (adsorbents). The retention volumes of a series of volatile compounds were measured and compared on Chromosorbs 101, 104, and 106 using strongly adsorbed carrier gases — helium, argon, carbon dioxide, sulfur hexafluoride, and water. The nonpolar Chromosorb 101 is⁶⁷ a copolymer of styrene and divinylbenzene, the polar Chromosorb 104 is a copolymer of acrylonitrile and divinylbenzene, while the nonpolar Chromosorb 106 is a polystyrene with a network structure. Table 4 presents the retention volumes of the sorbates when argon and steam are used as carrier gases. Analysis of the tabulated data shows that the replacement of argon by steam influences significantly the retention of the chromatographed compounds, especially polar ones.

It has been established experimentally¹⁴ that the use of heavy carrier gases induces a decrease in the retention volumes when both the weakly specific adsorbent Chromosorb 101 and the highly specific adsorbent Chromosorb 104 are employed. The influence of the nature of the carrier gas intensifies with increase in its adsorbability on the surface of the porous polymer: the energies of the interaction of the carrier gases investigated diminish in the

Table 4. The retention volumes (V_R /ml) of compounds of different classes on polymeric adsorbents at 150 °C using argon and steam as the carrier gases.¹⁴

Adsorbate	Adsorbent — Chromosorb 110			Adsorbent — Chromosorb 104		
	$V_R(\text{Ar})$	$V_R(\text{H}_2\text{O})$	$\frac{V_R(\text{Ar})}{V_R(\text{H}_2\text{O})}$	$V_R(\text{Ar})$	$V_R(\text{H}_2\text{O})$	$\frac{V_R(\text{Ar})}{V_R(\text{H}_2\text{O})}$
n-Alkanes						
pentane	10.05	6.75	1.55	6.9	2.95	2.34
hexane	22.0	15.10	1.46	14.1	6.75	2.09
heptane	50.4	31.50	1.60	28.7	13.60	2.11
octane	108.0	64.5	1.67	55.9	24.5	2.28
n-Alcohols						
methanol	4.81	3.55	1.35	14.7	8.70	1.69
ethanol	10.5	6.60	1.59	27.4	12.85	2.13
propanol	21.5	15.1	1.42	52.2	24.5	2.13
butanol	48.1	28.2	1.71	109.0	51.0	2.14
n-Acids						
acetic	33.3	37.0	0.90	122.0	114.5	1.07
propionic	72.8	51.0	1.43	223.0	165.0	1.35
butyric	159.0	95.0	1.67	338.0	287.0	1.18
pentanoic	318.0	174.0	1.83	868.0	500.0	1.74

sequence H₂O > CO₂ > SF₆ > He. According to Gvozdoch *et al.*,¹⁴ the dependence of the retention volume on the nature of the carrier gas is a result of the influence of two main processes: the adsorption of the carrier gas on the most active surface centres of the porous polymers (and the partial displacement of the sorbate by the carrier gas) and the interaction of the sorbate and carrier gas molecules.

The active role of the carrier gas in gas–solid chromatography and its influence on the retention have been noted also in the monograph Guiochon and Guillemin.⁷¹ Thus, when n-alkanes were eluted on silica gel of the type of Porasil C (with a specific surface of 50–100 m² g^{−1}) using carbon dioxide as the carrier gas at a column temperature of 80 °C, an appreciable decrease (30%–40%) in the retention factor (capacity factor) of the column following an increase in pressure from 1.3 to 5.1 atm was noted.⁷¹ Under these conditions, ~15% of the silica gel surface was covered by adsorbed carbon dioxide molecules.⁷¹

'Heavy' carrier gases may decrease significantly the adsorbability of the chromatographed compounds and hence influence the separation of gases and volatile compounds, especially when molecular sieves are employed. In gas chromatography on zeolites, the actively adsorbed carrier gases (such as steam and carbon dioxide) are hardly employed because they are selectively and strongly adsorbed by zeolites. For example, Kiselev and Yashin⁷² noted that the presence of water and carbon dioxide strongly influences the retention volumes on zeolites. For the stable operation of a column with zeolites, it is therefore necessary to remove thoroughly moisture and carbon dioxide from the carrier gas being analysed.

However, the use of strongly adsorbed carrier gases is in a number of instances justified by the separation of strongly adsorbable sorbates. Thus it has been shown⁷³ that the use of carbon dioxide as the carrier gas appreciably improves the separation of hydrocarbon gases on zeolites at a low column temperature and reduces the duration of analysis compared with the carrier gases employed traditionally (for example, helium or nitrogen). The nature of the carrier gas strongly influences the separation of hydrocarbon mixtures. For example, a six-component mixture of hydrocarbon gases may be fully separated on the NaY zeolite at 20 °C using carbon dioxide as the carrier gas (Fig. 3), whereas traditional carrier gases (hydrogen or helium) do not ensure the separation of this mixture even at elevated temperatures as a consequence of the strong retention of its components.

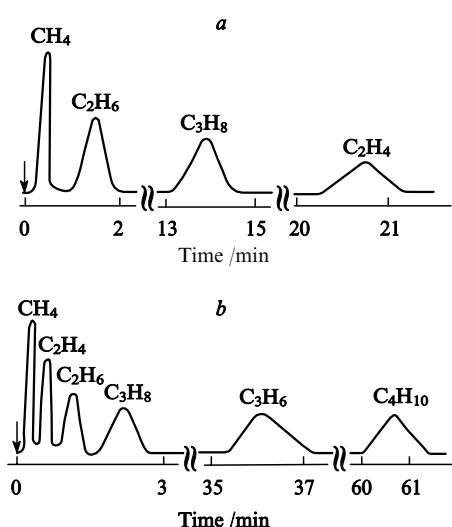


Figure 3. Chromatogram of C₁–C₄ hydrocarbon gases.⁷³ Experimental conditions: 0.5 m × 4 mm column, adsorbent — NaY, temperature 20 °C. Carrier gases: (a) helium; (b) carbon dioxide.

It is essential to note that the use of He or N₂ as carrier gases on this form of molecular sieve does not lead to the temperature inversion of the elution sequence of the components for the following pairs of hydrocarbon gases: propane–ethene, butane–propene. However, if the carrier gas is CO₂, then at certain temperatures the elution sequence of the above pairs of organic compounds is inverted. An appreciable decrease in the specific retention volumes of hydrocarbon gases has been noted⁷³ when carbon dioxide was used as the carrier gas on packed columns with the NaY and CdY zeolites. This effect is manifested most clearly at low column temperatures when CO₂ is appreciably adsorbed on zeolites. A consequence of this is the deactivation of the adsorbent surface.

The absolute retention of the chromatographed compounds on a given packed column is determined not only by the nature of the adsorbent but also by its form — bulk or surface-layer adsorbent. The amount of the adsorbent per unit volume is significantly greater for the traditional (bulk) adsorbent than for the surface-layer adsorbent, so that the use of the latter makes it

possible to reduce significantly the retention of the chromatographed compounds, *i.e.* to accelerate the analysis.

Andronikashvili, Berezkin, and coworkers investigated the joint influence of the carrier gas, the type of the adsorbent (bulk or surface-layer),^{18, 74} and the nature of the cation in the zeolite⁷⁴ on the chromatographic separation process. The retention times of the individual hydrocarbons in the NaY zeolites in the traditional and surface-layer forms are presented in Table 5. For all the hydrocarbons investigated and for all the carrier gases, a significant decrease in the retention time is observed on passing from the bulky to the surface-layer sorbents. The nature of the carrier gas also influences to an appreciable degree the retention times of the sorbates: the longest retention time is in helium, a shorter one is in nitrogen, and a still shorter retention time occurs in carbon dioxide. If the carrier gas is CO₂, its displacement effect can be made use of in many instances, *i.e.* carbon dioxide may serve simultaneously as a carrier gas and as a displacing gas.^{18, 74}

Using a mixture containing n-alkanes, Andronikashvili *et al.*⁷⁴ showed that the employment of carbon dioxide as the carrier gas and of surface-layer zeolite adsorbents improves significantly the effectiveness of chromatographic columns, reduces the duration of the analysis, and makes it possible to obtain a more symmetrical peak and also to expand appreciably the range of compounds which may be analysed on zeolites. The chromatograms for the separation of a mixture of hydrocarbons are presented in Fig. 4.

Thus, when account is taken of the foregoing, it is justifiable to recommend a wider application of CO₂ as the carrier gas in gas–solid chromatography on zeolites in the form of surface-layer adsorbents.

Parbuzin and Gulians²⁷ proposed a version of gas–solid chromatography using adsorbable carrier gases (hydrogen deuteride and deuterium) as well as protium for the separation of a five-component mixture (hydrogen deuteride and the *o*- and *p*-isomers of hydrogen and deuterium) on a column with the NaA molecular sieve at a temperature in the range between –321 and –161 °C. The employment of the traditional version of gas–solid chromatography using inert carrier gases for the physico-chemical investigation of the adsorption of hydrogen isotopes and isomers is restricted by the ‘zero’ degree of surface coverage of the adsorbent and by the temperature (–173 °C). The appearance of ‘negative’ peaks can be explained by the greater thermal conductivity of certain sorbates compared with that of the carrier gas. The application of deuterium-containing carrier gases which are adsorbed at low temperatures made it possible to obtain extensive

Table 5. The retention time of C₁–C₄ hydrocarbon gases (*t_R* /s) on a packed column with the NaY zeolite using helium, nitrogen, and carbon dioxide as the carrier gases.¹⁸

Sorbate	Helium			Nitrogen			Carbon dioxide		
	<i>t_R</i> (TAD)	<i>t_R</i> (SLAD)	$\frac{t_R(TAD)}{t_R(SLAD)}$	<i>t_R</i> (TAD)	<i>t_R</i> (SLAD)	$\frac{t_R(TAD)}{t_R(SLAD)}$	<i>t_R</i> (TAD)	<i>t_R</i> (SLAD)	$\frac{t_R(TAD)}{t_R(SLAD)}$
Temperature 20 °C									
CH ₄	17.0	5.0	3.4	36.0	5.0	7.2	9.0	5.0	1.8
C ₂ H ₆	115.0	10.0	11.5	108.0	10.0	10.8	50.0	8.0	6.3
C ₃ H ₈	848.0	48.0	17.7	—	47.0	—	353.0	20.0	17.7
C ₄ H ₁₀	—	329.0	—	—	—	—	4228.0	93.0	45.5
C ₂ H ₄	1308.0	70.0	18.7	—	80.0	—	208.0	14.0	14.9
C ₃ H ₆	—	—	—	—	—	—	2248.0	85.0	26.5
Temperature 100 °C									
CH ₄	12.0	5.0	2.4	10.0	4.0	2.5	7.0	4.0	1.8
C ₂ H ₆	46.0	7.0	6.6	41.0	7.0	5.9	25.0	5.0	5.0
C ₃ H ₈	241.0	15.0	16.1	210.0	14.0	15.0	102.0	11.0	9.3
C ₄ H ₁₀	1350.0	65.0	20.8	1005.0	62.0	16.2	555.0	40.0	13.9
C ₂ H ₄	225.0	14.0	16.1	181.0	10.0	18.1	71.0	9.0	7.9
C ₃ H ₆	2008.0	73.0	27.5	1315.0	68.0	19.3	450.0	36.0	12.0

Note. The following designations have been adopted: TAD = traditional (volumetric) adsorbent; SLAD = surface-layer adsorbent.

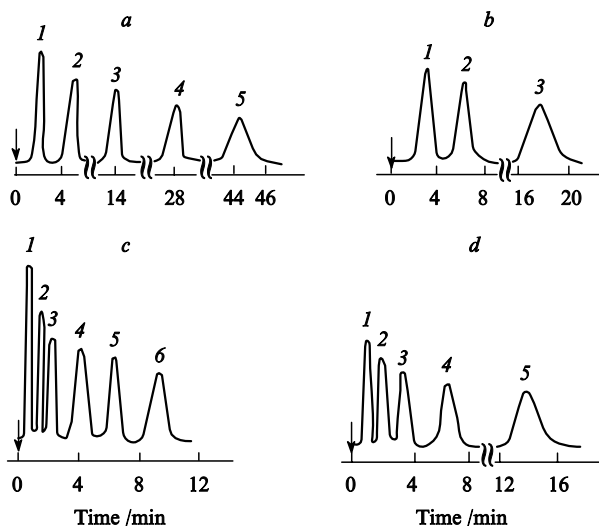


Figure 4. Chromatogram of a mixture of C_5 – C_{10} hydrocarbons on a packed column (0.5×4 mm) with the HY zeolite;⁷⁴ (a) and (b) volumetric adsorbent, temperature 300°C ; (c) and (d) surface-layer adsorbent, temperature 225°C . Carrier gases: (a) and (c) carbon dioxide; (b) and (d) helium. Sorbates: (1) pentane; (2) hexane; (3) heptane; (4) octane; (5) nonane; (6) decane.

information about the adsorption of such compounds on solid adsorbents over a wide temperature range and for different degrees of surface coverage of the adsorbent and also to separate the spin isomers and isotopes of hydrogen and to improve the symmetry of the peaks due to the components being separated (Fig. 5).²⁷

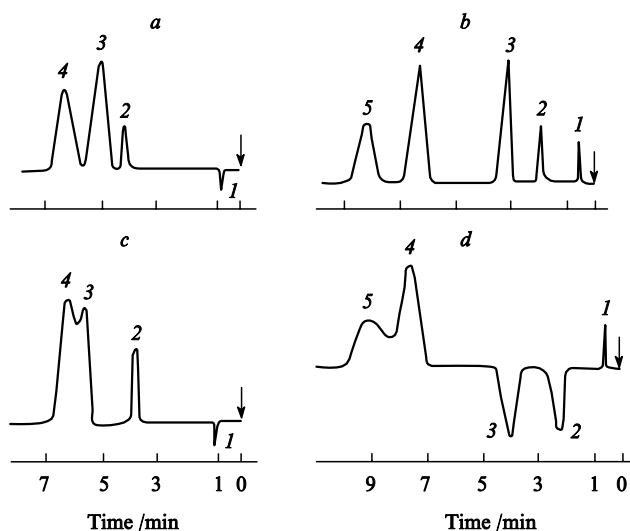


Figure 5. Chromatograms of a five-component mixture of isotopic and spin modifications of molecular hydrogen obtained on packed columns with the NaA zeolite using various carrier gases;²⁷ (a) carrier gas helium, $2 \text{ mm} \times 3 \text{ mm}$ column, temperature -140°C ; (1) ^3He ; (2) H_2 ; (3) HD; (4) D_2 ; (b) carrier gas — protium, $0.8 \text{ m} \times 2 \text{ mm}$ column, temperature -209.5°C ; (1) He; (2) H_2 ; (3) HD; (4) $o\text{-D}_2$, $p\text{-D}_2$; (c) carrier gas — deuterium, $0.6 \text{ m} \times 2 \text{ mm}$ column, temperature -195.7°C ; (1) He; (2) $p\text{-H}_2$; (3) $o\text{-H}_2$; (4) HD; (d) carrier gas — hydrogen deuteride $0.45 \text{ m} \times 3 \text{ mm}$ column, temperature -209.8°C ; (1) He; (2) $p\text{-H}_2$; (3) $o\text{-H}_2$; (4) $o\text{-D}_2$; (5) $p\text{-D}_2$.

2. The use of pure vapours of polar compounds or their mixtures in an inert carrier gas as the mobile phase for the dynamic modification of adsorbents

The vapours of highly polar organic and inorganic compounds, which are used as the mobile phase in a pure form or as an admixture in a fairly inert carrier gas, exert a strong and frequently nontraditional influence on the retention and the shape of the recorded peaks for the analytes. In this version of gas–solid chromatography, the mobile phase is, firstly, a transporting agent which moves the zones of the compounds separated along the column and, secondly, an agent modifying the adsorbent surface. The adsorbability of the sorbate in the mobile phase–sorbing medium system and hence the retention are altered as a result of the modification (the retention is usually reduced); the phase equilibrium of the sorbate in the mobile phase–adsorbent system is disturbed as a consequence of the nonideality of the mobile phase, which is usually manifested to an appreciable degree at an elevated pressure; the ‘sensitivity of the detector’ to the analytes is changed (in some cases, its increase is observed).

In the first studies employing organic eluents,⁶¹ steam,^{34, 35, 64} and of these substances as additives to the conventional carrier gases,^{39, 52} it was shown that transition to organic and mixed eluents significantly alters in many instances the picture in the gas-chromatographic separation of substances. The nature of the mobile phase influences appreciably both the retention of the chromatographed compound and the shape of the recorded peaks. For example, the vapours of the following substances may be used as the eluent (or its component): water,^{38, 39, 42–25, 62} ethanol,^{41, 48–50} carbon tetrachloride,⁴⁸ n-hexane, n-butyl chloride, ethyl acetate,⁴⁹ etc. Steam is most often employed^{38, 39, 42–45, 62, 75} and in this instance one speaks of a special vapour-phase version of chromatography.

The vapours of organic compounds as the mobile phase in gas–solid chromatography. The characteristic features of the application of gases and organic vapours as carrier gases and also as additives to the usual carrier gases have been examined in detail.^{76, 77} The authors note that in a traditional variant of gas chromatography at low pressures, the mobile phase performed as a rule the function only of the agent transporting the substances being separated along the column, which unjustifiably narrows the role of the carrier gas.

In the literature, it is possible to find numerous examples illustrating the influence of vapour-like mobile phases (VMP) on the results of the chromatographic process. For example, Tsuda *et al.*⁴⁹ present data demonstrating clearly the significant influence of the nature of the carrier gas on the retention volumes and the chromatographic separation of the analytes. Thus, when ethanol is used as the carrier gas and alumina as the adsorbent, the retention volume of benzene constitutes one hundredth of its retention volume when the carrier gas is nitrogen while the adsorbent is the same. The retention of benzene on a column with Porapak Q changes by 60% when the N_2 carrier gas is replaced by CCl_4 vapour. Similar results have been obtained also for other chromatographic systems.

A dependence of the retention volumes of the sorbates on the eluting power of the mobile phase, which is 0.00 for n-hexane, 0.30 for n-butyl chloride, 0.58 for ethyl acetate, and 0.88 for ethanol, is observed in gas–solid chromatography employing VMP (in both liquid and thin-layer chromatography).⁴⁹ With decrease in the eluting power, the retention volumes increase appreciably (Fig. 6), but the general characteristics of the retention, known for the carrier gases employed traditionally, are retained. Thus the linear dependence of the logarithms of the retention volumes of the sorbates on their boiling points is observed for all the vapour systems investigated. Tsuda and Ishii⁴⁸ also noted a change in the elution order for a mixture of n-hexane, cyclohexane, and benzene (Fig. 6). When helium is used as the carrier gas, the compounds are eluted in order of increasing boiling point [n-hexane (69°C),

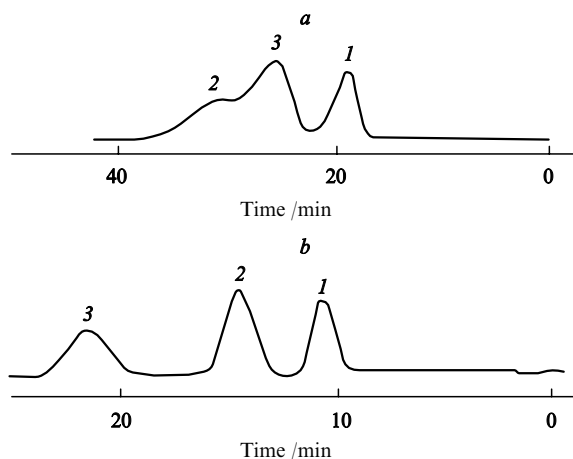


Figure 6. The change in the retention of C_6 hydrocarbons after the replacement of helium (a) by carbon tetrachloride vapour (b).⁴⁸ Experimental conditions: 1 m $\times$ 3 mm column, adsorbent — Porapak S (80–100 mesh). Sorbates: (1) n-hexane; (2) cyclohexane; (3) benzene.

benzene (80 °C), cyclohexane (81 °C)], while in the case where organic eluents are employed the elution order is determined by the polarisabilities of the chromatographed compounds and the retention time increases in the sequence n-hexane < cyclohexane < benzene.

Kyazimov and Agaeva⁵¹ investigated the retention of compounds of different classes (n-paraffins and aromatic hydrocarbons, n-alcohols, and ketones) on packed Chromaton-filled columns at different temperatures (75–250 °C) in a stream of hexane and ethanol vapours.

Multicomponent vapour-phase eluents are used in gas–solid chromatography and the components of such mixtures may be not only organic vapours but also permanent gases, steam, ammonia, *etc.* Such an approach makes it possible to regulate the selectivity

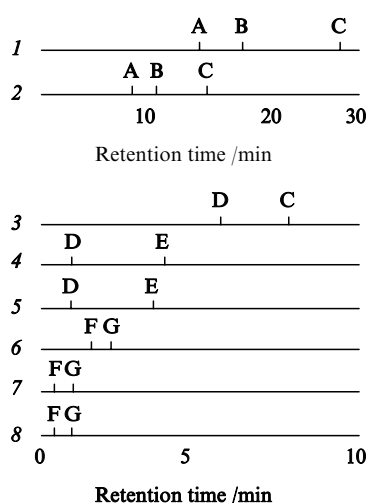


Figure 7. Chromatographic spectra indicating the influence of the nature of the mobile phase on the retention of sorbates.⁴⁹ Carrier vapour: (1) benzene; (2) ethanol containing 10% of benzene; (3) and (6) ethanol containing 1% of isooctane; (4) and (7) ethanol; (5) and (8) ethanol containing 1% of methanol; flow rate 200 μ l min⁻¹. Sorbates: A = phenol; B = *o*-cresol; C = *m*-cresol; D = *p*-diisopropylbenzene; E = admixture in component D; G = cumene; F = admixture in component G. Adsorbent: (1) and (2) silica gel K-923, 50 cm $\times$ 3 mm column, temperature 140 °C; (3)–(8) aluminium oxide, 1 m $\times$ 2 mm column, temperature 150 °C.

of the chromatographic system within very wide limits by varying the composition of the eluent and the concentration of the polar component. For example, in the analysis of a mixture of α - and β -naphthols on a silica gel column, the retention time of the naphthols increased by 5–8 min if a mixture of ethanol and water vapours⁴⁹ and not pure ethanol served as the eluent.⁴⁹ Similar effects were observed also when the vapours of mixtures of ethanol with methanol, isooctane, benzene,⁴⁹ and hexanes were employed.

The influence of the nature and composition of the eluent on the retention of the sorbate is illustrated in Fig. 7. Tsuda *et al.*⁴⁹ suggested that, when the carrier gas is adsorbed on the adsorbent surface, a thin layer of a modifying film is probably formed, which weakens the interaction of the analysed components and the adsorbent and hence accelerates their elution from the column. According to their data,⁴⁹ the thickness of the film is 2–10 molecules when ethanol is used as the carrier gas and alumina as the adsorbent at temperatures of 100–150 °C.

Steam as the mobile phase in gas–solid chromatography. Many investigators have paid particular attention to water as the mobile phase in gas–solid chromatography. Steam is capable of modifying the surfaces of solid adsorbents. As the mobile phase in gas–solid chromatography, water has the following advantages over other compounds: (1) it is a polar compound actively interacting (usually with formation of hydrogen bonds) with the polar groups, for example, the silanol groups, on the surfaces of solids; (2) the adsorbed water may interact with the polar components of the mixtures analysed, actively altering their retention; (3) water is a relatively stable compound and it can therefore be used for modification at high temperatures; (4) pure water is a comparatively cheap product; (5) water hardly gives rise to a signal when a flame-ionisation detector is used.

In the first communications concerning the employment of steam as the mobile phase⁶² and also in subsequent studies,^{35, 44, 54, 79} an advantage of the steam eluent, such as the blocking of the active centres on solid carriers and adsorbents promoting the appearance of symmetrical peaks in the separation of polar substances and the acceleration of analysis, was pointed out.

Sultanovich *et al.*⁸⁰ showed that, in the separation of high-boiling and polar compounds on Silochrom 80, the replacement of nitrogen as the carrier gas by steam lowers the retention times of the test components and leads to the formation of symmetrical peaks. The authors explained the influence of steam on chromatographic separation, firstly, by the blocking of individual active centres on the adsorbent surface by water molecules and, secondly, by the fact that the surface of Silochrom is covered by a thin water film, formed as a consequence of the multilayer adsorption of water and playing the role of a quasi-stationary phase. Since the usual vapour pressure of water under the conditions of the chromatographic experiment is many times greater than the partial pressure of water in the mobile phase, the thickness of the water film is extremely small and its properties differ from those of ordinary water at the temperature of the analysis. The nonideality of the gas phase can apparently also exert a small influence on the retention.

Thus steam improves the chromatographic properties of adsorbents (and in particular Silochrom) as well as the special (usually irreversible) methods for the modification of silica gels.

When any phenomenon is investigated, it is important to discover definite functional relations. It has been established⁸¹ that an increase in the steam content in the carrier gas leads to more complete deactivation of the active centres (Fig. 8). The logarithms of the retention factor decrease linearly under these conditions, which is naturally most notable in the separation of polar compounds (for example, acetone and ethyl methyl ketone). This feature is of definite interest for the development of analytical methods and their optimisation.

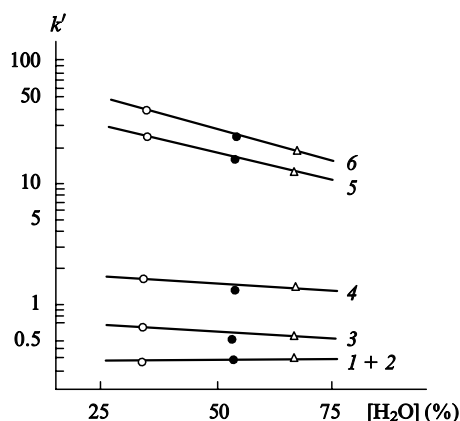


Figure 8. Dependence of the retention factors of sorbates on the content of water vapour in the carrier gas.⁸¹

Experimental conditions: 2 m × 4 mm column, adsorbent — Spherosil, 150–200 μm, column temperature 115 °C, carrier gas — nitrogen + water vapour, flow rate 50 cm³ min⁻¹. Sorbates: (1) 3-methylpentane; (2) cyclohexane; (3) n-heptane; (4) 1,2-dichloroethane; (5) acetone; (6) ethyl methyl ketone.

Rakhmankulov and Vigdergauz⁴³ investigated the possibility of modifying adsorbents by employing steam as the eluent in the pressure range from 1.6 to 7.2 atm in a chromatographic column filled with alumina (Table 6). In the case of nonpolar sorbates, a sharp decrease in the specific retention volume with increase in pressure was noted (by a factor of several tens for high-boiling paraffins). The authors explain this effect by the formation of an adsorbed water layer on the Al₂O₃ surface, although they do not rule out also the influence of the nonideality of the mobile phase. Unfortunately, no direct experiments permitting the characterisation of the state of water on the alumina surface were performed.

Table 6. The specific retention volumes (V_g^T /ml g⁻¹) of sorbates at different pressures of the eluent (steam).⁴³

Sorbate	Eluent pressure /atm			
	1.6	4.1	5.6	7.2
n-Octane	3.52	1.22	1.02	—
n-Nonane	6.3	2.28	1.54	—
n-Decane	11.48	3.82	2.31	1.54
n-Undecane	20.94	6.34	3.41	2.17
n-Dodecane	38.0	10.45	5.11	2.98
n-Tridecane	109.7	17.7	11.48	5.96
n-Pentadecane	187.7	45.06	16.86	8.43
n-Hexadecane	320.2	—	—	12.6
n-Heptadecane	545.0	—	—	17.6
n-Octadecane	926.8	—	—	24.4
n-Nonadecane	1575.0	—	—	32.8
n-Eicosane	2676.0	—	—	45.8
Isopropylbenzene	7.78	3.78	2.91	2.09
Acetone	3.72	3.78	3.76	3.02
Butyl acetate	35.76	20.56	11.86	7.78
Ethanol	10.6	6.91	6.3	—
Pyridine	14.26	10.82	10.19	8.00

It is of interest that the retention of polar sorbates soluble in water decreased less than that of nonpolar sorbates with increase in the water vapour pressure. A sharp decrease in the retention of n-alkanes leads to a significant increase in the Kovats indices (with n-alkanes as the standard) for polar compounds. For example, the retention index of pyridine at 7.2 atm is higher by 454 units than at

1.6 atm.⁴³ Such results indicate the possibility, in principle, of the group separation of nonpolar and polar compounds at an elevated vapour pressure.

In the separation of polar amines and organic acids, chromatographers encountered certain difficulties due to the reversible, semireversible, and irreversible adsorption of the compounds on the surface of the solid support (see, for example, Berezkin^{82,83}). Modification of the surface of the solid support by acid compounds (for the elution of acids) or basic compounds (for the elution of amines) usually permits a satisfactory solution of this problem.

We may note a non standard, in our view, solution of certain analytical problems in steam chromatography. Nonaka⁴⁴ suggested that an acid or basic modified surface be created by adding an acid (formic acid) or basic (hydrazine hydrate) reagent to the steam, which makes it possible to separate organic acids (with formic acid as the modifying agent) or amines (with hydrazine hydrate as the modifying agent).

Unusual results have been obtained on KY zeolites using a moist carrier gas.⁴² As noted above, the employment of a moist carrier gas is not recommended in gas chromatography. However, interesting results were obtained when the latter was employed. The water absorbed by the zeolite exerts a significant influence on its chromatographic properties (Fig. 9). At low temperatures, where much water is still adsorbed in the zeolite cavities, the specific retention volumes (V_d^T), for example, of ethane, decrease sharply and almost linearly with increase in the partial pressure of steam in the adsorbent–sorbate system. With increase in temperature against the background of an overall decrease in the retention volumes of the sorbates, a tendency towards a retardation of the decrease in V_d^T is manifested appreciably. At the minimum water vapour pressure (0.35 atm) and $T > 100$ °C, the opposite tendency towards an increase in the retention volumes of the chromatographed compounds is observed. An increase in the partial pressure of steam in the zeolite–sorbate system leads to a mutual approach, in terms of time, of the chromatographic zones of the eluted components owing to the intensifying shielding of the adsorption centres (in the first place cations) by water molecules and the duration of the chromatographic separation is also diminished. It is necessary to note that, when a moistened carrier gas is employed, the effectiveness of the separation of volatile compounds on zeolites increases appreciably. Thus the use of steam as the modifying agent for molecular sieves is, in our view, of interest and this version of chromatography can be easily realised in practice.

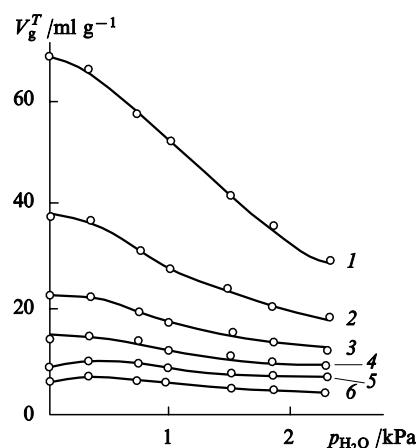


Figure 9. Dependence of the specific retention volume of ethane on the partial pressure of water vapour.⁴²
Experimental conditions: 1 m × 3 mm column, adsorbent — KY zeolite. Temperature (°C): (1) 60; (2) 80; (3) 100; (4) 120; (5) 140; (6) 160.

Modification of the adsorbent surfaces by water-soluble hydrophilic inorganic salts constitutes a possible new solution of the problem of creating selective polar sorbents for steam chromatography. Only the steam version gas–liquid chromatography has been realised at the present time.^{84–86} A new class of stationary liquid phases (aqueous salt solutions), which we have proposed, is autostable under the conditions of steam chromatography. On contact with steam over a wide range of temperatures, many salts form aqueous solutions which are characterised by a very high selectivity.^{84–86} This principle can undoubtedly serve as the basis of the modification of the surface of the adsorbent: if a salt is deposited on its surface at very low concentrations ($\sim 0.1\%$ – 0.01%), then aqueous salt phases are formed under the conditions of steam chromatography.

In conclusion, we may note that the use of steam significantly expands the possibilities of the traditional gas chromatography and in many instances permits an appreciable improvement of the separation process. It is noteworthy that the characteristics of steam chromatography (with steam or the vapours of other organic compounds) and liquid chromatography are similar. The introduction to the gas-chromatographic practice of its steam version will undoubtedly make it possible to simplify the solution of many practical problems.

IV. Capillary gas–solid chromatography

Capillary gas chromatography is nowadays most actively employed. Thus, according to Berezkin's data,^{87,88} more than 83% of the publications devoted to chromatographic problems relate to capillary gas chromatography; according to McNair's data,⁸⁹ 80% of the gas-chromatographic columns sold are capillary columns. A new type of capillary column — open (tubular) capillary gas–solid columns — has been successfully introduced into analytical practice. The characteristics influencing the changes in the retention of chromatographed compounds, for example characteristics such as the nature and pressure of the carrier gas, assume a particular importance in capillary chromatography. (The influence of these characteristics on the resolution had been established earlier for packed columns.)

A series of publications have been devoted to the theoretical and experimental study of the role of the carrier gas in capillary gas–liquid chromatography.^{90–94} The influence of the average column pressure of the carrier gas in the column on the retention volumes and indices at an inlet pressure > 5 atm at the inlet to the capillary column has been demonstrated experimentally.^{90–92} This is significantly greater than the pressure of the carrier gas in the traditional analytical experiment. The importance and value of the results obtained for the usual routine chromatographic analysis therefore remained obscure.

Berezkin and Korolev^{93,94} were the first to show that the relative retention data (retention factor, relative retention, and retention index) in capillary gas–liquid chromatography depend on the nature of the carrier gas and its average column pressure under the conditions of the traditional analytical experiment, *i.e.* at inlet pressures less than 3–5 atm.

Bearing in mind the common nature of the processes in gas–liquid and gas–solid chromatography, one may expect a dependence of the retention on the pressure and nature of the carrier gas for both types of chromatography.

Berezkin and Volkov²⁰ confirmed a previously established feature of chromatography in a gas–solid system, namely the relation between the retention and the nature of the carrier gas. It was shown that transition from light carrier gases to heavy ones leads to a dynamic modification of the adsorbent surface by the carrier gas molecules and hence to a decrease in the partition coefficients of the chromatographed compounds in the solid adsorbent–carrier gas system and therefore to a decrease in the retention time. The experimental data obtained on a Chrompack capillary gas–solid column (50 m $\times$ 0.32 mm) with alumina at 100 °C may serve as an example illustrating the dependence of the

retention factors of hydrocarbon gases on the nature of the carrier gas:²⁰ the retention for C₃–C₄ hydrocarbon gases are virtually the same when helium and nitrogen are used as carrier gases but decrease significantly when they are replaced by carbon dioxide. For example, the retention factors diminished by $\sim 30\%$ following the replacement of nitrogen by carbon dioxide.¹⁷ Thus, by selecting the carrier gas, it is possible to reduce significantly the duration of the chromatographic experiment.

Two studies by Berezkin and coworkers^{95,96} were devoted to the systematic investigation of the influence of the average column pressure of the carrier gas in the column on the relative retention of the chromatographed compounds in high-performance capillary chromatography in a gas–solid system. Different carrier gases and pressure ranges traditionally employed in analytical capillary gas chromatography (1–5 atm at the inlet to the capillary column) were used. The results of the study of the dependence of the retention factors of hydrocarbon gases on a capillary column with alumina modified by potassium chloride on the average column carrier gas pressure in the column are presented in Table 7.⁹⁶ It is seen that the retention depends both on the nature of the carrier gas and on its column pressure.

Table 7. The retention factors of hydrocarbon gases at different carrier gas pressures in a capillary column with Al₂O₃/KCl (temperature 90 °C).⁹⁶

<i>P</i> /atm	Propene	Butane	But-1-ene
Carrier gas — helium			
1.0	0.88	1.68	3.66
4.1	0.88	1.69	3.63
Carrier gas — hydrogen			
1.0	0.80	1.51	3.27
3.4	0.81	1.53	3.22
Carrier gas — nitrogen			
1.0	0.87	1.65	3.61
4.1	0.85	1.59	3.45
Carrier gas — carbon dioxide			
1.0	0.64	1.17	2.46
4.1	0.44	0.80	1.58

The influence of steam as the modifier of the Al₂O₃ adsorbent surface on the change in retention in capillary gas–solid chromatography has been noted by de Nijs.⁹⁷ Water is strongly adsorbed on the hydrophilic surface of the polar alumina, which lowers its sorption activity. With increase in the concentration of water in the carrier gas (and hence on the adsorbent surface), the retention factors of the sorbates are therefore reduced.

Not only the nature of the carrier gas but also the characteristics of the chromatographic system as a whole exert a significant influence on the retention of the sorbate. In this connection, one should note the study of Armstrong *et al.*,⁹⁸ who investigated the influence of steam and carbon dioxide on the characteristics of two capillary adsorption columns, in one of which alumina and in the other GasProTM were employed as the adsorbents. Water and carbon dioxide are known to influence strongly the retention and selectivity in the separation of sorbates and also the effectiveness of the operation of the chromatographic column, for example, an alumina column.^{30,99–101} In contrast to columns based on alumina, neither water, nor carbon dioxide nor sulfur-containing gases are adsorbed appreciably on the surface of capillary columns with GasProTM and they do not therefore influence the separation of the analytes and the column characteristics.⁹⁸ Figure 10 presents the results of the study of the influence of the repeated introduction of water samples and aqueous acetone samples on the retention of the analytes. Evidently even repeated introduction of water samples does not affect the column characteristics, the retention, and the separation of the analytes. The retention of the chromatographed compounds hardly depends on the water vapour pressure on the nonpolar adsorbent GasProTM and this

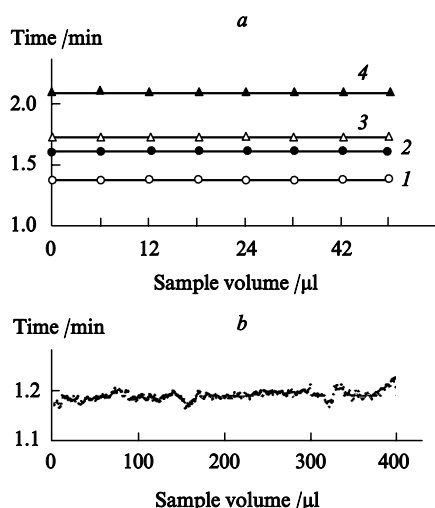


Figure 10. The influence of repeated introduction of samples of water (a) and an aqueous sample of acetone (b) on the retention times of the compounds analysed on a GasPro™ capillary column.⁹⁸ Experimental conditions: (a) 30 m × 0.32 mm column, carrier gas — nitrogen (40 cm s⁻¹), temperature 85 °C; (b) 5 m × 0.32 mm column, carrier gas — helium. Sorbates: (1) methane; (2) ethane; (3) ethene; (4) ethyne.

enabled the authors of the present review to express the view that the principal processes in the carrier gas–chromatographed compound interaction occur on the surface of the solid adsorbent and that the influence of these interactions in the gas phase is slight for the systems investigated.

Many gases and volatile compounds are retained fairly strongly on GasPro™ columns, but in relation to organic compounds of various classes these columns are more inert than those with alumina. Consequently, the compounds analysed, which undergo catalytic degradation on Al₂O₃ at elevated temperatures, may be readily separated and determined quantitatively on GasPro™ columns.

Thus the nature of the carrier gas and its pressure are important characteristics of the chromatographic experiment. The study of the characteristic features of the variation of the retention factors (capacity factors) of the chromatographed compounds on passing from one carrier gas (G₁) to another (G₂) on the same chromatographic column is of practical interest in this connection. The following correlation has been established recently (Fig. 11):¹⁰¹

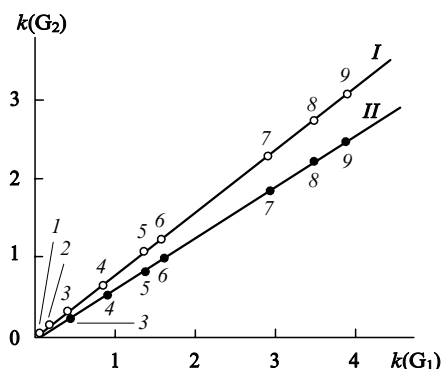


Figure 11. Correlation between the retention factors using the carrier gases G₁ = H₂, G₂ = N₂ (I) or CO₂ (II).¹⁰¹ Experimental conditions: 50 m × 0.32 mm column, adsorbent — Al₂O₃/KCl, T = 90 °C. Chromatographed compounds: (1) ethane; (2) ethene; (3) propane; (4) propene; (5) isobutane; (6) n-butane; (7) *trans*-but-2-ene; (8) isobutene; (9) *cis*-but-2-ene.

$$k(G_2) = Ak(G_1) + B, \quad (6)$$

where $k(G_1)$ and $k(G_2)$ are the retention factors (capacity coefficients) of the compound when the carrier gases G₁ and G₂ respectively are employed and A and B are constants.

Experimental studies performed using various chromatographic systems revealed the following features of the influence of different carrier gases on the retention.

1. Permanent carrier gases (helium, hydrogen, argon, nitrogen, *etc.*), as well as carbon dioxide exert an appreciable influence on the retention of the chromatographed compounds. The influence of such carrier gases on the retention usually increases in the sequence helium < hydrogen < nitrogen < carbon dioxide. The relations established may be used to reduce (by 20%–30%) the retention, *i.e.* to reduce the duration of the chromatographic process, and for the deliberate alteration of the selectivity of the separation.

2. Steam as well as the vapours of organic compounds (carbon tetrachloride, ethanol, *etc.*) influence to a greater extent the retention process than gaseous eluents. The change in retention is especially significant when 'strong' adsorbents are employed (for example, adsorbents of the type of molecular sieves, organic polymeric adsorbents, *etc.*). A change in the elution sequence of the analytes after the replacement of the mobile phase has been noted for a series of chromatographic systems investigated.

3. On passing from one carrier gas to another, it is possible to determine the retention of the chromatographed compounds for 'another' carrier gas using the linear correlation equation.

The studies of the influence of the carrier gas on retention cannot be regarded as complete. By no means all the new analytical possibilities of gas–solid chromatography, determined by the rational selection of the active mobile phase, have been discussed and examined in the literature. Thus the influence of superheavy carrier gases (for example, SF₆) using specific adsorbents such as molecular sieves, *etc.* has not been investigated systematically.

The expansion of steam chromatography is held back, in our view, by the lack of simple and effective apparatus permitting the performance of the steam chromatographic process on any gas chromatograph.

V. Theoretical aspects of the influence of the nature of the carrier gas and of its pressure on the retention in gas–solid chromatography

1. The retention of a strongly adsorbed sorbate in a poorly adsorbed carrier gas

The mechanism of retention has been discussed in detail in monographs.^{1, 2, 6, 71, 102, 103} Kiselev *et al.*^{6, 103} proposed the concept of the net retention volume for gas–solid chromatography and showed that the net retention volume V_N is directly proportional, firstly, to the surface area of the adsorbent (S) in the column (it is postulated that the accessibility of the adsorbent surface does not change for low degrees of coverage of the latter) and, secondly, to the partition coefficient [see Eqn (3)].

The net retention volume can be determined from the equation

$$V_{Ni} = V_{Ri} - V_M, \quad (7)$$

where

$$V_{Ri} = t_R F j,$$

$$V_M = t_M F j, \quad (8)$$

t_R is the retention time of the sorbate, F the flow rate of the carrier gas at the column outlet, j the James–Martin correction taking into account the pressure drop along the column, V_M is the dead retention volume, and t_M is the dead time.

Naturally Eqn (7) should be modified in relation to specific cases (for example, when it is necessary to take into account the

nonideality of the carrier gas, the nonlinearity of the adsorption isotherm for the chromatographed compound, *etc.*).

In the monograph by Zhukhovitskii and Turkel'taub,⁴ attention is drawn to the fact that in gas–solid chromatography account should be taken primarily of the influence of the carrier gas on the sorbability of the components of the mixture being separated (Table 8). In discussing the results of a study of the retention of the components of four mixtures (propane–butane, helium–methane, carbon monoxide–methane, helium–carbon monoxide) on the AG-2 charcoal using three carrier gases (hydrogen, air, and carbon dioxide) at 25 °C, the authors note that the retention volume of a poorly sorbable substance diminishes sharply when hydrogen is replaced by carbon dioxide.

Table 8. The influence of the nature of the carrier gas on the separation of mixtures using the AG-2 charcoal as the adsorbent (temperature 25 °C).⁴

Carrier gas	Mixture	V_N /ml
Carbon dioxide	propane + butane	25 + 247
Air	ditto	99 + 305
Hydrogen	"	255 + 630
Carbon dioxide	helium + methane	10 + 1739
Air	ditto	151 + 3744
Hydrogen	"	237 + 464
Carbon dioxide	helium + carbon monoxide	10 + 682
Air	ditto	151 + 1235
Hydrogen	"	237 + 1540

At the time of the publication by the monograph of Zhukhovitskii and Turkel'taub,⁴ there was no unambiguous answer in the literature to the question of the dependence of the retention volume on the carrier gas pressure. This is associated, in particular, with the low accuracy of the chromatographic measurements in the initial period of the development of gas–solid chromatography and the limited choice of carrier gases. The introduction into chromatographic practice of capillary columns, characterised by an increased resolution compared with packed columns, made it possible to establish a clear dependence of the relative retention on the carrier gas pressure even in the region of low pressures.

In conclusion, we may note that the development of the theory of retention in gas–liquid chromatography has had a positive influence on the development of gas–solid chromatography. The influence of the interaction of the sorbate with the carrier gas in the gas phase on the retention was demonstrated within the framework of this theory (see the relevant monographs^{77, 104, 105}). The study of the interactions of the chromatographed compound in both gas and stationary (adsorbent) phases became a logical extension of the development of the theory of retention in gas chromatography.

2. The retention of the sorbate taking into account the interactions in the gas and solid phases

The theoretical aspects of the influence of the nature and pressure of the carrier gas on the net retention volume or the partition coefficient in gas–liquid chromatography have been examined in a series of investigations (see, for example, Refs 106–112). It has been shown that the influence of the carrier gas on the retention is determined by the interaction of the molecules of both the sorbate and the carrier gas in the gas phase, on the one hand, and of the carrier gas and sorbate dissolved in the stationary phase, on the other, as well as the change in the properties of the stationary liquid phase when the carrier gas is dissolved in it.

The effects of the carrier gas on the adsorption of the chromatographed compound, and not its interactions with the sorbate in the gas phase, apparently exert the greatest influence on the separation process in gas–solid chromatography. In this

connection, one should note the study by Sato *et al.*,¹⁷ in which the influence of the carrier gas on the absolute retention is considered (within the framework of the Langmuir adsorption theory) as a result of its adsorption. Despite the fact that the results of this approach make it possible to establish the causes of the experimentally observed decrease in the retention volume as a function of the carrier gas, a fully adequate explanation of all the principal features has not been given.

This problem was examined in adequate detail in relation to gas adsorption chromatography for the first time by Locke.¹¹³ For certain chromatographic systems, differing in the type of adsorption isotherm and in the nature of the carrier gas, he proposed a series of equations relating the partition coefficient to pressure and taking into account the nonideality of the carrier gas. As in gas–liquid chromatography (see, for example, Desty *et al.*¹⁰⁷), the partition coefficient in these equations depends on the average column pressure and diminishes with increase in the pressure of the nonideal carrier gas.

Despite the correct and prior formulation of this important problem, the expressions obtained by Locke contained a series of inaccuracies. One of them was noted by Young,¹¹⁴ whilst the remaining ones were discussed by Gzubrut *et al.*¹³

The interphase partition coefficient is defined by the following expression according to Locke¹¹³

$$K = \frac{N_a V_m}{N_m S}, \quad (9)$$

where N_a and N_m are the numbers of moles of the sorbate adsorbed on the adsorbent surface and in the gas (mobile) phase respectively, V_m is the volume of the mobile phase in the column, and S is the surface area of the adsorbent.

According to Locke,¹¹³ the following expression can be written for N_a :

$$N_a = k S f, \quad (10)$$

where k is the adsorption constant and f the fugacity of the sorbate.

The following relation holds for the fugacity:

$$\ln f = \ln P_s + \frac{P_m}{RT} [B_{22} - (1 - y)^2 (B_{11} - 2B_{12} + B_{22})], \quad (11)$$

where P_s is the partial pressure of the sorbate, P_m is the average pressure of the carrier gas, y is the mole fraction of the sorbate in the carrier gas, B_{11} and B_{22} are the second virial coefficients of the pure sorbate and the carrier gas respectively, and B_{12} is the second virial coefficient reflecting the interaction between the molecules of the sorbate and the carrier gas.

Using the same approach and the same assumptions as Locke¹¹³ (namely that the sample size is small and that the adsorption isotherms of the sorbates are therefore linear), Gzubrut *et al.*¹³ established the following expression for the partition coefficient taking into account both the influence of the nonideality of the carrier gas in the gas phase and its adsorption on the adsorbent surface:

$$\ln K = \ln K_0 + \frac{(2B_{12} - V_0)}{RT} P_m, \quad (12)$$

where

$$K_0 = K(P \rightarrow 0), \quad (13)$$

V_0 is the molar volume of the pure sorbate,

$$P_m = P_0 J_3^4, \quad (14)$$

$$J_3^4 = \frac{3}{4} \frac{(P_i/P_0)^4 - 1}{(P_i/P_0)^3 - 1}, \quad (15)$$

and P_i and P_0 are the inlet and outlet pressures of the carrier gas, respectively.

Using the equations presented above, Gzbrut *et al.*¹³ explained the experimental data on the retention of methane obtained on a packed column with Porapak S at 0 °C, using He, Ar, and CO₂ as the carrier gases. It was found that in all cases the influence of the nonideality of the carrier gas on the net retention volume is very much smaller than the influence of the adsorption of the carrier gas. The relative degree of adsorption of the carrier gas increases in the sequence He < Ar < CO₂.

The equations for the retention volume or the retention time taking into account the nonlinearity of the adsorption isotherm have been obtained by numerous investigators. The most general equations, taking into account the deviation of the adsorption isotherm of the sorbate from linearity owing to the intermolecular sorbate–sorbate and sorbate–carrier gas interactions in the gas phase, have been proposed by Valentin and Guiochon:¹¹⁵

$$n_1^g = f \frac{yV_m}{RT}, \quad (16)$$

$$f = P \left(1 - \frac{BP_s}{RT} \right), \quad (17)$$

$$B = B_{11}y^2 + 2B_{12}y(1-y) + B_{22}(1-y)^2, \quad (18)$$

where n_1^g is the number of moles of the adsorbate in the gas phase, y is the mole fraction of the sorbate in the gas phase, V_m is the volume of the gas phase in the column, B is the second virial coefficient of the gas mixture (the carrier gas sorbate), B_{11} and B_{12} are the second virial coefficients of the pure sorbate (1) and the carrier gas (2) respectively, B_{12} is the second virial coefficient characterising the interactions of the sorbate and the carrier gas.

The influence of the nonideality of the mobile phase and of its adsorption on the adsorbent in gas–solid chromatography was taken into account by Martire¹¹⁶ in the equation relating the true specific retention volume $V_{g,0}^T$, which would be observed for an ideal unretained gas or for the ‘zero’ gas pressure, to the measured specific retention volume:

$$\log V_{g,0}^T = \log V_{g,0}^T + \frac{2B_{12}P_m}{RT} \left(1 - \frac{\phi}{y} \right), \quad (19)$$

where B_{12} is the second mixed virial coefficient of the sorbate and the carrier gas, while ϕ and y are the fractions of the sorbate in the adsorbed monolayer and in the gas phase respectively at equilibrium; the equation was obtained on the assumption that a uniform adsorbent is employed.

The ratio ϕ/y is called the retention factor for the given carrier gas. In the derivation of Eqn (19), it was assumed that this coefficient is small and Henry’s law therefore still holds for the carrier gas in the range of pressures employed and that P_m is relatively small, the degree of adsorption of the carrier gas therefore remaining negligible.

Poshkus¹¹ obtained the virial equation for the retention volume taking into account the influence of the pair interactions of the sorbate and carrier gas molecules both in the gas phase ($A_g \dots B_g$) and in the adsorbed state ($A_{ads} \dots B_{ads}$) and also the sorbate–sorbate interactions ($A_{ads} \dots A_{ads}$):

$$V_N(\hat{a}_1) = K_{1,1} + 2(K_{2,11} + 2K_{1,1}B_{11})\hat{a}_1 + K_{2,12} + 2K_{1,1}B_{12}[(\hat{a}_2 - \hat{a}_1) - 2(B_{12} - B_{22})\hat{a}_1\hat{a}_2], \quad (20)$$

where $K_{1,1}$ is Henry’s constant for the sorbate, $K_{2,11}$ and $K_{2,12}$ are the second virial adsorption coefficients taking into account the pair interactions between the adsorbed adsorbate molecules ($A_{ads} \dots A_{ads}$) and between the adsorbed sorbate and carrier gas molecules ($A_{ads} \dots B_{ads}$) respectively B_{11} and B_{22} are the second virial coefficients for the pure sorbate and the pure carrier gas respectively, c_1 and c_2 are the concentrations of the sorbate (1) and the carrier gas (2) respectively, and B_{12} is the second virial coefficient characterising the intermolecular sorbate–carrier gas interactions.

According to Poshkus’s data,¹¹ the relative difference between the quantities V_N and $K_{1,1}$, caused by the influence on V_N by the interactions of the adsorbate and carrier gas molecules, is expressed by the equation

$$\frac{V_N - K_{1,1}}{K_{1,1}} = \left(\frac{K_{2,12}}{K_{1,1}} + 2B_{12} \right) \frac{P_m}{RT}. \quad (21)$$

For a series of sorbate (argon, benzene, cyclohexane)–carrier gas (He, H₂, N₂, Ar)–adsorbent (graphitised thermal black) systems, the contributions of the pair interactions to the retention volume of the sorbate have been estimated theoretically. In the range of temperatures at which the $K_{1,1}$ were determined using He as the carrier gas, the sorbate–carrier gas interactions increase V_N by tenths per cent mainly due to the intermolecular interactions in the gas phase. When other carrier gases are employed (H₂, N₂, Ar), the $A_g \dots B_g$ as well as the $A_{ads} \dots B_{ads}$ intermolecular interactions diminish the true retention volume, the contributions of both interactions being close as regards order of magnitude. At $P = 101$ kPa, the overall influence of the above interactions on V_N may reach several per cent.

Rudzinski¹¹⁷ described in detail and rigorously the dependence of the retention volume on the nonideal interactions of the sorbate in the gas and solid phases.

In all the studies examined above, the specific retention volume was used as the retention parameter. However, for the calculation of this quantity, it is essential to know the amount of the adsorbent in the column, the exact determination of which involves certain difficulties, especially in capillary columns. Furthermore, the specific retention volume is an absolute quantity and in gas chromatography the determination of absolute quantities involves significantly greater errors than the determination of relative retention data. It therefore appeared useful to obtain the corresponding equations for the relative retention data (the retention factor, the relative retention time, the retention index), reflecting their dependence on the pressure (and nature) of the carrier gas.

We employed a new version of the Langmuir equation⁹⁵ based on the allowance for the substitution of the adsorbed carrier gas molecules by sorbate molecules:

$$a_i = \frac{l_i a_{mi} K_i P_i}{1 + K_i l_i P_i + K_{imi} l_m P_m}, \quad (22a)$$

$$a_i = \frac{a_{mi} K_i c_i}{1 + K_i c_i + K_{imi} l_m P_m}, \quad (22b)$$

$$a_i = \frac{a_{mi} b_i P_i}{1 + b_i P_i + b_{mi} P_m}, \quad (22c)$$

where a_i is the surface concentration of the adsorbed compound i , l_i and l_m are constant conversion coefficients for compounds i and m respectively, P_i and c_i are respectively the partial pressure and the concentration of compound i in the mixture with the carrier gas, $K_{imi} = K_i/K_{im}$, K_{im} is the equilibrium constant of the reversible process involving the substitution of the adsorbed compound m by compound i , P_m is the average column pressure of the carrier gas, $c_i = l_i P_i$, $c_m = l_m P_m$, a_{ami} is the capacity of the monolayer for compound i , K_i is the equilibrium constant of the reversible adsorption process involving compound i in the gas–adsorbent system, $b_i = l_i K_i$, and $b_{mi} = l_m K_{imi}$.

The main difference in the treatment of the above equations and the classical equation of the Langmuir adsorption isotherm for a mixture of substances¹¹⁸ consists in the fact that the adsorption coefficient at P_m is determined by the properties of both the carrier gas and the chromatographed compound, which is a consequence of the allowance for the substitution reaction.

The rate of migration of the chromatographic zone w_i for compound i in a chromatographic column filled with the adsorbent may be described by the equation^{119–121}

$$w_i = u \left[1 + \frac{V_s}{V_m} \left(\frac{\partial a_i}{\partial c_i} \right)_{P_m} \right]^{-1}, \quad (23)$$

where u is the linear velocity of the carrier gas in the column, V_s and V_m are the volumes of the solid (adsorbent) and gas phases in the column respectively, a_i is the concentration of the volatile chromatographed compound i in the adsorbent, and c_i is the concentration of the sorbate i in the gas phase.

The equation for the retention time t_i of the chromatographed compound follows from Eqn (23):

$$t_i = \frac{L}{w_i} = \frac{L}{u} \left[1 + \frac{V_s}{V_m} \left(\frac{\partial a_i}{\partial c_i} \right)_{P_m} \right] = t_M \left[1 + \frac{V_s}{V_m} \left(\frac{\partial a_i}{\partial c_i} \right)_{P_m} \right], \quad (24)$$

where L is the column length (the carrier gas pressure drop along the column is not taken into account) and $t_M = L/u$ is the dead time of the column (the retention time of the unretained component).

Having transformed Eqn (24), it is possible to obtain the following simple expression for the retention factor k_i for compound i :

$$k_i(C_i, P_m) = \frac{t_i - t_M}{t_M} = \frac{V_s}{V_m} \left(\frac{\partial a_i}{\partial c_i} \right)_{P_m}. \quad (25)$$

For the special case where the adsorption isotherm is linear ($a_i = K_i c_i$), the following familiar expression for the retention factor is obtained from Eqn (25):⁶⁵

$$k_i = K_i \left(\frac{1}{\beta} \right), \quad (26)$$

where K_i is the distribution constant of the chromatographed compound i between the stationary and mobile phases and $\beta = V_m/V_s$ is the phase ratio in the column.

In the general case, the retention factor can also be represented by the equation⁶⁵

$$k_i = \frac{V_{Ri}(c_i, P_m) - V_M}{V_M}, \quad (27)$$

where V_{Ri} is the retention volume of compound i .

On combining Eqns (25) and (27), we obtain

$$\left(\frac{\partial a_i}{\partial c_i} \right)_{P_m} = \frac{V_{Ri}(c_i, P_m) - V_M}{V_s} = V_V(c_i, P_m), \quad (28a)$$

where V_V is the volume of the sorbent.

If a_i is expressed in units of the surface concentration, then

$$\left(\frac{\partial a_i}{\partial c_i} \right)_{P_m} = \frac{V_{Ri}(c_i, P_m) - V_M}{S} = V_s(c_i, P_m). \quad (28b)$$

Thus the derivative of the adsorption isotherm represents the specific retention volume calculated per unit volume of the sorbent V_V or per unit surface of the adsorbent V_s . We may note that previously (see, for example, Ref. 83), the quantity $\partial a_i / \partial c_i$ was designated in our communications as the effective distribution constant, because $\partial a_i / \partial c_i = K_{i, \text{eff}}$ for a linear isotherm.

In order to obtain the analytical dependence of the retention factor on the carrier gas pressure P_m , we make use of Eqn (25), whilst Eqns (22b) and (22c) are adopted as the expressions for the adsorption isotherm. After simple transformations, we obtain

$$k_i = g_i \frac{(1 + b_{mi} P_m)}{(1 + b_i P_i + b_{mi} P_m)^2}, \quad (29)$$

where $g_i = a_{mi} b_i / \beta l_i$.

Since the adsorption of the traditionally employed carrier gases on the adsorbent is usually extremely slight (*i.e.* $b_{mi} P_m \ll 1$), Eqn (29) can be usefully expanded in Maclaurin's series in $b_{mi} P_m$. We restrict the expansion to the first two terms of this series:

$$k_i \approx k_{i0} - k_{i0} \frac{b_{mi}(1 - b_i P_i)}{(1 + b_i P_i)} P_m = k_{i0} \left[1 - \frac{b_{mi}(1 - b_i P_i)}{1 + b_i P_i} P_m \right], \quad (30)$$

$$k_{i0} = k_i(\text{at } P_m = 0) = \frac{g_i}{(1 + b_i P_i)^2}. \quad (31)$$

We may note that, according to d'Alembert's criterion,¹²² the above Maclaurin's series is convergent if $b_i P_i < 1$. According to our estimate, this condition holds for the sorption of hydrocarbon gases on Al_2O_3 in the range of carrier gas pressures up to 10 atm (*i.e.* in the range of pressures traditionally employed in gas chromatography).

As a result of the expansion in Maclaurin's series, the fraction $(1 - b_i P_i)/(1 + b_i P_i)$ can be expressed approximately as follows:

$$\frac{1 - b_i P_i}{1 + b_i P_i} \approx 1 - 2b_i P_i, \quad (32)$$

so that

$$k_i \approx k_{i0} - k_{i0} b_{mi} (1 - 2b_i P_i) P_m. \quad (33)$$

If $b_i P_i \ll 1$, then Eqn (33) can be represented also in a simpler form:

$$k_i \approx k_{i0} - k_{i0} b_{mi} P_m. \quad (34)$$

Thus the retention factor in gas–solid chromatography is a linear function of the average carrier gas pressure P_m . We may also note that, with increase in carrier gas pressure, we have, firstly, a decrease in the retention factor k_i and, secondly, the first term of Eqn (34) then represents the retention factor of the chromatographed compound at the 'zero' pressure of the carrier gas, *i.e.* precisely the quantity which could be considered as the chromatographic constant of the sorbate.

Table 9. Parameters of Eqn (34) for the following experimental conditions: 50 m $\times$ 0.32 mm quartz capillary column, $\text{Al}_2\text{O}_3/\text{KCl}$ adsorbent, temperature 90 °C, carrier gases — N_2 and CO_2 , inlet pressure at the inlet to the capillary column 1–5 atm.⁹⁵

Sorbate	k_{i0}		$k_{i0} b_{mi}$		Correlation coefficient		Standard deviation	
	N_2	CO_2	N_2	CO_2	N_2	CO_2	N_2	CO_2
Propane	0.887	0.699	0.008	0.062	0.937	0.993	0.005	0.011
Butane	1.703	1.278	0.025	0.117	0.937	0.998	0.014	0.008
But-1-ene	3.708	2.719	0.057	0.286	0.961	0.996	0.024	0.035

In order to check the equation obtained, we used the experimental data for the dependence of the retention factors of hydrocarbon gases on the average pressures of various carrier gases in capillary columns with alumina (Table 9). It follows from the data presented in the table that the $k_i = f_i(P_m)$ relations are linear and are characterised by a negative slope, *i.e.* the linear equation (34) agrees well with the experimental data (the correlation coefficient is > 0.9 in all the cases considered).

A similar approach has been used to obtain the dependence of the relative retention time and the retention index on the carrier gas pressure.

We shall examine the dependence of the relative retention times for two carrier compounds i and j on the average carrier gas pressure P_m :

$$a_{ij} = \frac{k_i}{k_j} = \frac{k_{i0}}{k_{j0}} \left(1 - \frac{b_{mi}(1 - b_i P_i)}{1 + b_i P_i} P_m \right) / \left(1 - \frac{b_{mj}(1 - b_j P_j)}{1 + b_j P_j} P_m \right). \quad (35)$$

Having expanded Eqn (35) in Maclaurin's series in P_m and having restricted the expansion to the first two members of the series, we obtain

$$\alpha_{ij} \approx \alpha_{ij0} + \alpha_{ij0}(b_{mj}\lambda_j - b_{mi}\lambda_i)P_m, \quad (36)$$

where $\alpha_{ij0} = k_{i0}k_{j0}$ is the limiting relative retention at $P_m \rightarrow 0$, $\lambda_i = (1 - b_iP_i)/(1 + b_iP_i)$, and $\lambda_j = (1 - b_jP_j)/(1 + b_jP_j)$.

Since usually $b_iP_i \ll 1$ and $b_jP_j \ll 1$, it follows that λ_i and λ_j are close to unity, so that

$$\alpha_{ij} \approx \alpha_{ij0} + \alpha_{ij0}(b_{mj} - b_{mi})P_m. \quad (37)$$

Thus the relative retention in the region of low carrier gas pressures also depends linearly on the carrier gas pressure. For example, for open capillary columns with the Al_2O_3 as an adsorbent (with KCl as the modifying agent), the experimental dependence of the relative retention for but-1-ene (with propene as the standard) on the average carrier gas pressure P_m is described by a linear equation of type (37). The correlation coefficient in the description of experimental data by Eqn (37) is 0.93 and the standard deviation is 0.092.

Since the retention index is also used in gas-solid chromatography,² we present an expression for the linear dependence of this quantity on the average column gas pressure of the carrier gas in the chromatographic column:

$$I_i = I_{0i} + b_{li}P_m, \quad (38)$$

where I_{0i} is the limiting value of the retention index i as P_m approaches to zero,

$$I_{0i} = 100n + 100 \frac{\log \alpha_{in0}}{\log \alpha_{(n+1)n0}}, \quad (39)$$

where b_{li} is a coefficient:

$$b_{li} = \frac{43.43}{[\log \alpha_{(n+1)n0}]^2} [(b_{mn} - b_{mi}) \log \alpha_{(n+1)n0} - (b_{mn} - b_{m(n+1)}) \log \alpha_{in0}], \quad (40)$$

Here α_{in0} is the limiting retention of compound i relative to the standard, the molecule of which contains n carbon atoms and $\alpha_{(n+1)n0}$ are the limiting retentions of standards (for example, n -alkanes the molecules of which contain $n+1$ and n carbon atoms).

The approach developed by Berezkin and Malyukova⁹⁵ made it possible to develop new ideas concerning the influence of the carrier gas on the relative retentions in gas-solid chromatography. The linear dependences of the relative retention on the average column pressure of the carrier gas agree satisfactorily with experimental data. The general relations established in the above study⁹⁵ can be usefully taken into account in precise analytical and physicochemical studies.

VI. The influence of the carrier gas on band broadening in gas-solid chromatography

The broadening of chromatographic bands during their migration along the column is influenced by the nature of the movement of the carrier gas in the column, the diffusion of the compounds being separated in the mobile and stationary phases, the rate of interphase mass transfer, and the characteristics of the adsorption layer employed.^{6, 71, 107, 123–150} The theory of the broadening of chromatographic bands has been examined in detail in monographs^{2, 65, 71} and other communications.^{20, 125–127, 131–134} For this reason, the authors of this review have written this section in a compact form.

The main contribution to the development of the theory of band broadening in chromatographic columns has been made by Van Deemter,¹³⁵ Golay,^{125–127, 132} and Giddings,^{133, 134} the

results of the theoretical researches of which have been applied successfully in chromatography.

1. Packed columns

Van Deemter's equation is most widely used in chromatography on packed columns.¹³⁵ For gas-solid chromatography, it can be represented in the form of the dependence of the height equivalent to the theoretical plate (H) on the carrier gas flow rate (u):

$$H = A + \frac{B}{u} + C_s u, \quad (41)$$

$$A = 2\lambda d_p, \quad (42)$$

$$B = 2\gamma D_g, \quad (43)$$

$$C_s = C \frac{k}{(1+k)^2} \frac{d_p}{D_s}, \quad (44)$$

where λ is a dimensionless coefficient characterising the nonuniformity of the column packing, d_p the diameter of the particles of the packing, γ is the tortuosity coefficient, D_g is the diffusion coefficient of the sorbate in the gas phase, k is the retention factor, D_s is the diffusion coefficient of the sorbate in the stationary phase, and C is a constant coefficient.

We shall examine the physical meaning of the individual terms of Van Deemter's equation.

The term A takes into account eddy diffusion. Eddy diffusion as a spreading factor in packed columns is due to the multiplicity of the paths followed by the carrier gas in the packing and their nonidentity (for this reason the times of the transfer of individual molecules of the compound by the flow of carrier along the column are different). As a result of the processes indicated above, the chromatographic zones do in fact undergo broadening associated with eddy diffusion.

The term B/u takes into account the longitudinal molecular diffusion. The longitudinal diffusion is determined by the familiar Fick's laws of diffusion, which operate not only in the stationary gas phase but also in the moving flow. The diffusion of the sorbate in the direction of lower concentrations leads to the symmetrical broadening of the band.

The term $C_s u$ takes into account the resistance to mass transfer in the gas-adsorbent system. The quantity C_s is determined by the slowness of the mass transfer between the gas phase and the adsorbent.

The band broadening process is a fairly complex physical phenomenon. For this reason, Van Deemter's equation (like, incidentally, other equations) only approximately describes the principal physical spreading processes in our view. This standpoint is supported also by the fact that a whole series of equations have been proposed for the description of band broadening processes.⁷¹

The most general expression taking into account the principal factors influencing the band broadening in a packed column over a wide range of carrier gas flow rates is the Giddings equation:¹²⁴

$$H = \left[\frac{1}{A} + \frac{1}{C_m u} \right]^{-1} + \frac{B}{u} + C_u. \quad (45)$$

The physical meaning of the quantities A and B/u was elucidated above. Here $B = 2D_g$ (D_g is the diffusion coefficient of the chromatographed compound in the gas phase), $C_m = \beta^2 d_p^2 / 2D_g$ is the coefficient of the resistance to mass transfer in the gas phase associated with the coupled eddy diffusion coefficient, β is a coefficient characterising the multichannel nature of the packing and the diffusion into gas cavities, and the quantity C_u is determined by internal and external diffusion mass transfer.

All the terms of this equation (with the exception of $C_m u$) have been used in the classical Van Deemter's equation¹³⁵ for the description of the broadening of the bands of the chromatographed compounds. The coupled theory of eddy diffusion, developed by Giddings, made it possible to eliminate a series of

contradictions observed in the interpretation of experimental data using Van Deemter's equation (for example, the dependence of the term A on the carrier gas flow rate, the negative values of A , etc.). However, it is fairly difficult to determine the coefficients of the Giddings equation. In certain cases, the use of graphical methods yields satisfactory results.¹³⁶

Keller and Giddings¹³⁷ proposed a version of this equation in the following form:

$$H = \left[\frac{1}{2\lambda d_p} + \frac{1}{\omega(d_p^2/D_g)u} \right]^{-1} + \frac{2\gamma D_g}{u} + \mu \frac{d_p^2}{D_g} u + \nu \frac{d_p^2}{D_g} u^2, \quad (46)$$

where ω , μ , and ν are constants depending on the capacity retention factor of the chromatographed compound. The penultimate term of the equation is determined by the external diffusion mass transfer, whilst the last term is determined by the internal diffusion mass transfer.

When account is taken of the pressure gradient (see, for example, the monograph by Guiochon and Guilleman⁷¹), the component influenced by the properties of the carrier gas (the diffusion coefficient in the gas phase, as well as the pressure drop and the carrier gas flow rate at the column outlet, which also depend on viscosity of the carrier gas) may be isolated from the preceding equation.

$$H_g = \left\{ \frac{2\gamma D_g}{u_0} + \left[\frac{1}{2\lambda d_p} + \frac{1}{\omega(d_p^2/D_g)u} \right]^{-1} + \mu \frac{d_p^2}{D_g} u \right\} f, \quad (47)$$

$$f = \frac{9}{8} \frac{[(P_i/P_0)^4 - 1][(P_i/P_0)^2 - 1]}{[(P_i/P_0)^3 - 1]^2}. \quad (48)$$

The quantity f is a function of the ratio of the inlet and outlet pressures at the inlet to (P_i/P_0) . The dependence of f on P_i/P_0 is presented in Fig. 12. For P_i/P_0 in the range from 1.0 to 7.0, the quantity f increases by $\sim 10\%$. Therefore the quantity f may be neglected in approximate calculations.

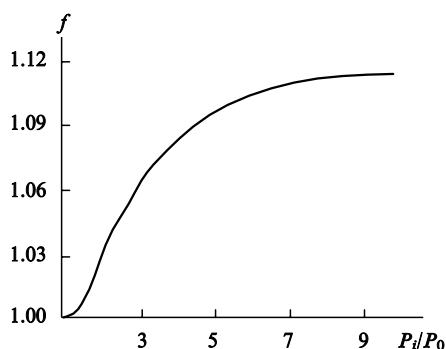


Figure 12. Dependence of the correction coefficient f on the ratio of the inlet and outlet pressures of the carrier gas.¹³⁰

It follows from the equations presented above that the properties of the carrier gas employed have an appreciable influence on the height equivalent to the theoretical plate (HETP).

The limiting factor in band broadening is usually the slowness of the mass transfer. In the region of high carrier gas velocities, the use of hydrogen (instead of, for example, carbon dioxide) makes it possible to increase the efficiency of the chromatographic column and hence to reduce the duration of the analysis. This feature of the chromatographic process in the region of high velocities is due to the high diffusion coefficients of the chromatographed compounds in hydrogen.

The few tests of the equations reflecting the dependence of the HETP on the carrier gas flow rate have in the main confirmed them (see, for example, Refs 15, 18, 65, 138, and 139).

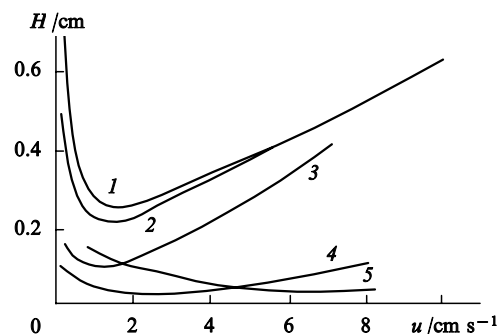


Figure 13. Dependence of the column efficiency on the carrier gas flow rate and on the nature of the carrier gas.⁴⁹ Carrier gases: (1) methane; (2) nitrogen, ethane, ethene; (3) carbon tetrachloride; (4) nitrogen; (5) helium.

We may note that the calculated diffusion coefficients in the carrier gas may be used for the estimation of the individual terms of the equations presented above. These methods have been described in detail.^{136, 140} As an example, Fig. 13 presents the $H = f(u)$ relations for various carrier gases obtained on a packed column with Porapak S.

When carrier gases with a lower diffusion coefficient (higher molecular mass) than that of hydrogen are employed, an increase in the efficiency of the chromatographic column is observed at low gas flow rates, but for high-speed analysis it is desirable to employ gases with a high rate of mass transfer, i.e. with a high diffusion coefficient.

2. Capillary gas–solid columns

The term due to eddy diffusion, associated with the multiple path nature of the movement of the gas in packed columns, is absent in the case of capillary columns. The dependence of the HETP on the carrier gas flow rate in capillary gas–solid chromatography has been discussed in greatest detail in the book of Berezkin and de Zeeuw.²

Golay obtained the following equation for the description of the band broadening in open capillary columns with a porous layer and containing a stationary liquid phase:¹²⁷

$$H = \frac{2D_g}{u} + \left[\frac{1 + 6k + 11k^2}{(1 + k)^2} + \frac{(8 + 32k)a_2}{(1 + k)^2} + \frac{8k^2}{(1 + k)^2} \frac{a_1^2}{a_2} \right] \frac{r^2 u}{24D_g} + \left[\frac{k^3}{6(1 + k)^2} \frac{1 + 2a_2}{r_s} \right] \frac{r^2 u}{K^2 D_1}, \quad (49)$$

where k is the retention factor of the chromatographed substance, $a_1 = d/r$ (d is the average length of the twisted channels in the porous layer on the internal walls of the column), r_s is the ratio of the surface areas of the sorbent (liquid phase) and of the capillary wall, $a_2 = d_g/r$ (d_g is the effective thickness of the gas layer in the porous layer of the sorbent located on the inner walls of the column and r is the internal radius of the capillary column), K is the partition (equilibrium) coefficient of the chromatographed compound between the stationary and mobile phases, and D_1 is the diffusion coefficient of the chromatographed compound in the sorbing phase.

The last term, reflecting the resistance to mass transfer in the film of the liquid phase located on the solid carrier, is inversely proportional to r_s . Thus Eqn (49) reflects the fact that, with increase in the porosity of the wall layer, the efficiency of the capillary column should increase (the HETP should diminish with increase in r_s). Hence the idea of creating a capillary with a porous layer of solid carrier on its inner walls was introduced already in the derivation of this equation.

However, it is essential to note that this equation like, incidentally, Golay's other equations, apply directly primarily to gas–liquid–solid (or gas–liquid) chromatography, but, as noted

in the monograph of Berezkin and de Zeeuw,² Eqn (49) may be fully applicable also to gas–solid chromatography if it is assumed that r_s is the ratio of the surface areas of the adsorbent and the capillary wall and D_1 is replaced by D_s , *i.e.* by the diffusion coefficient of the chromatographed compound in the adsorbent layer.

An equation for the dependence of the HETP on the linear carrier gas flow rate for gas–solid chromatography has also been proposed by Giddings.^{133, 134} The Giddings equation does not differ functionally from the Golay equation and the first terms of the Giddings equation are virtually identical with those of the Golay equation. The difference consists, firstly, in the term reflecting the resistance to mass transfer in the adsorption layer located on the inner walls of the capillary column and, secondly, in the allowance for the influence of the carrier gas pressure drop in the column on the band broadening. The Giddings equation can be expressed in the following form:

$$H = \frac{2D_g}{u_0} + \left[\frac{1 + 6k + 11k^2}{24(1+k)^2} \right] \frac{r^2 u}{D_g} f_1 + \quad (50)$$

$$+ \frac{8}{a_k u_m} \left(\frac{k}{k+1} \right)^2 \frac{V_m}{S} f_h u_0 f_2,$$

$$u_0 = \frac{L}{t_M f_2}, \quad (51)$$

$$f_2 = \frac{3}{2} \frac{[(P_i/P_0)^2 - 1]}{[(P_i/P_0)^3 - 1]}, \quad (52)$$

where a_k is the accommodation coefficient, u_m the average velocity of the molecules of the chromatographed compound in the gas phase, V_m the volume of the gas phase in the column, S the overall surface area of the adsorbent layer in the column, and f_h the adsorbent heterogeneity factor.

If the influence of the pressure drop on the band broadening is neglected (*i.e.* it is assumed that $f_2 \approx 1$ and $f_1/f_2 \approx 1$),²⁰ then Eqn (50) can be expressed in the form

$$H = \frac{2D_g}{u} + \left(\frac{C'_m}{D_g} + C_A \right) u, \quad (53)$$

or

$$H = \frac{2D_g}{u} + Cu, \quad (54)$$

$$Hu = 2D_g + Cu^2, \quad (55)$$

(we note that $2D_g = B$), where

$$C = \frac{C'_m}{D_g} + C_A = C_m + C_A, \quad (56)$$

$$C'_m = \frac{1 + 6k + 11k^2}{24(1+k)^2} r^2, \quad (57)$$

$$C_A = \frac{8}{a_k u_m} \frac{V_m}{S} f_h \frac{k}{(1+k)^2}, \quad (58)$$

$$C_m = \frac{C'_m}{D_g}. \quad (59)$$

The coefficients of the resistance to mass transfer were first estimated on the basis of Eqn (55) for buta-1,3-diene on an open capillary adsorption (with alumina as the adsorbent) column were first estimated by the Dutch investigators de Nijs and de Zeeuw.¹⁴¹ They determined the coefficients of the resistance to mass transfer for buta-1,3-diene; in the gas phase, $G_m(\text{He}) = 1.3 \times 10^{-4}$ s and $G_m(\text{N}_2) = 4.6 \times 10^{-4}$ s, whilst in the stationary phase $C_A = 1.8 \times 10^{-4}$ s. The data presented show that the nature of the carrier gas influences the quantity G_m : the smaller the diffusion coefficient (the greater the molecular mass of the carrier gas), the

greater the broadening of the chromatographic band occurring as a result of the increase in the contribution of the resistance to mass transfer in the gas phase and the greater the diminution in column efficiency in the region of high rates.

Berezkin and Volkov²⁰ carried out a similar investigation for the capillary adsorption column with $\text{Al}_2\text{O}_3/\text{KCl}$ (Chrompack, Holland). The results are presented in Table 10. It follows from the tabulated data that the principal contribution to the broadening of the bands of the chromatographed compounds is made by the term C reflecting the resistance to mass transfer.

Table 10. The coefficients of Eqn (55) for hydrocarbon gases separated on a capillary column with alumina.²⁰

Carrier gas	Calculated		Experimental	
	$D_g/\text{cm}^2 \text{ s}^{-1}$	$B/\text{cm}^2 \text{ s}^{-1}$	$B/\text{cm}^2 \text{ s}^{-1}$	C/s
Chromatographed compound — ethane				
He	0.68	1.36	1.2	2.4
N ₂	0.22	0.44	0.45	6.8
CO ₂	0.175	0.35	0.36	8.0
Chromatographed compound — propane				
He	0.56	1.12	0.96	3.0
N ₂	0.17	0.34	0.36	8.6
CO ₂	0.14	0.28	0.29	11.0
Chromatographed compound — n-butane				
He	0.43	0.86	0.80	7.2
CO ₂	0.11	0.22	0.22	24.0

The influence of the carrier gas on the coefficients of the resistance to external and internal mass transfer for a capillary adsorption column with alumina has been estimated.¹⁴² The data obtained are presented in Table 11. Evidently, the overall coefficient of the resistance to mass transfer for n-butane (C) is smaller by a factor of 2.4 with hydrogen as the carrier gas than in nitrogen and this difference is due to the corresponding difference between the coefficients of the resistance to mass transfer in the alumina layer. In order to employ the column under the conditions of high-speed analysis, it is therefore essential to use hydrogen as the carrier gas.

Table 11. Diffusion coefficients and resistances to mass transfer for n-butane with hydrogen and nitrogen as the carrier gases.¹⁴²

Parameter	Carrier gas	
	hydrogen	nitrogen
$D_g/\text{cm}^2 \text{ s}^{-1}$	0.625	0.162
Coefficient of resistance to mass transfer $/10^{-3}$ s		
C_m	1.8	6.9
C_s	1.8	1.8
C	3.6	8.7

Relatively 'heavy' carrier gases should increase significantly the efficiency of the chromatographic column in the region of low carrier gas flow rates by diminishing the broadening of the chromatographic bands due to longitudinal molecular diffusion. This has been confirmed experimentally.¹⁰¹ Analysis of the experimental data presented in Table 12 and in Fig. 14 made it possible to discover¹⁰¹ the following feature of the band broadening process in capillary gas–solid chromatography: the greatest efficiency of the chromatographic column may be achieved by employing the 'heavy' carbon dioxide and the greatest 'gain' in efficiency is observed for 'light' chromatographed compounds. The maximum column efficiency increases for all the sorbates investigated ($H_{\min}$ diminishes in the following series of carrier gases: hydrogen < helium < nitrogen < carbon dioxide).

Table 12. Parameters of a capillary adsorption column for different carrier gases.¹⁰¹

Parameter	Chromatographed compound		
	propene	butane	isobutene
Carrier gas — hydrogen			
k	0.81	1.54	3.45
$H_{\min}/\text{mm}$	0.60	0.48	0.46
Carrier gas — helium			
k	0.79	1.51	3.35
$H_{\min}/\text{mm}$	0.43	0.41	0.45
Carrier gas — nitrogen			
k	0.68	1.26	2.77
$H_{\min}/\text{mm}$	0.29	0.31	0.33
Carrier gas — carbon dioxide			
k	0.58	1.06	2.24
$H_{\min}/\text{mm}$	0.25	0.29	0.36

The experimental and calculated coefficients of the resistance to mass transfer in the gas phase for certain carrier gases are presented in Table 13. The values of D_g have been calculated¹⁰¹ from the Fuller–Schettler–Giddings equation.¹⁴⁰ It follows from the data in Table 13 that the main band broadening takes place in the gas phase. However, publications have appeared in the literature in which it is noted that the observed dependences of

Table 13. Coefficients of resistance to mass transfer for the following experimental conditions: 50 m × 0.32 mm column, adsorbent — Al₂O₃/KCl, temperature 90 °C.¹⁰¹

Parameter	Chromatographed compound	
	propene	isobutene
Carrier gas — hydrogen		
k	0.81	3.45
$D_g(\text{calc.})/\text{cm}^2 \text{ s}^{-1}$	0.365	0.228
$C_m(\text{calc.})/10^{-3} \text{ s}$	0.47	1.40
$C_m(\text{exp})/10^{-3} \text{ s}$	1.4	0.8
Carrier gas — carbon dioxide		
k	0.58	2.24
$D_g(\text{calc.})/\text{cm}^2 \text{ s}^{-1}$	0.081	0.067
$C_m(\text{calc.})/10^{-3} \text{ s}$	1.7	4.2
$C_m(\text{exp})/10^{-3} \text{ s}$	1.8	2.8

the HETP on the linear carrier gas flow rate for capillary adsorption columns are inconsistent with the Golay–Giddings equation (see, for example, Refs 28, 143, and 144).

Thus the consistency of the Van Deemter [Eqn (41)], Golay–Giddings [Eqn (54)], and the extended Golay–Giddings equations with the authors' experimental data and certain literature data has been analysed¹⁴⁴ in order to determine the most suitable equation for the description of the dependence of the HETP on the linear carrier gas flow rate in capillary gas–solid columns with various adsorbents.

The extended Golay–Giddings equation describes satisfactorily the $H = f(u)$ relation in the region of high carrier gas flow rates:¹⁴⁵

$$H = \frac{B}{u} + Cu + Du^2, \quad (60)$$

where

$$B = 2D_g \quad (61)$$

$$C = \frac{1 + 6k + 11k^2}{24(1 + k)^2} \frac{r^2}{D_g} + \frac{2k}{3(1 + k)^2} \frac{d_f^2}{D_1}, \quad (62)$$

$$D = \frac{\sigma^2(tEC)}{(1 + k)^2 L}, \quad (63)$$

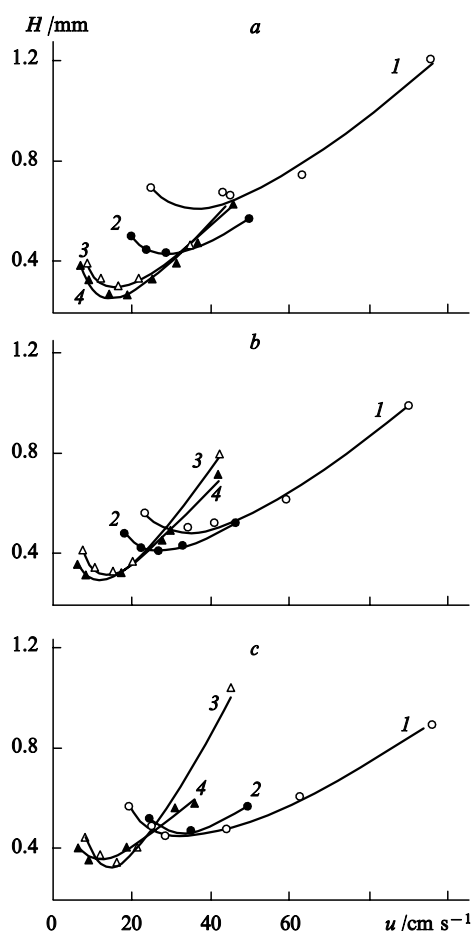
r is the internal radius of the capillary column, d_f the film thickness in the column, D_1 the diffusion coefficient in the stationary liquid phase, $\sigma^2(tEC)$ the characteristic of the extra column contribution, and L the column length.

Analysis of the results obtained¹⁴⁴ showed that, among the 32 examples considered, Eqn (54) is the most suitable for the description of experimental data in only two cases (6%), the Van Deemter equation [Eqn (41)] is suitable in nine cases (28%), while the extended Golay–Giddings equation [Eqn (60)] is suitable in 21 cases (66%).

Thus the extended Golay–Giddings equation should be more widely employed for the description of the $H = f(u)$ relation in capillary adsorption columns. However, it is essential to put forward a well founded theoretical interpretation of this relation, because virtually all the examples considered refer to the usual experimental conditions and not to high-speed analysis.

VII. Conclusion

As shown by numerous investigators, the nature of the carrier gas (and its pressure in the chromatographic column) employed in gas–solid chromatography exerts an appreciable influence on the principal chromatographic characteristics of sorbates, namely on the retention parameters and band broadening. Unfortunately, due attention to the role of the carrier gas employed is not always

**Figure 14.** Dependence of the HETP on the linear carrier gas flow rate for certain hydrocarbon gases characterised by different retention factors;¹⁰¹ (a) propene; (b) butane; (c) isobutene.

Carrier gases: (1) hydrogen; (2) helium; (3) nitrogen; (4) carbon dioxide. Experimental conditions: 50 m × 0.32 mm, stationary phase — Al₂O₃/KCl, $T = 90^\circ\text{C}$.

paid in the scientific literature and particularly in chromatographic practice.

The analysis of the results of published studies carried out in the present review indicates a real possibility of a significant improvement of analytical separation with the aid of a simple and nontraditional method such as the alteration of the carrier gas and of its column pressure. It is essential to note that this factor assumes a particular importance for high-performance capillary chromatography.

In the optimisation of the analytical separation process, the dependence of the column efficiency on the carrier gas flow rate is important. The results of the latest studies have shown that the classical Golay–Giddings equation for capillary gas–solid chromatography, reflecting this dependence, is not optimal for the description of experimental data and that this must be taken into account in chromatographic practice.

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Preparation of polymeric biomaterials with the aid of radiation-chemical methods

V Ya Kabanov

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Abstract. The results of the application of radiation-chemical methods for the preparation of polymeric biomaterials are surveyed and treated systematically. The characteristic features of these methods and their advantages and disadvantages are indicated. The properties of polymeric biomaterials prepared using ionising radiation are examined. Particular attention is devoted to studies carried out during the last 10–15 years. The bibliography includes 492 references.

I. Introduction

Polymeric biomaterials are usually understood as polymeric materials and articles made from them which are used in medicine or biotechnology. Such materials are frequently prepared by the specific modification of well known polymers. The range, scale of manufacture, and importance of biomaterials have increased appreciably during recent years.

A series of reviews and monographs have been devoted to problems of their preparation, properties, and applications (see, for example, Refs 1–6).

Radiation-chemical technology has now become one of the effective methods for the preparation of polymeric biomaterials. The studies on the employment of radiation-chemical methods for the synthesis of polymeric biomaterials have been carried out on the following lines: radiation-induced modification of various polymers and articles made from them in order to obtain haemocompatible polymers (polymers which are in prolonged contact with blood during their employment), polymeric sorbents, prostheses for blood vessels, *etc.*; immobilisation of various biologically active substances (BAS) (enzymes, medicinal drugs, *etc.*) in polymeric matrices using radiation-induced polymerisation; radiation-chemical synthesis of polymeric carriers for medicinal preparations; radiation-induced cross-linking of polymers in order to obtain mechanically strong hydrogels (BAS carriers, dressings, eye lenses, *etc.*).

An advantage of the radiation-chemical methods for the preparation of polymeric biomaterials compared with traditional methods is the purity of the materials (there is no need to add additional ingredients during the synthesis), the possibility of carrying out the processes at reduced temperatures, and the ease of regulation of the rate of the processes by altering the radiation dose rate. Another advantage of the radiation-chemical methods is the fact that the biomaterials can in certain cases be sterilised on the same sources of ionising radiation which were used for their preparation. It is essential to note that in the majority of cases low radiation doses, as a rule not exceeding 30 kGy, are required for the preparation of polymeric biomaterials, which makes it possible to use low-power radiation sources.

A disadvantage of radiation-chemical methods is the necessity to use, as a rule, γ -radiation sources and electron accelerators which are comparatively expensive and difficult to use.

The mechanisms of the radiation-chemical processes, the devices, the dosimetry, and the methods involving the employment of ionising radiation sources have been described in detail in a series of monographs (see, for example, Pikaev and Woods ^{7,8}). In the present review, these questions are not considered.

II. Preparation of haemocompatible polymeric materials

The preparation of haemocompatible polymeric materials is an extremely complex problem. When polymers come into contact with blood, biochemical reactions inducing a change in the physiological functions of blood are initiated and the blood clotting system with subsequent thrombus formation on the surface of the polymer is 'switched on'. Reviews have been devoted to the mechanisms of thrombogenesis on the surface of polymers.^{9–15} Important factors increasing the haemocompatibility of polymers are their properties such as minimal capacity for the adhesion and aggregation of thrombocytes, the lack of activation of blood clotting contact factors, participation in the lysis of the thrombus formed, and a selective capacity for the adsorption of blood plasma proteins, especially albumin. According to current ideas, the first stage, when the polymer comes into contact with blood, is rapid sorption of proteins from blood plasma. The nature and conformational state of the protein determine the subsequent biochemical reactions.

The problems of the sorption of proteins on various polymeric surfaces have been considered in numerous investigations (see, for example, Refs 1, 16, and 17). Unfortunately, at the present time

V Yu Kabanov Institute of Physical Chemistry, Russian Academy of Sciences, Leninskii prosp. 31, 117915 Moscow, Russian Federation.
Fax (7-095) 335 17 78. Tel. (7-095) 335 20 02

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the level of our knowledge precludes sufficiently effective prediction of the nature and properties of the polymer surface which would fully satisfy the requirement of haemocompatibility.

It is clear from the foregoing that the surfaces of polymers must be modified in order to obtain haemocompatible materials. The following measures are taken for this purpose.

1. Polymers are created with surfaces possessing a reduced adsorption capacity in relation to protein and are close in their nature to the natural medium of the organism. In the main, these are hydrogel surfaces. It has been assumed¹⁷ that both an approximate equality, pairwise, of the dispersion and polar components of the free surface energy of blood and materials and the closeness of the distribution of the above energy parameters, also pairwise, are needed for haemocompatible materials.

2. Polymeric materials with a definite domain structure of the surface (polyurethanes) are created.

3. Polymeric hydrocarbon materials (polyethylenes) are created.

4. Polymers are created the surfaces of which model, in terms of their nature, blood anticoagulants (this is achieved by introducing sulfo- and carboxy-groups into the surface layers of polymers, by generating a negative charge on the surfaces of polymers). It is usually endeavoured to obtain a heparin-like surface, since the widely used method for the preparation of haemocompatible materials by introducing heparin suffers from a series of disadvantages due to the partial loss of activity by the heparin on covalent immobilisation and its weak anticomplement activity and biodegradation.

5. Physiologically active substances (blood anticoagulants, enzymes, *etc.*), interacting with blood components and arresting the thrombogenic process, are introduced into the surface hydrogel layers.

In selecting the method for the modification of the polymer surface, it is essential to bear in mind the principle that the physicochemical parameters of the initial polymer should not change significantly on modification. One of the methods for the modification of polymers is radiation-induced graft polymerisation.

A series of reviews have been devoted to various problems of the radiation-induced graft polymerisation and the methods for carrying it out.^{7, 18–22} Its advantages as a method for the modification of polymeric materials in order to increase their haemocompatibility are, firstly, a high universality which makes it possible to modify over a wide temperature range virtually any polymeric materials (stitches, catheters, tubes, tablets, powders, grafts, *etc.*) and secondly the possibility of creating on the polymer surface of modified layers of different thickness. The thickness of the layer depends on the conditions under which the graft polymerisation is carried out — the dose rate, the choice of the solvent for the monomer, *etc.* The modified layer is then strongly bound to the support and is not washed off on contact with the medium of the living organism.

All these features promote a fairly wide-scale employment of radiation-induced graft polymerisation for the solution of problems associated with the enhancement of the haemocompatibility of various polymeric materials and articles made from them. The principal task of such investigations is the creation of polymers with a functionalised surface, definite hydrophilic-hydrophobic properties, and a negative charge on the surface.^{23–25} A large number of studies have been carried out on the modification of various polymers using highly hydrophilic monomers such as *N*-vinylpyrrolidone, 2-hydroxyethyl methacrylate, and acrylamide and its derivatives.^{26–72} In a series of investigations, fairly complex copolymers have been used for modification.^{73–87} Thus, polyurethanes, polyesters, and natural rubber have been mainly used for the manufacture of blood vessel prostheses.^{88–118}

Table 1 presents data on the employment of the radiation-induced graft polymerisation methods for the modification of polymers. The radiation-induced graft polymerisation was carried out in most cases by the direct method from aqueous alcoholic solutions with low irradiation doses. In certain cases, especially in

the grafting of acrylamide, the method involving preirradiation was used.⁴¹

The investigations carried out led to the preparation of a wide variety of modified polymeric materials with hydrogel surfaces. These materials are fairly strong and soft and exhibit a high swellability in water. The biomacromolecules in such materials are characterised by enhanced diffusion. The polymeric hydrogels obtained by radiation-chemical methods have been tested for haemocompatibility in experiments *in vitro* and *in vivo* on monkeys, sheep, and dogs. The tests for the haemocompatibility of the radiation-grafted polymeric hydrogels revealed the following general features: with increase in the water content from 15% to 85%, the sorption of proteins diminishes, the rate of desorption increases, and thrombogenesis takes place on the hydrogels, but the bond between the thrombus and the hydrogel surface is appreciably weakened compared with the bond between them and the unmodified polymers. The appreciable decrease in the interfacial tension between the hydrogel and the aqueous solution is very important. The hydrogel coating on the polymers should be prepared from very pure monomers. Thus a slight methacrylic acid impurity in 2-hydroxyethyl methacrylate appreciably impairs the quality of the hydrogel coating and its haemocompatible properties.⁹³

Interesting results have been obtained in the study of the copolymers of 2-hydroxyethyl methacrylate (a hydrophilic monomer) with ethyl methacrylate (a hydrophobic monomer) radiation-grafted onto polyethylene (PE).⁹³ For a low water content (~10%), the above graft copolymers were characterised by unexpectedly low thrombocyte adsorption parameters, which was not due to the water content but to the composition of the copolymer. For a higher water content, the adsorption of thrombocytes was inversely proportional to the water content. Evidently, the composition of the copolymers and the state of water in it are important. The surface of radiation-grafted copolymers is very nonuniform (there are mounds, projections, *etc.*) and the thickness of the modified layer is as a rule 15–45 μm . Hoffman *et al.*⁹³ concluded that a definite combination of hydrophilic and hydrophobic sections on the surface is needed to increase the haemocompatibility.

The state of water in radiation-grafted copolymers has been investigated.^{94, 95} The state of water in radiation-grafted PE hydrogels with grafted polyacrylamide has been studied.⁹⁴ It has been established by differential scanning calorimetry (DSC) that the water in hydrogels does not freeze down to -50°C and that the amount of unfrozen water per unit surface of the modified polymer which has undergone equilibrium swelling or per mole of the grafted polyacrylamide depends on the methods used to carry out the graft polymerisation. The presence of unfreezing water in radiation-grafted hydrogels with polyacrylamide chains is due to the rearrangement of the water framework in the hydrogel owing to the formation of a strong hydrogen bond between the H_2O molecule and the carbonyl group of polyacrylamide, which has been demonstrated by IR Fourier spectroscopy.⁹⁴ Data on the employment of the ESCA method for the investigation of the influence of hydration on the state of the grafted chains in a thin layer on the surfaces of polymers ~50 Å thick have been published.⁹⁵ The following systems have been investigated: low-density polyethylene (LDPE) + grafted poly(2-hydroxyethyl methacrylate), LDPE + grafted polyacrylamide, silicone rubber (Silastik) + poly(2-hydroxyethyl methacrylate), and polyurethane (Tufthane) + poly(2-hydroxyethyl methacrylate). The surface was analysed by studying the C_{1s} , O_{1s} , and Si_{2p} peaks. The C/Si , O/Si , C/O , C/N , and O/N peak ratios for the hydrated and dehydrated surfaces of various radiation-grafted copolymers have been published.⁹⁵ These data make it possible to determine the location of the grafted chains in the surface layer of the polymers in the hydrated and dehydrated states. For example, in the case of the grafting of poly(2-hydroxyethyl methacrylate) on polyurethanes, the concentration of the grafted chains on the surface diminishes appreciably after dehydration. On the other hand,

Table 1. Radiation-induced graft polymerisation of monomers for the preparation of various polymers with the aim of regulating haemocompatibility.

Monomer	Conditions in radiation-induced graft polymerisation	Remarks	Ref.
<i>Polymer — polyethylene</i>			
Acrylic acid	post-radiation grafting	the adsorption of antitumour preparations on adsorbents with grafted poly(acrylic acid) was studied	29
	direct grafting from aqueous phase	the hydrophilic properties of the surface were studied in detail	96, 97
	ditto	the carboxy groups were converted into acid chloride groups by treating the surface with thionyl chloride and the latter were used for the covalent binding of BAS	90
Acrylic acid chloride	direct grafting from vapour phase		23, 26
Acrylic acid, acrolein; mixture of monomers	direct grafting from liquid phase	sulfonation of graft copolymer	31
Acrylamide	grafting by the preirradiation method from aqueous and acetone solutions	the amide groups of the grafted polyacrylamide were converted into amino groups; heparin was bound to the amino groups; tests <i>in vivo</i> and <i>in vitro</i>	27
	ditto	polymer tubes were used; tests <i>in vivo</i>	28
	direct grafting from solution	the surface of the modified polymer was studied	33
	various grafting methods, including grafting from the vapour phase, were used		107
Acrylamide, <i>N,N'</i> -methylene-bisacrylamide	direct grafting from 10% aqueous alcoholic solution in the presence of Fe ²⁺		24
Allylamine	direct grafting in the presence of phosphoric acid	phosphoric acid increases the yield of the graft polymer	25
Diallyldimethylammonium chloride, sodium styrene sulfonate	direct grafting		35
2-Hydroxyethyl methacrylate, ethyl methacrylate; mixture of monomers	direct grafting from water–methanol mixture at low dose rates	surfaces with different hydrophilicities were obtained	30, 37
4-Vinylpyridine + 2-(<i>N,N</i> -diethyl-amino)ethyl methacrylate; 4-vinylpyridine + methyl methacrylate; 4-vinylpyridine + methacrylic acid	direct grafting of monomers from vapour phase	alkylation of graft copolymer	32
<i>N</i> -Vinylpyrrolidone	grafting from liquid phase by the preirradiation method		36
Methyl acrylate	direct grafting from water–acetone mixture	hydrazinolysis of graft copolymers	59
Styrene	direct grafting	introduction of sulfonate and sulfonamide groups; tests <i>in vitro</i>	48
2-Hydroxyethyl methacrylate, 2-hydroxyethyl methacrylate + ethyl methacrylate	direct grafting from liquid phase	the structure of the surface was investigated by electron microscopy	93
2-Hydroxyethyl methacrylate, <i>N</i> -vinylpyrrolidone, acrylamide	ditto		106
<i>Polymer — polyethylene, silicone rubber</i>			
2-Hydroxyethyl methacrylate, acrylamide	direct grafting from liquid phase	the state of water was investigated by the DSC and ESCA methods	94, 95

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisation	Remarks	Ref.
<i>Polymer — polypropylene</i>			
2-Hydroxyethyl methacrylate	direct grafting from 20% monomer solution	a grafting maximum is observed for a dose of 5 kGy	39
	grafting by the preirradiation method	hydrophilisation of polypropylene stitch material	98
Monomer mixtures: <i>N</i> -vinylpyrrolidone + acrylic acid; vinyl acetate + crotonic acid	direct grafting	the polyacrylic acid in the modified polymer was partly neutralised with alkali	40
Acrylamide	postradiation grafting after vacuum irradiation of polymer		41
<i>Polymers — polyethylene, polypropylene, polyesters, poly-4-methylpentene, polyvinyltrimethylsilane</i>			
Acrylic acid, methacrylic acid, 4-vinyl-pyridine	grafting from vapour phase	the formation of polyelectrolytic complexes on the surfaces of the polymers was investigated	34
<i>Polymers — polyethylene, polypropylene, polyamides, polyurethanes, etc.</i>			
<i>N</i> -Methyl- <i>N</i> -vinylacetamide	direct grafting from liquid phase	the properties of the surfaces of the modified polymers were characterised by the critical surface tension; polymer tubes were used for modification	89
<i>Polymers — polyethylene, polypropylene</i>			
Vinylidene chloride	direct grafting from gas phase	dehydrochlorination of materials obtained	101–104
<i>Polymer — ethylene-propylene rubber</i>			
2-Hydroxyethyl methacrylate, <i>N,N</i> -dimethylacrylamide, 2-(<i>N,N</i> -dimethylamino)ethyl methacrylate	direct grafting from aqueous medium in the presence of Cu ²⁺ ion		70
Acrylamide, <i>N</i> -vinyl-pyrrolidone, 2-hydroxyethyl methacrylate	direct grafting from aqueous monomer solution	the morphology of the surface and the influence of O ₂ on the grafting were investigated	71
Different vinyl monomers	direct grafting from liquid phase	grafting onto a film, a tube, and a fibre was studied; the surface properties were investigated	42
<i>Polymer — ethene-propene copolymer</i>			
<i>N</i> -Vinylpyrrolidone, 2-hydroxyethyl methacrylate, acrylamide	direct grafting from liquid phase		86
<i>Polymers — polyolefins</i>			
Macromonomers	direct grafting	review of studies on the grafting of macromonomers; macromonomers were obtained by the acylation of the amino groups in enzymes or heparin using acrylic acid chloride	91
<i>Polymer — polytetrafluoroethylene</i>			
Acrylic acid chloride	direct grafting from monomer gas phase		23
<i>N,N</i> -Dimethylacrylamide	direct grafting from liquid phase	the influence of dose rate, solvent, and temperature on the grafting was investigated	45
Acrylamide	grafting by the preirradiation method	the surface of the polymer was investigated by the ESCA method and by scanning electron microscopy	46
<i>tert</i> -Butyl crotonate + methyl acrylate + sulfonic acid	direct grafting from liquid phase	the influence of the graft polymer on the haemocompatibility was investigated	47
Methyl methacrylate phase	direct grafting from liquid phase	modification of blood vessel prostheses	49
Styrene	ditto	the grafted chains were nitrated and the nitro groups were reduced to amino groups	43

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisation	Remarks	Ref.
<i>Polymers — polytetrafluoroethylene, tetrafluoroethene–ethene copolymer</i>			
<i>N,N</i> -Dimethylacrylamide	direct grafting at different dose rates		50
<i>Polymer — tetrafluoroethene–propene copolymer</i>			
<i>N,N</i> -Dimethyl acrylamide	direct grafting from liquid phase	the influence of solvents on the grafting was investigated	76
<i>Polymer — poly(vinyl fluoride)</i>			
2-Hydroxyethyl methacrylate, vinyl acetate, acrylic acid, <i>N</i> -vinylpyrrolidone, 4-vinylpyridine, acrylamide, vinylene carbonate	grafting by the preirradiation method from the liquid phase of the monomer; irradiation by electron accelerator	the kinetics of graft polymerisation were investigated	51
<i>Polymer — poly(vinylidene fluoride–hexafluoropropene)</i>			
Styrene	grafting by the preirradiation method; irradiation by accelerated heavy ions	functionalisation of grafted chains; modification of blood vessel prostheses	62
<i>Polymers — poly(vinylidene fluoride), hexafluoropropene–vinylidene difluoride copolymer</i>			
Styrene	grafting by the preirradiation method; irradiation with accelerated heavy ions	introduction of sulfo groups; formation of a heparin-like surface	87
Organosilicon polymers			
<i>N</i> -Vinylpyrrolidone	direct grafting from monomer solution in methanol or toluene	grafting on silicone rubber tubes	52, 58
	direct grafting from liquid phase	review of studies on radiation-induced grafting of <i>N</i> -vinylpyrrolidone	60
<i>N</i> -Vinylpyrrolidone, 2-hydroxyethyl methacrylate; grafted layer and the degree of grafting mixture of monomers	direct grafting from aqueous monomer	the influence of Cu^{2+} on the distribution of solution in the presence of Cu^{2+} ions	57 the
	direct grafting from 20% aqueous solution	was investigated	
<i>N</i> -Vinylpyrrolidone mixture of <i>N</i> -vinylpyrrolidone and 2-hydroxyethyl methacrylate	direct grafting from aqueous solution of monomers	the influence of the irradiation dose on the grafting and the swelling of the modified polymers in water was investigated	53
			63
2-Hydroxyethyl methacrylate	direct grafting		64
Different hydrophilic monomers	grafting from aqueous solution		67
2-Hydroxyethyl methacrylate, ethyl acrylate; mixture of monomers	direct grafting from water–methanol mixture	the rate of grafting depends significantly on the water : monomer ratio	54
2-Hydroxyethyl methacrylate, ethyl methacrylate; mixture of monomers	direct grafting from aqueous phase	separate grafting of each monomer and of the mixture of monomers; the surface of polymers was investigated by scanning electron microscopy	56
Acrylamide	direct grafting from liquid phase in the presence of Cu^{2+} ions		55
<i>Polymers — polyurethane, silicon rubber</i>			
Acrylamide	direct grafting from liquid phase	sections through films and the swelling of the polymers in water were investigated	38
<i>N</i> -Vinylpyrrolidone	ditto	grafting onto polymer tubes; tests for haemocompatibility <i>in vivo</i>	69

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisation	Remarks	Ref.
<i>Polymer — segmented polyurethane</i>			
<i>N</i> -Vinylpyrrolidone	direct grafting from monomer solution in water	the influence of the degree of swelling and of the irradiation dose on the grafting was investigated	75
2-Hydroxyethyl methacrylate	direct grafting in swollen state	the influence of the degree of swelling and temperature on the grafting was investigated	74
<i>Polymer — polyesterurethane</i>			
2-Hydroxyethyl methacrylate	direct grafting from water–ethanol mixture	modified blood vessel prostheses were obtained; the swelling of the modified polymers was investigated	72
<i>Polymer — polyurethanepolyester (Upjohn)</i>			
<i>N</i> -Vinylpyrrolidone	direct grafting from monomer solution in water, benzene, toluene, and Freon	the influence of temperature on the grafting and the cross-sectional distribution of the grafted polymer was investigated; the grafting was carried out on tubes	77
<i>Polymer — polyurethane</i>			
2,3-Epoxypropyl methacrylate, acrylamide, 2-hydroxyethyl methacrylate	direct grafting from liquid phase	the influence of solvents on the grafting was investigated; the best solvent is acetone	73
Monomers with sulfonate groups	ditto	the haemocompatibility was investigated <i>in vivo</i>	105
<i>Polymer — polyamide 6</i>			
Various monomers	direct grafting from liquid phase	the grafting was carried out from solvents with a specific solubility parameter; modification of polyamide beads; preparation of new adsorbents	61
2-Hydroxyethyl methacrylate, glycidyl methacrylate	ditto	grafting onto polymer beads; the modified beads obtained were used as carriers for affinity chromatography	84
<i>Polymer — poly[bis(trifluoroethoxyphosphazene)]</i>			
<i>N</i> -Vinylpyrrolidone	direct grafting from aqueous monomer solution		67
<i>Polymers — polyphosphazenes</i>			
<i>N</i> -Vinylpyrrolidone	direct grafting from aqueous monomer solution	heparinisation; tests <i>in vivo</i>	68
<i>Polymer — natural rubber</i>			
<i>N,N</i> -Dimethyl acrylamide	direct grafting from monomer solution in CCl ₄		99
	grafting by the preirradiation method as a result of the decomposition of hydroperoxy groups	the haemocompatibility was investigated	108
2-(<i>N,N</i> -Dimethylamino)-ethyl methacrylate	direct grafting from monomer solution in CCl ₄ tubes	grafting onto polymer tubes	92
<i>Polymer — natural leather</i>			
Butyl methacrylate, styrene, methyl methacrylate	direct grafting		81
<i>Polymers — poly(vinyl alcohol), polyamide 6</i>			
Acrylamide, <i>N</i> -vinylpyrrolidone, 2-hydroxyethyl methacrylate, 2-(<i>N,N</i> -dimethylamino)ethyl methacrylate	direct grafting from aqueous solution in the presence of added formamide and tetrahydrofuran	adsorbents for affinity chromatography	44
<i>Polymer — poly(ethylene glycol dimethacrylate)</i>			
2-Hydroxyhexyl methacrylate	direct grafting	the adsorption of γ -globulin on the polymers obtained was investigated	66

Table 1 (continued).

Monomer	Conditions in radiation-induced graft polymerisation	Remarks	Ref.
<i>Polymers — polystyrene, polyester</i>			
<i>N</i> -Vinylpyrrolidone, 2-hydroxyethyl phase methacrylate	direct grafting from liquid phase	hydrophilisation of polystyrene articles for immunodiagnostics; modification of polyester blood vessel prostheses in order to increase haemocompatibility	78
<i>Polymer — polystyrene</i>			
<i>N</i> -Isopropylacrylamide	direct grafting	transition from a hydrophilic to a hydrophobic surface with the increase in temperature; the study of the adhesion of endothelial cells	79
<i>Polymer — polycarbonatepolysiloxane</i>			
Acrylic acid	grafting by the preirradiation method; irradiation by electron accelerator		82
<i>Polymer — triblock copolymer (styrene–butadiene–styrene)</i>			
2-Hydroxyethyl methacrylate	direct grafting from aqueous monomer solution	the modified specimens were investigated by electron microscopy and IR spectroscopy; the wetting angles were measured	83
<i>Polymer — poly(vinyl chloride)</i>			
2-(<i>N,N</i> -Dimethylamino)-ethyl methacrylate	grafting by the preirradiation method	grafting on polymer powder; preparation of immunoadsorbents	85
<i>Polymer — poly(ethylene terephthalate)</i>			
Acrylamide	direct grafting	modification of blood vessel prostheses	80
<i>Polymer — poly(methyl methacrylate)</i>			
Acrylic acid	direct grafting	binding of enzymes to the polymer surface	88

when poly(2-hydroxyethyl methacrylate) is grafted on the LDPE surface, dehydration does not affect the concentration of the grafted chains in the surface layer while the concentration of polyacrylamide grafted on polyurethanes does not change on the surface after dehydration.

In the case of organosilicon rubbers, the number of grafted chains on the surface diminishes as dehydration proceeds and the grafted chains are gradually immersed in the film. The second process occurring on dehydration is the formation of clusters by the grafted chains. The clusters are formed from several macromolecules. The disposition of the clusters on the surface depends on the degree of dehydration. Hydration significantly increases the concentration of the grafted chains on the polymer surfaces. This is particularly notable in the case of radiation-grafted silicone rubbers. Such data are important for the biomedical employment of the hydrogels obtained by radiation-induced graft polymerisation, since it is essential to take into account the change in the state of the grafted chains in the hydrogels on contact with blood or other biological liquids.

The hydrophilic properties of LDPE with grafted poly(acrylic acid) have been investigated.^{96,97} It was established that the hydrophilic properties are stabilised after a 15%–17% graft (complete surface coverage). The polar component of the free surface energy then increases appreciably and the molecules of poly(acrylic acid) are reorganised under the influence of water.

The preparation of a hydrophilic stitch material by the radiation-induced grafting of 2-hydroxyethyl methacrylate on a single polypropylene fibre has been described.⁹⁸ The influence of solvents and irradiation conditions on the graft has been investigated. Hydrophilic polypropylene filaments were obtained as a result.

The view has been expressed in certain investigations that the modified layer must be of definite thickness for the successful increase in haemocompatibility. In a study of the radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate

and acrylamide on polyolefin films and blood vessel prostheses, it has been established⁷² that the adsorption of proteins is reduced if the amount grafted does not exceed 10%. On the other hand, an appreciable decrease in interfacial tension and in the adsorption of thrombocytes is observed only after the attainment of a 20%–30% graft. The adhesion of thrombocytes diminishes significantly after the film has been coated with albumin. Haemocompatibility (investigated *in vivo* on sheep) as a rule increases significantly only for comparatively high amounts grafted (exceeding 30%).^{33,72,75} The study of the haemocompatibility of high density polyethylene (HDPE) modified by the radiation-induced grafting of polyacrylamide (the tests were carried out *in vivo*) showed³³ that after modification the thromboresistance of the polymer increases several fold. The haemocompatibility of segmented polyurethane after the radiation-induced grafting of *N*-vinylpyrrolidone has been investigated by Hongfei *et al.*⁷⁵ The influence of pH on the radiation-induced grafting of *N*-vinylpyrrolidone has been studied. The surface of the modified polymer is rough and its swelling in water increases exponentially with the amount grafted. An appreciable increase in thromboresistance is achieved in tests *in vivo* after the attainment of a 20% graft.

The haemocompatibility of modified silicone tubes (*in vivo* tests) has been investigated by Chapiro *et al.*⁵² The modification was carried out by the radiation-induced grafting of *N*-vinylpyrrolidone from a solution of the monomer in methanol or toluene. It was established that the haemocompatibility increases significantly after a 33% graft. On the other hand, the adsorption parameters of the proteins have a minimum at a certain thickness of the grafted layer. For example, in a study of the radiation-induced grafting of methoxypoly(ethylene glycol methacrylate) with 2-hydroxyethyl methacrylate by the direct method onto silicone rubber (Silastik), it was observed that the adsorption of fibrinogen has a minimum for an 8% graft.

The texture of the surface also influences the haemocompatibility. The radiation-induced graft polymerisation of *N,N*-dimethylacrylamide on polytetrafluoroethylene and the tetrafluoroethene–ethene copolymer (Aflon) has been investigated.^{27, 50} The influence of the monomer concentration and the dose rate on the haemocompatibility of the modified polymers obtained was studied. It was established that a decrease in dose rate from 1 to 0.1 kGy h⁻¹ increases the haemocompatibility (*in vivo* tests), which is associated with the increase in the smoothness of the surface. Collin *et al.*⁸⁵ studied the adhesion of red blood cells on polycationic carriers, which were prepared by modifying poly(vinyl chloride) grains by means of radiation-induced graft polymerisation of dimethylaminoethyl methacrylate; electron micrographs of the system with adhering cells have been published.

The radiation-induced graft polymerisation of acrylamide on polypropylene (PP) films by the post-effect method in order to render them hydrophilic is also promising.¹⁰⁰

Another method for the preparation of haemocompatible polymeric material involves the creation of hydrocarbon polymers (polyethylenes). For this purpose, vinylidene chloride was radiation-grafted from the gas phase onto polymeric materials with subsequent dehydrochlorination of the modified polymers obtained. These materials are used in endosurgery.^{101–104}

One of the methods of increasing haemocompatibility involves the use of radiation-induced graft polymerisation in order to obtain negatively charged surfaces of polymers containing carboxy, hydroxy and sulfo groups in the surface layers. The communication of Stever *et al.*¹⁰⁵ is devoted to the study of polyurethanes modified by the grafting of propanesulfonate functional groups. It was established in experiments *in vivo* that the haemocompatibility of such polyurethanes increases, the adhesion of blood cells to the surface is low, and the adhering cells do not undergo marked changes. The conversion of the adsorbed fibrinogen into fibrin is blocked and inhibited, *i.e.* the surface modification acts in approximately the same way as heparin — a blood anticoagulant. The radiation-induced grafting of the bisulfite derivative of acrolein mixed with acrylic acid followed by the sulfonation of the grafted layer with sulfurous acid and neutralisation of the sulfo and carboxy groups has been investigated.³¹ Modified materials with a thromboresistant effect were created.

Ratner *et al.*¹⁰⁶ described a study of the influence of the nature of the monomer used for radiation-induced graft polymerisation on the antithrombogenic properties of the modified materials. The authors studied the thrombogenic properties (*in vivo*) of the hydrogels obtained by the radiation-induced grafting of 2-hydroxyethyl methacrylate, acrylamide, a mixture of 2-hydroxyethyl methacrylate and ethyl methacrylate, and a mixture of 2-hydroxyethyl methacrylate and *N*-vinylpyrrolidone on LDPE. The influence of the composition of the copolymer and the water content on the deposition of thrombi is described in detail. It has been noted that the use of radiation-modified polyphosphazenes as haemocompatible materials is promising.⁷⁰ It has been shown⁷² that the number of attached thrombocytes diminishes with decrease in the interfacial free energy (*in vivo* tests in the canine carotid arteries of polyurethane tubes modified by the grafting of 2-hydroxyethyl methacrylate). The interfacial free energy decreases significantly after the grafting of 30% of 2-hydroxyethyl methacrylate. The coating of the graft polymer with albumin or γ -globulin decreases the adhesion of thrombocytes. In a study of the influence of the radiation-induced grafting of acrylamide on LDPE and PP tubes on the antithrombogenic properties, it was established that the best antithrombogenic properties are attained for a 30% graft (the wetting angle is $< 28^\circ$).^{27, 28, 41} The influence of the conditions in the graft polymerisation on the antithrombogenic properties has been demonstrated. When *N*-vinylpyrrolidone is grafted on polyurethane; the best antithrombogenic properties are also attained for a 30%–35% graft (experiments on the blood circulatory system of sheep).⁶⁹ The study of the radiation-induced grafting of acrylamide and acrylic acid on

LDPE and HDPE showed that the radiation-induced graft polymerisation of acrylamide takes place most effectively in the case of HDPE.^{24, 33, 107} The modified PE polymers with grafted polyacrylamide have a low wetting angle and exhibit enhanced antithrombogenic properties in tests *in vivo* in the carotid arteries of rats. The thrombus formation time increases several fold compared with pure PE.³³ The cross-linking of the polyacrylamide chains in the radiation-induced grafting of acrylamide together with the *N,N'*-methylenebisacrylamide cross-linking agent leads to a decrease in thromboresistance.²⁸

The radiation-induced graft polymerisation of *N,N*-dimethylacrylamide on natural rubber tubes has been studied in detail.^{92, 108} It was established that the best solvent for grafting is CCl₄ and that satisfactory haemocompatibility is manifested for a 30% graft.

The presence on the polymer surface of uniformly distributed negatively charged functional groups is important for increasing haemocompatibility.⁴⁷

Studies on the use of radiation-induced graft polymerisation for the modification of blood vessel prostheses made from polyester materials have been carried out in Poland (Institute of Applied Radiation Chemistry, Lodz). Acrylamide was used for the radiation-induced graft polymerisation. The influence of the dose and the monomer concentration on the process was investigated. Grafting results and an increase in hydrophilicity and a decrease in the gas-permeability of the prostheses. Tests on the prostheses demonstrated their fairly satisfactory biocompatibility. Thus acrylamide and its derivatives are promising monomers for increasing the hydrophilicity and biocompatibility of various polymeric materials. Another monomer which being vigorously employed for increasing biocompatibility is the highly hydrophilic monomer *N*-vinylpyrrolidone.^{48, 52, 58, 60, 67, 68, 75, 78} The radiation-induced grafting of *N*-vinylpyrrolidone is as a rule carried out by the direct method from its solutions in water, toluene, or methanol, using low radiation doses. As in the case of acrylamide, after the graft polymerisation of *N*-vinylpyrrolidone the hydrophilicity increases significantly with increasing amount of the grafted material. The antithrombogenic properties of polyesterurethane tubes modified by the radiation-induced grafting of 2-hydroxyethyl methacrylate have been investigated.¹⁰⁹ Tests *in vivo* showed that a considerable amount of graft is required for an appreciable enhancement of the antithrombogenic properties. The radiation-induced grafting of 4-vinylpyridine (4-VP) + 2-(*N,N*-diethylamino)ethyl methacrylate and 4-vinylpyridine + methacrylic acid mixtures on polyethylene catheters has been studied.¹¹⁰ The catheters were tested *in vivo*. The operational lifetime of the catheters depends significantly on the amount of graft. The haemocompatibility of the radiation-grafted PE polymers with poly(2-hydroxyethyl methacrylate) and poly(2,3-dihydroxypropyl methacrylate) has been studied.¹¹¹ In the investigation of the adhesion of thrombocytes on poly(vinyl chloride) with radiation-grafted polyacrylic acid, it was established that the adhesion of thrombocytes diminishes significantly with increase in the amount of graft and with decrease in the wetting angle.¹¹² One of the ways of enhancing the antithrombogenic properties of polymers involves the formation on their surfaces of polyelectrolyte complexes (PEC).^{113, 114} PEC are formed on the surfaces of polymers as a result of the interaction of the radiation-grafted poly(acrylic acid) with polyamines. The appearance of PEC gives rise to the formation of a microheterogeneous structure with alternation of hydrophilic and hydrophobic sections.

Lundell *et al.*⁴⁰ investigated the radiation-induced grafting on the surfaces of PP of mixtures of *N*-vinylpyrrolidone and acrylic acid and also vinyl acetate and crotonic acid. Pronounced antithrombogenic properties were attained after partial neutralisation of crotonic acid with alkali. It was concluded that the negative surface charge plays an important role.^{40–47} It was established⁴² that polymers with grafted poly(vinyl acetate)

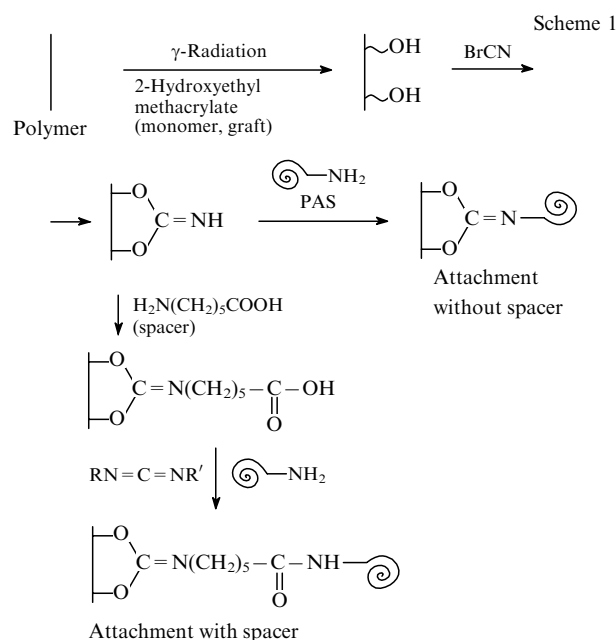
(with subsequent partial hydrolysis of the acetate groups) and *N*-methyl-*N*-vinylacetamide exhibit the best haemocompatibility.

The main conclusion which may be reached from the data described above concerning the use of hydrophilic monomers in order to enhance the antithrombogenic properties of polymers is that, with increase in the water content, thrombogenesis diminishes, but, in prolonged tests *in vivo* the minimum thrombogenesis is attained for a definite water content.¹⁰⁵ Radiation-induced grafting of *N*-vinylpyrrolidone as well as acrylamide and its derivatives affords good results. The presence of negatively charged groups on the surface is important.¹¹⁵ The adsorption of enzymes and blood cells diminishes with increase in the amount of graft.¹¹⁶ The presence of certain admixtures in the monomers employed for radiation-induced graft polymerisation influences significantly the haemocompatibility because it can alter the nature of the sorption of proteins.¹¹⁷

An extremely promising aspect of the preparation of antithrombogenic polymeric materials involves the modification of the surface of polymeric materials by radiation-induced graft polymerisation followed by the introduction into the modified layers of physiologically active substances (PAS), which act in the blood clotting stage. The radiation-induced grafting of monomers with active functional groups capable of reacting with the PAS is usually carried out for this purpose. The form of the bond between the PAS and the polymer (covalent, ionic, or physical capture) as well as the microenvironment of the PAS in the polymer are important. Radiation-induced graft polymerisation has been used^{63, 118–122} to obtain modified polymeric materials containing on the surface organic cations to which heparin is attached as a result of the formation of ionic bonds. As an example, styrene was grafted to different polymers with subsequent chloromethylation and quaternisation.¹¹⁸ 4-Vinylpyridine was used for radiation-induced grafting followed by quaternisation.¹¹⁹ Polyolefins, silicone rubber, and polytetrafluoroethylene have been used as the polymers. The modified polymers thus obtained exhibited a satisfactory haemocompatibility, possibly as a result of the partial washing away of heparin during use.¹²³ Another monomer which is employed for grafting to achieve ionic binding of heparin is 2-(*N,N*-diethylamino)ethyl methacrylate.^{124, 125} In all probability, the covalent binding of PAS is more promising. Radiation-grafted polymers with grafted poly(2-hydroxyethyl methacrylate) chains, which were activated by bromocyanogen with subsequent addition of streptokinase (lysis of fibrinogen on the surfaces), were obtained.¹²³ Another method of binding enzymes is the radiation-induced grafting of methacrylic acid followed by the application of the carbodiimide method in order to bind the BAS.^{123, 125} The employment of a spacer for the attachment of biomacromolecules to radiation-grafted polymers is very important in this procedure.¹²³

The binding of albumin to the radiation-grafted hydrogel, obtained by the radiation-induced grafting of a mixture of *N*-vinylpyrrolidone and 2-hydroxyethyl methacrylate, greatly increases when a spacer is used.^{123, 126} The process involving the attachment of PAS to modified polymer surfaces using bromocyanogen is illustrated in Scheme 1.¹²⁶

A significant increase in the sorption of albumin after the modification of polytetrafluoroethylene by the radiation-induced grafting of *N*-vinylpyrrolidone has been established.¹²⁷ The copolymers obtained by the radiation-induced grafting of acrylic acid, 2-hydroxyethyl methacrylate, a mixture of maleic anhydride and acrylic acid, as well as a mixture of acrylic acid and acrylamide, which are used for the immobilisation of human albumin, were grafted by Müller-Schulte and Horster.¹²⁸ In the covalent binding of albumin, bromocyanogen, hydrazine and glutaraldehyde, as well as 1-hydroxybenzotriazole, which ensures the maximum binding of human albumin, were used as the condensing agents. Glutaraldehyde has also been used for the covalent binding of PAS to radiation-grafted polyacrylamide.¹²³



Novel methods for the enhancement of haemocompatibility using radiation-induced graft copolymerisation have been described.^{23–26} One of them consists in the radiation-induced grafting on polymer surfaces of acrylic acid chlorides²³ and subsequent introduction of PAS.²⁶ Modified polymers containing on the surface heparin, various enzymes (for example, fibrinolysin), albumin, *etc.* have been obtained in this way. The simultaneous presence of heparin and enzymes on the polymer surface gives rise to effective thromboresistant properties of polymeric materials.²⁶ Reactive acid chloride groups may be obtained also by treating with thionyl chloride radiation-grafted copolymers with polyacrylic acid.¹²⁹ Another procedure consists in the radiation-induced grafting of allylamine on the polymer surface. The grafting of this monomer was achieved solely in the presence of orthophosphoric acid (suppression of the degradative chain transfer in the polymerisation of allylic monomers). Glutaraldehyde has been used to bind enzymes with an amino group.²⁵ Hydrazide groups may be used for the immobilisation of PAS. The hydrazidation of radiation-grafted copolymers of PE with acrylic monomers has been investigated.^{59, 130}

Methods have been developed for the modification of polymer surfaces by the radiation-induced grafting of macromonomers in the presence of hydrophilic monomers (acrylamide, *N*-vinylpyrrolidone, *etc.*) and a cross-linking agent.^{26, 131–133} The macromonomers may be obtained by introducing an active double bond into the PAS (heparin, enzymes) molecules in acylation by the chlorides of acrylic and methacrylic acids.^{25, 134–136} It was established that the acylation process does not affect the structure of the molecules of the PAS and its physiological activity. The macromonomers are capable of entering into the copolymerisation reaction with various monomers (acrylamide, *N*-vinylpyrrolidone).¹³⁴ The homopolymerisation of macromonomers leads to the formation mainly of products with a low degree of polymerisation.¹³⁶

The radiation-induced grafting of PAS macromonomers jointly with hydrophilic monomers on various polymeric materials afforded biospecific sorbents and modified materials employed in contact with blood. In the latter case, the polymer was modified by grafting the heparin macromonomer and trypsin or fibrinolysin as the fibrinolytic enzyme. It was shown that the polymers modified by a mixture of heparin and trypsin exhibit a higher haemocompatibility than the polymers containing only heparin. The increased thromboresistance of such materials, which has been investigated in experiments *in vitro* and *in vivo*, can be explained by the fact that heparin binds fibrinogen, which is

lysed by trypsin.^{137–139} The grafting of a mixture of acrylamide and the cholesterol ester of *N*-methacryloyl- ω -aminocaproic acid on PE has been investigated.¹⁴⁰ The graft results in the formation on the PE surface of a hydrophilic layer in which cholesterol groups are immobilised covalently. This led to the formation of modified polymers capable of adsorbing heparin selectively from the blood flow.

It has been shown^{89, 141} that the employment of *N*-methyl-*N*-vinylacetamide for the modification of polymers in order to increase their haemocompatibility is promising.^{89, 141} Diverse polymers, modified by grafting *N*-methyl-*N*-vinylacetamide, have been investigated in detail by various physicochemical methods.¹⁴¹ The haemocompatibility of ethylene–propylene rubber, modified by the radiation-induced grafting of acrylamide, *N*-vinylpyrrolidone, and 2-hydroxyethyl methacrylate, has been studied.^{142, 143} The experiments were performed *in vitro*. It was established that there is no linear relation between the amount of the graft and the hydrophilicity, on the one hand, and the degree of haemocompatibility, on the other. The relation is complex.

During recent years, there has been a growth of interest in the use of polyphosphazenes as biomaterials. The radiolysis of polyphosphazenes has been investigated¹⁴⁴ and it has also been established (in experiments *in vivo*) that the modification of polyphosphazenes by the radiation-induced grafting of *N*-vinylpyrrolidone makes it possible to increase their haemocompatibility.¹⁴⁵ The influence of the preliminary ⁶⁰Co γ -irradiation of polyurethane on its coating with albumin has been studied.¹⁴⁶

Radiation-induced graft polymerisation has been used to modify various polymers in order to accelerate the growth of endothelial cells on the surface.^{147, 148}

It has been suggested¹⁰ that the lack of success in the creation of polymeric materials designed for prolonged use in contact with blood within a living organism is associated with the inadequate knowledge of the biochemical processes occurring at the implant–blood interface and also with the attempts to relate to haemocompatibility to any one parameter of the surface (hydrophilicity, free surface, morphology, *etc.*).

Radiation-induced graft polymerisation has been used in a series of investigations^{64, 149, 150} to modify the surfaces of polymeric articles used in contact with blood and its components. Studies have been performed in recent years on the preparation of haemocompatible polymers by radiation-induced graft polymerisation initiated when polymers are irradiated with accelerated heavy ions.⁶²

Studies have been carried out on the use of radiation-induced graft polymerisation for the creation of various medical polymeric materials: blood vessel prostheses, intravenous catheters, implants, tissue-protecting, antiinflammatory, and ophthalmological materials, *etc.* The materials have been called ‘hydrografts’.¹⁵⁰

III. Preparation of special sorbents

Radiation-induced graft polymerisation is used in the creation of carriers for affinity chromatography,^{44, 61, 155} immunoabsorbents,^{156–165} and biospecific sorbents^{66, 148, 166, 167} and also for the growth of endothelial cells.^{147, 168–171}

Effective sorbents for affinity chromatography, obtained by modifying polyamide-6 beads by means of radiation-induced graft polymerisation, have been described. Mainly 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone, and acrylamide have been used as the monomers.^{44, 61, 151, 153–155} The conditions in the graft polymerisation and primarily the choice of solvents with specific solubility parameters, as well as the choice of swelling agents are very important.^{61, 154} Compared with the known sorbents (agarose), the capacity of the sorbents obtained is appreciably higher in the separation of low-density lipoproteins and antibody immunoglobulin G. The properties of the adsorbents may be varied by varying the conditions in the graft polymerisation. The carriers

obtained for affinity chromatography are cheaper compared with the known and expensive carrier — sepharose with protein A.⁶¹

The sorbents obtained may be used for the removal of excess cholesterol in patients suffering from cholesterinemia.⁶¹

It has been established that, when sorbents based on polyamide-6 modified by radiation-induced graft polymerisation are used, the amount of lectin extracted from mistletoe increases appreciably. Sorbents with immobilised urease may be used for the rapid determination of the content of urea in kidney diseases. The method is based on the continuous and rapid enzymic hydrolysis of urea and the determination of ammonia.¹⁵⁵

The modification of polystyrene plates by the radiation-induced grafting of monomers containing hydrazide groups has been described.¹⁵⁶ The modified plates adsorbed effectively immunoglobulin E and low-molecular proteins. In order to increase the hydrophilicity of polystyrene, it is ⁶⁰Co γ -irradiated. By employing the modified polystyrene plates, it is possible to determine the concentration of immunoglobulin E (down to 0.1 μ g ml^{–1}).¹⁵⁶

The modification of LDPE, poly(vinyl chloride) and polystyrene by the radiation-induced graft polymerisation of methacrylic acid and acrylamide with subsequent immobilisation of the Brucella antigen resulted in the formation of systems for diagnostic tests (ELISA). The sensitivity was improved and the reactivity of the antibodies increased significantly.¹⁶⁴

Methods have been developed for the modification of agarose,⁶⁶ sepharose, and sephadex¹⁶⁶ by the radiation-induced grafting of *N*-acryloyloxysuccinimide with subsequent addition of bovine serum albumin (BSA). The separation of D,L-tryptophans was studied.¹⁶⁶

Radiation cross-linked poly(vinyl alcohol) has been used in affinity chromatography. The carriers based on this polymer are distinguished by a satisfactory morphology, biocompatibility, and a high capacity.^{152, 153}

Blood detoxicants based on modified polypropylene fibres have been obtained.¹⁴⁰ Specific sorbents for the removal of heparin have been created with the aid of radiation-induced grafting.¹⁴⁰

Radiation-induced graft polymerisation has been used to modify various polymers in order to form on their surface a coating comprising endothelial cells.

This problem has been examined in greatest detail by Kirkpatrick *et al.*¹⁴⁷ The radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone and 2-(*N,N*-dimethylamino)ethyl methacrylate on a whole series of polymers (LDPE, polytetrafluoroethylene, polyamide, *etc.*) has been investigated. It was established that the conditions in the graft polymerisation (solvent, composition of copolymers, *etc.*) are very important for the successful growth of cells. Electron micrographs of the surface with layers of endothelial cells have been obtained. It was noted that the presence of OH groups on the surfaces of polymers is important for cell growth.

Methods have been devised for the modification of polymeric materials, as a result of the application of which the polymers can undergo a change in their hydrophilic and hydrophobic properties under the influence of small changes in temperature. This makes it possible to regulate the adhesion and viability of the cultures.¹⁶⁸

IV. Synthesis of polymeric carriers for medicinal preparations

Radiation-induced polymerisation is used in the synthesis of polymeric carriers for medicinal preparations (antibiotics, antiseptics, *etc.*). The following advantages of the radiation initiation of polymerisation in the synthesis of polymeric carriers for medicinal preparations compared with ‘material’ initiation have been noted. Firstly, fairly pure polymers are obtained (without initiator residues). Secondly, it is possible to regulate comparatively easily the molecular-mass characteristics of the polymers by

varying the radiation dose rate. Thirdly, in a number of instances the yield of the polymers is much higher than the yield obtained on initiation with 'material' initiators.

Radiation-induced polymerisation has been used in a series of studies^{172–175} for the creation of copolymers based on *N*-vinylpyrrolidone with undecenoic, oleic, and crotonic acids. Modifying agents for PAS, ensuring a fairly intense hydrophobic interaction between the copolymer and the PAS, are obtained in this case. On initiation using 'material' initiators, it is impossible to obtain copolymers in a sufficiently high yield. The radiation-induced copolymerisation of *N*-vinylpyrrolidone with undecenoic and oleic acids in ethanol for doses of 50–150 kGy (dose rates of 0.23 and 0.04 Gy s⁻¹) has been investigated.¹⁷² It was established that the yield of the copolymer and the rate of copolymerisation depend significantly on the mixture composition, a statistical copolymer without adjacent COOH units being formed. The relative reactivity of the acids is zero, while the reactivities of *N*-vinylpyrrolidone vary in the ranges $0.61 < r < 0.94$ for undecenoic acid and $0.90 < r < 1.31$ for oleic acid. The copolymer units are enriched in *N*-vinylpyrrolidone.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with crotonic acid in ethanol at different dose rates in the range 0.25–3.26 Gy s⁻¹ has been investigated.¹⁷³ In the initial stage, the rate of polymerisation is proportional to the radiation dose rate raised to the power 0.5, but, with increase in the degree of conversion, the above parameter tends to 0.8. With increase in dose rate and degree of conversion, the molecular mass of the copolymer diminishes. The composition of the copolymer is independent of the dose rate and its molecular mass may be regulated by varying the dose rate. Copolymers with a viscosity-based mean molecular mass of 1.2×10^4 – 7.0×10^4 have been obtained.

The dependence of the molecular mass and the molecular mass distribution in the radiation-induced copolymerisation of *N*-vinylpyrrolidone with crotonic acid (CA) in ethanol or 2-propanol on the dose for a constant monomer ratio *N*-vinylpyrrolidone:CA = 85:15 has been examined.¹⁷⁴ It was established that the molecular mass distribution can be regulated by selecting the radiation dose. It was shown that in alcohols the yield of the copolymer is high (93%–98%) for a dose of 4.5×10^4 Gy. The radiation-chemical yield of the copolymerisation is $(6–7) \times 10^3$ molecules per 100 eV (dose rate 0.28 Gy s⁻¹). The radiation-induced copolymerisation of *N*-vinylpyrrolidone with allylamine and 2-(*N,N*-dimethylamino)ethyl methacrylate in aqueous organic solvents and the properties of the copolymers have been studied. In this process, the copolymers are obtained in a high yield and with a narrow molecular mass distribution in the molecular mass range from 10^3 to 4×10^6 .¹⁷⁵

Thus copolymers based on *N*-vinylpyrrolidone can be obtained by the radiation-induced polymerisation method with a fairly high yield and their molecular mass characteristics may be varied in the required direction by selecting the polymerisation conditions. The rate of polymerisation depends significantly on the mixture composition, while the composition of the copolymer is independent of the dose rate. A distinctive feature of these copolymers is that, together with the strongly hydrophilic component (carboxy groups, *N*-vinylpyrrolidone units), the polymer chain contains a significant hydrophobic component (the hydrocarbon part of the carboxylic acids). Such copolymers are non-toxic.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with allyl alcohol in ethanol or 2-propanol at a dose rate of 2 Gy s⁻¹ (for doses in the range 30–200 kGy) has been studied by Solovskii *et al.*¹⁷⁶ The radiation-induced and 'material' copolymerisations were compared. The yields in the radiation-induced copolymerisation exceed by a factor greater than 2 the yields in the 'material' polymerisation. The yield of the copolymer is 50%–90% and diminishes with increase in the concentration of allyl alcohol. The maximum yield occurs for a 30% content of the comonomers in the alcohol. Conditions for the preparation of

copolymers with a low molecular mass and a narrow molecular mass distribution have been found.

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with vinyl acetate at 5 °C and a dose rate of 14.5 Gy min⁻¹ has been studied^{177,178} and the copolymerisation constants have been determined.

Panarin *et al.*,¹⁷⁹ investigated the radiation-induced polymerisation of *N*-vinylpyrrolidone under various conditions. The molecular-mass characteristics of *N*-vinylpyrrolidone were determined. An important advance in radiation-induced polymerisation is in this case the possibility of the fine regulation of the molecular-mass characteristics, which is particularly important for this polymer, used as a blood plasma substitute.

The carriers based on *N*-substituted acrylamide and methacrylamide are extremely interesting. The water content in these hydrogels depends significantly on the external conditions (temperature, pressure, *etc.*), which makes it possible to increase the effectiveness of the action of the medicinal preparations immobilised in them.¹⁸⁰

The study of methacrylic acid–triethylene glycol dimethacrylate copolymers as carriers for medicinal substances (insulin) demonstrated their resistance to the action of the acid medium in the stomach and the rapid liberation of the hormone on entering the intestine.¹⁸¹

The radiation-induced copolymerisation of *N*-vinylpyrrolidone with various aminoacrylates and methacrylates has been investigated. Polymeric carriers for BAS with a high molecular mass have been obtained in a satisfactory yield.^{182,183}

The radiation-induced polymerisation of hydrophilic monomers is used for the creation of porous polymeric carriers for the immobilisation of insulin and interleukin. The pore dimensions and the rate of liberation of medicinal substances are regulated by the polymerisation conditions.¹⁸⁴ The radiation-induced copolymerisation of 2-hydroxyethyl methacrylate and methacrylic acid is used to prepare carriers for contraceptives.¹⁸⁵

The radiation-induced polymerisation of acrylamide and *N*-vinylpyrrolidone in aqueous solutions has been investigated.¹⁸⁶ The influence of the dose rate and the concentration of monomers on the rate of polymerisation was studied. The role of the water radiolysis products in the initiation of polymerisation was established and the dependence of the gel formation dose on the concentration of monomers was determined.

The methods for the preparation and properties of antimicrobial polymers have been described in a monograph.¹⁸⁷

Foss and Ebersol¹⁸⁸ used the radiation-induced polymerisation of acrylamide for the preparation of thin (0.25–1 mm) films of polyacrylamide gels with a specified pore distribution. The standard size distribution of pores was ensured by the conditions in the ⁶⁰Co γ -irradiation with computer control. The films were used for the high-resolution separation of proteins by electrofocusing and electrophoretic methods.

The employment of radiation-induced polymerisation for the preparation of polymer microspheres occupies a special place. The formation of microspheres from various acrylates as a result of radiation-induced polymerisation has been examined in a number of studies.^{189–200} The diameter of the microspheres increases with increasing hydrophilicity of the monomer¹⁸⁹ and the nature of the solvent is also important.¹⁹⁰ Polymer microspheres containing amino acids have been obtained with the aid of radiation-induced polymerisation. The microspheres have been used for immunochemical assay in relation to malaria.¹⁹¹

The preparation of microspheres by the radiation-induced copolymerisation of diethylene glycol dimethacrylate with acrylamide has been described in review.¹⁹² The size of the microspheres was 10–10 000 Å. The microspheres are used mainly for immunoassay. The synthesis of microspheres based on polyacrylamide, poly(2-hydroxyethyl methacrylate), poly(methyl methacrylate), and poly(acrylic acid) by radiation-induced suspension polymerisation in methanol has been described.¹⁹⁴ The radiation-

induced grafting of 2-hydroxyethyl methacrylate, acrylamide, and their mixtures on microspheres has been studied.¹⁹⁴

The preparation of microspheres based on polyacrolein, on the surface of which there are aldehyde groups which react readily with proteins, is of significant interest.^{195–197} Cross-linked polyacrolein has been synthesised by the radiation-induced polymerisation of acrolein in bulk or in a water–acetone mixture at temperatures ranging from -15 to 25°C . The yield of this polymer depends on the reaction conditions and may reach 100%. The principal polyacrolein unit is a six-membered oxygen-containing ring and the interchain cross-links are formed by ester bonds; furthermore, free aldehyde groups are present in polyacrolein. It has been established by electron microscopy that polyacrolein consists of microspheres with a particle size of $1\text{--}30\text{ }\mu\text{m}$. The size of the particles depends on the conditions in the preparation of the polymer. The formation of microspheres in the radiation-induced copolymerisation of acrolein with hydroxyethyl methacrylate or poly(ethylene glycol dimethacrylate) in 1% PVA solution at -78°C has been studied.¹⁹⁶ The yield of the copolymers depends on the content of the vinyl monomer. The size of the microspheres increases with increase in the concentration of the vinyl monomer. The properties of the microspheres obtained, containing aldehyde groups, have been investigated.¹⁹⁷ Microspheres of the ‘core–shell’ type, having aldehyde groups on the surface, have been synthesised with the aid of the radiation-chemical modification of polystyrene particles ($0.6\text{ }\mu\text{m}$ in diameter) by acrolein. The structure and properties of the polymers obtained were studied by various methods.¹⁹⁸ It was established that the content of aldehyde groups is 60% of the theoretically possible. A structure was proposed for graft polyacrolein. It was shown that the radical polymerisation of acrolein involves mainly the vinyl bond. The form of the microspheres does not change as a result of the polymerisation.¹⁹⁹

The principal advantages of the preparation of polymer microspheres with the aid of radiation-chemical methods are the high purity of the product (the absence of impurities arising from the initiator) and the possibility of carrying out the polymerisation under a wide range of conditions (temperature, rate of initiation), and this makes it possible to regulate the size of the microspheres comparatively readily. It is sometimes possible to achieve relatively easily the radiation-induced cross-linking of the microspheres, which is difficult to do by traditional methods.

Thus the radiation-induced polymerisation is a promising method for the creation of polymeric materials used as carriers for medicinal preparations. In many instances, it is possible to achieve the synthesis of unique copolymers, the preparation of which with the aid of ‘material’ initiators is very difficult. The vast majority of studies have been devoted to the synthesis of copolymers based on *N*-vinylpyrrolidone. The choice of the solvent, of the radiation dose and of the radiation dose rate is very important for radiation-induced polymerisation, determining the yield of the copolymer and its molecular-mass characteristics.

V. Immobilisation of biologically active substances

1. Immobilisation of enzymes

During recent years, radiation-induced polymerisation has been used for the immobilisation of various BAS in polymer matrices. Such a process is carried out in order to fix the BAS for reuse in order to achieve economies in their employment (some are very expensive), in order to stabilise the BAS in relation to thermal influences, solvents, and pH, in order to prepare polymeric articles of different shape (films, tablets, needles, cylinders, *etc.*), for the controlled liberation of BAS under the conditions of a specific application, and for the employment of effects associated with the polymer matrix (strength, rheology, *etc.*). The immobilisation of BAS in polymer matrices is achieved by the joint polymerisation of monomers mixed with the BAS or by the covalent attachment of these compounds to different polymers with active functional groups. Reviews have been devoted to various aspects of the

preparation of polymeric biomaterials by radiation-induced polymerisation and grafting.^{201–211} A wide range of substances have been used as the BAS: enzymes,^{212–265} yeast cells,^{266–270} haemoglobin,^{271–275} anticancer preparations,^{276–279} chloroplasts,^{280,281} various medicines, antibodies, microorganisms and microbial cells.^{281–297} Polymeric biomaterials with immobilised BAS have a wide range of applications. Allowance for the specific features of particular spheres of their application is important. Table 2 presents data on the immobilisation of BAS using radiation-chemical methods.

The radiation-induced polymerisation for the immobilisation of BAS has the following advantages.^{201,202}

1. The possibility of carrying out the process over a wide range of conditions, including polymerisation at low temperatures of supercooled viscous monomers, solid monomers and multiphase systems.
2. A fairly wide selection of monomers for polymerisation.
3. A decrease in the inhibiting effect of oxygen and other impurities.
4. The absence of residual amounts of the catalyst and the unpolymerised monomer in the polymer. The latter is very important, since a partly unpolymerised monomer has a toxic effect, particularly in the immobilisation of cells.
5. The ease of cross-linking to different extents by selecting the dose absorbed.
6. The comparative simplicity of the preparation of porous and complex composite structures.
7. The simplicity of the manufacture of preparations of any arbitrary shape (tablets, cylinders, needles, *etc.*).
8. A decrease in the deactivation of unstable BAS in the polymer.
9. The high productivity of the immobilisation apparatus when electron accelerators are used as the sources of radiation.
10. The possibility of preparing ultrathin particles and membranes.

There are three main immobilisation methods: covalent binding of the BAS to the polymer — the chemical method, ionic binding or physical adsorption of the BAS, and physical capture of BAS in the polymer. An advantage of the chemical method is the solid-phase fixation of the BAS and the impossibility of its removal on prolonged use. The disadvantage of the method are as follows: a comparatively low yield of the activity of the BAS (a significant loss of activity in the immobilisation process), an appreciable selectivity in relation to the BAS reaction conditions, and the difficulty of its employment for the immobilisation of microorganisms. The chemical immobilisation method works as a result of the formation of chemically reactive functional groups in

the polymer, mainly $-\text{COOH}$, $-\text{OH}$, $-\text{NH}_2$, $-\text{C}=\text{O}$ and others

capable of covalent binding of the BAS. The reactive functional groups are introduced into the polymer by radiation-induced graft polymerisation (for more details, see Section II as well as other communications 2, 4, 18, 26, 210, 211). Mainly the immobilisation of BAS as a result of physical capture, ionic binding, or physical adsorption in polymer matrices is considered in this section. The advantages of the physical capture method are as follows: comparative ease of application, a fairly high reactivity and universality of the BAS (BAS without specific functional groups — various microorganisms, cells, *etc.* — may be used for immobilisation), and the possibility of employing monomers with a wide range of hydrophilic and hydrophobic properties. The physical capture of the BAS in polymers is achieved by means of the radiation-induced polymerisation of the monomer mixed with the BAS.

Radiation-induced polymerisation for the immobilisation of enzymes was first described by Dobo,²¹² who obtained immobilised enzymes in polyacrylamide matrices by the solid-phase polymerisation of acrylamides mixed with the enzyme. Subsequently Kaetsu and co-workers^{201–205} developed a method for the immobilisation of BAS mixed with monomers capable of

Table 2. Immobilisation of BAS in polymer matrices with the aid of radiation-induced polymerisation.

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — trypsin</i>			
Acrylamide	radiation-induced polymerisation of acrylamide mixed with the enzyme	solid-phase polymerisation using ^{60}Co γ -radiation	212
2-Hydroxyethyl methacrylate, tris(hydroxymethyl)propane triacrylate, 2-hydroxyethyl acrylate, poly(ethylene glycol diacrylate), methoxypoly(ethylene glycol methacrylate)	radiation-induced polymerisation of monomers mixed with aqueous BAS solution; irradiation was carried out at -78°C with a dose of 10 kGy	polymerisation resulted in the formation of a porous structure; the influence of pore size on enzyme activity and the thermal stability of the immobilised trypsin were investigated	216
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation on polyethylene powder, hydrolysis of the copolymer and the attachment of the enzyme to the functional groups with the aid of the carbodiimide method	the influence of pH on the stability of the enzyme was studied	218
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation on natural rubber by the preirradiation method	the activity of the immobilised enzyme was studied	221
<i>p</i> -Nitrostyrene	direct radiation-induced graft polymerisation of <i>p</i> -nitrostyrene on polypropylene and poly(vinyl chloride)	the nitro groups in the graft copolymer are converted into isothiocyanate groups	219
	radiation-induced grafting of <i>p</i> -nitrostyrene to different polymers; radiation-induced grafting of polystyrene with subsequent nitration of polystyrene	the mechanism of the action of additives accelerating the graft polymerisation was examined	220
Acrylic acid, acrylonitrile, 2-hydroxyethyl methacrylate, <i>N</i> -vinylpyrrolidone, acrylamide	radiation-induced graft polymerisation using a wide range of monomers; trypsin was attached covalently with the aid of the carbodiimide method or glutaric dialdehyde	preparation of polymer membranes; the study of prospects for the employment of these membranes in the milk industry in order to diminish the allergenic effect of milk (decomposition of proteins with a low molecular mass)	217
<i>BAS — trypsin, glucose oxidase</i>			
2-Hydroxyethyl methacrylate	radiation-induced graft polymerisation by three different methods	it was established that the immobilised enzymes are stable over a wide pH range	222
<i>BAS — α-chymotrypsin, ribose, urease, ribonuclease</i>			
Methacrylic acid esters, acrylamide, and its derivatives	radiation-induced polymerisation of monomers in a mixture with aqueous enzyme solutions; irradiation at -20°C ; dose 5 kGy		224
<i>BAS — α-chymotrypsin, trypsin, glucose oxidase, papain</i>			
Methacrylic acid, 2-hydroxyethyl methacrylate	radiation-induced graft polymerisation of 2-hydroxyethyl methacrylate and methacrylic acid on polyethylene	covalent immobilisation on the grafted chains	259
<i>BAS — α-chymotrypsin, trypsin, fibrinolysin</i>			
Acrylic acid chloride, allylamine	radiation-induced graft polymerisation of acrylic acid chloride on various monomers with subsequent addition of the BAS <i>via</i> the acylation of the acid chloride group; graft polymerisation of allylamine and attachment of the BAS with the aid of glutaric dialdehyde	covalent binding of the BAS	215
<i>BAS — urease</i>			
Acrylamide	starch with grafted polyacrylamide	the dependence of the enzyme activity on the method of application was studied	213
Poly(dimethoxyethoxy)phosphazene	irradiation of enzyme in polymer solution	retention of 80% of enzyme activity	223
<i>BAS — glucoamylase</i>			
Poly(ethylene glycol diacrylate), 2-hydroxyethyl acrylate, tris(hydroxymethyl)propane triacrylate	irradiation by electron accelerator; dose 50 kGy	specimens of planar polymeric materials with immobilised enzymes were obtained	234

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — glucoamylase</i>			
Hydroxyalkyl methacrylate, poly(ethylene glycol diacrylate)	radiation-induced polymerisation at a low temperature	the influence of the nature of the monomer on the character of the immobilisation of the enzyme was studied	252, 253
2-Hydroxyethyl methacrylate, <i>N</i> -vinylpyrrolidone, acrylamide	radiation-induced copolymerisation of 2-hydroxyethyl methacrylate with comonomers at a low temperature	immobilisation of enzymes in different copolymers; the influence of the composition of the copolymer on the immobilisation was studied	255
2-Hydroxyethyl methacrylate, diethylene glycol dimethacrylate	radiation-induced polymerisation at reduced temperature of the monomers mixed with an aqueous enzyme solution	the distribution of the enzyme in the polymer matrix and the rate of its liberation were investigated	235
Poly(vinyl alcohol) (PVA)	irradiation of aqueous PVA solutions in the presence of the enzyme up to a dose of 40 kGy	the influence of the irradiation dose on the enzyme activity was studied	236
	PVA was mixed with the enzyme and irradiated on an electron accelerator up to doses of 60–360 kGy	a linear accelerator with a beam energy of 7.5 MeV was used; a PVA strip 20 cm wide and containing the enzyme was irradiated	237
<i>BAS — glucoamylase, β-galactosidase, invertase</i>			
Acrylamide, <i>N,N</i> -dimethylacrylamide, 2-hydroxyethyl methacrylate, <i>N</i> -vinylpyrrolidinone, acrylic acid salts, acrylic acid	electron irradiation on accelerators was employed; radiation-induced grafting of poly(acrylic acid) with subsequent immobilisation of the BAS	the influence of the irradiation dose on the rate of liberation of the enzyme was studied, methods were developed for the preparation of membranes with immobilised enzymes, and procedures were devised for the preparation of spherical particles with immobilised enzymes	225–229
<i>BAS — glucoamylase, AFP-antibodies</i>			
Poly(ethylene glycol dimethacrylate), poly(ethylene glycol diacrylate), tris(hydroxymethyl)propane triacrylate	irradiation on an electron accelerator of thin monomer films containing the BAS at temperatures from –75 to 35 °C and for electron energies of 150–300 KeV	preparation of polymer membranes containing the BAS; the influence of the monomer concentration and of the dose on the enzyme activity was studied	233
<i>BAS — glucoamylase, invertase, β-galactosidase</i>			
Acrylamide	irradiation of enzymes in aqueous acrylamide solution	the method of preparation of the specimens was described in detail; the irradiation doses are given	256
<i>BAS — amylase, yeast cells</i>			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) on low- and high-density polyethylene by the direct method from aqueous solution	covalent binding of the BAS	232
<i>BAS — protease (<i>Bacillus mesentericus</i>)</i>			
Acrylic acid, allyl alcohol	direct grafting of the monomers on polyethylene	preparation of polymers with hydrazide and azide groups; covalent binding	214
<i>BAS — lipase</i>			
2-Hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, poly(ethylene glycol diacrylate), tris(hydroxymethyl)propane trimethacrylate	radiation-induced polymerisation in the presence of the enzyme at a low temperature; dose 10 kGy	the influence of the structure of the polymer matrix and the monomer concentration on the enzyme activity was studied	238
<i>BAS — cellulase</i>			
Hydroxylated acrylates	radiation-induced polymerisation at a low temperature	membranes with different monomer concentrations and different hydrophilicities were prepared	240
Poly(ethylene glycol diacrylate)	radiation-induced polymerisation at a low temperature; dose 10 kGy	the structure and nature of the pores in the polymer matrix and its influence on the enzyme activity were studied	

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — cellulase</i>			
Glycidyl methacrylate, polystyrene	radiation-induced polymerisation of glycidyl methacrylate in the presence of polystyrene at -78°C with subsequent immersion in cooled methanol; dose 10 kGy	polymer microspheres were obtained; the influence of the conditions in the preparation on the number and diameter of the microspheres were studied	242
Dispersed polyurethane prepolymer	toluylene and 2-hydroxyethyl methacrylate were mixed; the mixture was kept for several minutes and treated with an aqueous solution of cellulase; irradiation at -78°C ; dose 10 kGy	disperse particles of different size were obtained	243
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at -78°C in the presence of aqueous enzyme solution	discs 1 mm thick were prepared; the influence of the thickness of the disc and the monomer concentration on the enzyme activity was studied	244
2-Hydroxyethyl methacrylate, tetra-ethylene glycol diacrylate	radiation-induced polymerisation of monomers on the surfaces of tubes	tubular enzyme reactors were created	251
2-Hydroxyethyl methacrylate, neopentyl glycol dimethacrylate	radiation-induced polymerisation in the presence of sodium acetate	polymer particles 50–1000 μm in diameter were obtained; the influence of various factors on the enzyme activity was studied	254
<i>BAS — cellulase, cellobiase</i>			
2-Hydroxyethyl methacrylate	radiation-induced polymerisation of aqueous monomer solution in the presence of the enzyme; irradiation at -78°C	discs 1–2 mm thick were prepared; the influence of added silica gel and poly(ethylene glycol) on the enzyme activity was studied	239
Acrylamide	radiation-induced polymerisation of acrylamide	the hydrolysis of plant raw material with the aid of immobilised cellulase is described in detail; methods for the determination of the activity of cellulolytic enzymes are described	245
<i>BAS — catalase</i>			
Acrylamide	radiation-induced polymerisation of the monomer at -78°C in the presence of <i>N,N'</i> -methylene-bisacrylamide	the enzyme was immobilised on polyacrylamide gels modified by acyl azide	246
<i>BAS — glucose oxidase</i>			
2-Hydroxyethyl methacrylate	the enzyme was deposited on a nylon net in the presence of the monomer with subsequent radiation-induced polymerisation	network materials with immobilised enzymes were obtained	248
Acrylic acid, methacrylic acid	radiation-induced graft polymerisation of the monomers on polyethylene	immobilisation using the carbodiimide method	263
<i>BAS — glucose oxidase, α-amylase</i>			
Acrylamide	irradiation of the enzyme mixed with an aqueous acrylamide solution	dose < 5 kGy	296
<i>BAS — glucose oxidase, glucose peroxidase, urokinase</i>			
Hydrophilic monomers	radiation-induced polymerisation at -78°C ; dose 5 kGy	immobilisation of the BAS on the surfaces of polyethylene and poly(vinyl chloride) tubes	249
<i>BAS — penicillin acylase</i>			
Acrylates, <i>N</i> -vinyl-pyrrolidone	irradiation of comonomers mixed with the BAS in the presence of a cross-linking agent — tris(hydroxymethyl) propane methacrylate; irradiation time 3.5 h at -78°C ; dose rate 0.65 Gy s^{-1}	the influence of the nature of the monomer and of the degree of its conversion on the amount of immobilised acylase and the rate of its liberation were investigated	250
<i>BAS — asparaginase</i>			
Methacrylic acid	radiation-induced grafting of poly(methacrylic acid) on porous polypropylene fibres	covalent immobilisation	257
	Radiation-induced grafting by the preirradiation method on ethylene–propylene rubber, a polypropylene film, and a porous polypropylene fibre	ditto	258

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — β-galactosidase, pepsin, invertase, phosphatase</i>			
Acrylic acid	radiation-induced graft polymerisation of acrylic acid from aqueous solution on polyamide powder	the modified polyamide powder was used for the immobilisation of enzymes	260
<i>BAS — tryptophan, insulin, albumin, lysozyme, peptides</i>			
2-Hydroxyethyl methacrylate + poly(ethylene glycol)	radiation-induced polymerisation	the influence of the molecular mass of the BAS on the rate of their liberation was investigated	230
<i>BAS — invertase, phosphatase, albumin, trypsin, galactosidase</i>			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) on polyethylene	activation of the graft copolymer by SOCl_2 and attachment of the BAS via the acid chloride groups or by means of the carbodiimide method	262
<i>BAS — albumin, β-galactosidase, phosphatase</i>			
Acrylonitrile	radiation-induced grafting of polyacrylonitrile to nylon	hydrolysis of the graft copolymer and the attachment of the enzymes to the hydrolysed groups; immobilisation of the enzymes in the nylon polymeric materials	265
<i>BAS — horseradish peroxidase</i>			
Acrylic acid, acrylamide	grafting on polyurethanes by the preirradiation method in air; grafting from aqueous solution in the presence of Fe^{2+} ions	immobilisation of the enzyme on the graft copolymers	261
<i>BAS — yeast cells</i>			
Methoxypoly(ethylene glycol methacrylate), glycol methacrylate, hexanediol methacrylate, 2-hydroxyethyl methacrylate	radiation-induced polymerisation of monomer mixtures; irradiation at -78°C	the influence of the composition of the mixture of monomers on the activity of the cells was studied	266
2-Hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, <i>N,N</i> -dimethylacrylamide, <i>N</i> -vinylpyrrolidone methoxypoly(ethylene glycol methacrylate)	polymer hydrogels were obtained by the radiation-induced polymerisation of the monomers in water. Irradiation with ^{60}Co γ -rays at -78°C	the adhesion method for immobilisation on the prepared polymeric materials was used; electron micrographs of the polymer particles are presented; the fermentation of glucose was investigated and the yield of ethanol was determined as a function of the nature of the polymer used for immobilisation	267
Methoxypoly(ethylene glycol methacrylate), 2-hydroxyethyl methacrylate	radiation-induced polymerisation; irradiation at -78°C ; dose 10 kGy	adsorption of the cells on porous polymeric carriers	268
Tetraethylene glycol dimethacrylate	the monomer was deposited on muslin and irradiated with ^{60}Co γ -rays	the specific surface of the modified muslin is important for the enzyme activity	269
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at a low temperature; dose 10 kGy	specimens of different forms were prepared	270
<i>BAS — haemoglobin</i>			
2-Hydroxyethyl methacrylate	radiation-induced polymerisation of the monomer in the presence of haemoglobin	the interaction of haemoglobin with CO and O_2 was investigated	271
Phospholipids with double bonds	radiation-induced postpolymerisation of the phospholipids; preparation of vesicles 200 nm in size	the radiation-stability of haemoglobin within the vesicles was studied	274, 275
<i>BAS — CO-haemoglobin</i>			
2-Hydroxyethyl methacrylate, tetraethylene glycol dimethacrylate	irradiation of the monomers jointly with haemoglobin at -5°C ; dose 5–15 kGy; preparation of semisynthetic blood	the CO-haemoglobin phase was obtained immediately after the removal of blood from the animal and oxyhaemoglobin was saturated with CO; CO-haemoglobin does not induce antibody–antigen reactions; a polymer film containing 0.4% of CO-haemoglobin was prepared	272
2-Hydroxyethyl methacrylate	radiation-induced polymerisation at a low temperature	the absorption of oxygen was studied	273

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — antitumour preparations (Ara-C)</i>			
Methyl methacrylate, ethyl methacrylate, butyl methacrylate, 2-hydroxyethyl methacrylate	the immobilisation of anticancer preparations in polymer matrices obtained by radiation-induced polymerisation at room temperature was studied	the influence of various factors on the rate of liberation of medicinal substances from polymer matrices was investigated	231
2-Hydroxyethyl methacrylate with added hydrophobic monomers	radiation-induced polymerisation of the hydrophilic monomer with added hydrophobic monomers	the influence of various factors on the rate of liberation of Ara-C was investigated; it was established that the addition of hydrophobic monomers diminishes the rate of liberation of Ara-C	295
<i>BAS — antitumour preparations (Ara-A)</i>			
Methyl ester of <i>N</i> -acryloyl-L-proline	radiation-induced polymerisation	immobilisation of Ara-A in a thermosensitive gel	247
<i>BAS — antitumour preparations: mitomycin, 5-fluorouracil, 1-(2-tetrahydrofuryl)-5-fluorouracil</i>			
2-Hydroxyethyl methacrylate	immobilisation of anticancer preparations in a poly(2-hydroxyethyl methacrylate) matrix	the effect of ionising radiation on the anticancer preparation was investigated	264
<i>BAS — antitumour preparations: mitomycin, adriamycin, 1-(2-tetrahydrofuryl)-5-fluorouracil</i>			
Diethylene glycol dimethacrylate, tris(hydroxymethyl)propane trimethacrylate	radiation-induced polymerisation at -78°C	the rate of liberation of medicinal substances from polymer matrices was investigated	276
<i>BAS — antitumour preparations: mitomycin, bleomycin, 5-fluorouracil</i>			
Diethylene glycol dimethacrylate	irradiation at -78°C of the monomer in a mixture with anticancer preparations and added polystyrene, poly(methyl methacrylate), polyvinylformal, and poly(ethylene glycol); dose 20 kGy	the specimens were prepared in the form of discs, a powder, etc.; the rate of liberation of medicinal substances from the specimens was studied	277
<i>BAS — antitumour preparation: methoxyprogesterone acetate</i>			
Poly(ethylene oxide)	radiation-induced crosslinking of poly(ethylene oxide) with incorporation of the BAS	tests <i>in vivo</i> and <i>in vitro</i>	278
<i>BAS — antitumour preparation: narciclasine</i>			
2-Hydroxyethyl methacrylate, tris(hydroxymethyl)propane trimethacrylate, methyl ester of poly(ethyleneglycol)	radiation-induced polymerisation; additives regulate the rate of liberation of the medicinal substance	tests <i>in vivo</i> ; the structure of the matrix was investigated	279
<i>BAS — chloroplasts</i>			
2-Hydroxyethyl methacrylate, poly(ethylene glycol) dimethacrylate, methoxypoly(ethylene glycol methacrylate), glycidyl methacrylate, tetraethylene glycol diacrylate, tetraethylene glycol dimethacrylate	radiation-induced polymerisation at -78°C ; dose 10 kGy	the influence of the nature of the monomer on the activity of chloroplasts and the distribution of the chloroplasts in the polymer matrix were investigated	280
<i>BAS — chloroplasts from spinach</i>			
2-Hydroxyethyl methacrylate, poly(ethylene glycol)	radiation-induced polymerisation at -24°C in the presence of additives preventing the deactivation of chloroplasts	the liberation of O_2 and the influence of ^{60}Co γ -radiation were investigated; the stability of chloroplasts increases appreciably on immobilisation	281
<i>BAS — pilocarpine hydrochloride</i>			
Acrylamide	radiation-induced grafting of polyacrylamide on polyester materials by impregnating the monomer with subsequent irradiation	a review article on the modification of polyester blood vessel prostheses by the grafting of polyacrylamide; preparation of polyacrylamide disc containing pilocarpine hydrochloride	282

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>BAS — salicylic acid</i>			
Methyl methacrylate, methacrylic acid	radiation-induced graft polymerisation of a mixture of methyl methacrylate with methacrylic acid on porous cellulose spheres	the sorption of salicylic acid on a modified polymer from aqueous alcoholic solution was investigated	283
<i>BAS — steroids: cholic acid, testosterone, progesterone, corticosterone</i>			
Styrene	radiation-induced grafting of polystyrene on polytetrafluoroethylene, polyamides, poly(<i>p</i> -xylene); nitration of the graft polystyrene and reduction of the nitro group to an amino group	introduction of the thiosemicarbazide group, which is capable of reacting with the carbonyl group of steroids	284
<i>BAS — acetylcholine, serotonin, secretin, actinomycin</i>			
2-Hydroxyethyl methacrylate, methyl, ethyl, glycidyl, and lauryl (meth)acrylates, acrylic acid, acrylonitrile, vinyl acetate, styrene	radiation-induced polymerisation at 28 °C for 2 h; dose rate 5 kGy h ⁻¹	the rate of liberation of the BAS from the polymer matrices was investigated; it was established that the rate of liberation of medicinal substances may be controlled by selecting the polymerisation conditions	286
<i>BAS — thermolysin</i>			
2-Hydroxyethyl methacrylate, tetradecaethylene glycol dimethacrylate	radiation-induced polymerisation at room temperature	the thermal stability of the immobilised thermo lysin was investigated	287
<i>BAS — medicinal drugs with antiandrogenic properties, steroids, and hormones</i>			
Diethylene glycol dimethacrylate, poly(ethylene glycol dimethacrylate)	the medicinal drugs were mixed with the monomer and irradiated with ⁶⁰ Co γ-rays at -78 °C for 2 h; dose rate 5 kGy h ⁻¹	the rate of liberation of the medicinal substances was investigated; tests <i>in vivo</i> and <i>in vitro</i>	285
Microorganisms			
Acrylic and methacrylic acid chlorides	radiation-induced graft polymerisation of acrylic or methacrylic acid chlorides and covalent binding of photobacteria	a review article on the covalent immobilisation of cells; biosensors based on the immobilisation of photobacteria were made; the functional activity of cells may be regulated	288
<i>A fumarase producing microorganism</i>			
Acrylamide	irradiation of the BAS mixed with an aqueous solution of acrylamide in the presence of a cross-linking agent; dose 0.5 kGy	the immobilised microorganism exhibits a high fumarase activity and converts fumaric acid into L-malic acid; the preparation was produced in the form of grains	289
Enzymes and subcellular organelles			
Acrylic acid, allyl alcohol	radiation-induced graft polymerisation of acrylic acid and allyl alcohol on polyethylene	the enzymes were attached to graft polymers by the carbodiimide method; the stability of the enzymes was investigated; the use of the immobilised enzymes in the hydroxylation reaction was investigated	290
<i>Enzymes, antibodies</i>			
Diallyldimethylammonium chloride	the monomer was deposited on electrodes and irradiated; dose 10 kGy	cross-linked products containing enzymes strongly bound to the electrode were obtained	293
<i>Various BAS</i>			
Diethylene glycol dimethacrylate, acrylamide	radiation-induced polymerisation	preparation of polymer microspheres	191
<i>Various BAS containing an NH₂ group</i>			
Acrolein	radiation-induced polymerisation of acrolein	preparation of microspheres with aldehyde groups for the immobilisation of the BAS	195
<i>Mixture of the BAS isolated from leeches</i>			
Acrylic acid	radiation-induced grafting of poly(acrylic acid) to polyethylene and treatment with SOCl ₂	the components of the BAS are bound covalently to the modified polymer	90

Table 2 (continued).

Monomers, immobilisation components	Immobilisation conditions	Remarks	Ref.
<i>Bacillus Stearothermophilus cells</i>			
Maleic anhydride, styrene vinyl acetate	reaction copolymerisation of the monomers	immobilisation of the cells on the copolymer	291
<i>Microbial cells</i>			
2-Hydroxyethyl methacrylate	2-hydroxyethyl methacrylate deposited on a sheet of paper and irradiated with ^{60}Co γ -rays; a medium for the dilution of microbes was created	it was established that an increase in the hydrophilicity by adding methoxytetraethylene glycol methacrylate leads to an appreciable increase in the activity of the microbes	297
<i>Monoclonal antibodies</i>			
Methacrylic acid	radiation-induced grafting of poly(methacrylic acid) on the ethene-propene copolymer	immobilisation of antibodies with the aid of the carbodiimide method	292
<i>BAS — transferrin, heparin, rabbit antibodies</i>			
Glycidyl methacrylate	radiation-induced grafting of poly(glycidyl methacrylate) on polyethylene and polystyrene	the BAS were attached to the copolymer via the epoxide groups; the biological activity was retained	294

forming glassy viscous liquids in the supercooled state (usually at -78°C , dry ice). In the supercooled state, the BAS are little damaged on irradiation and the yield of their activity is high. Doses of 10 kGy (^{60}Co γ -radiation) and a dose rate of 5 kGy h^{-1} are usually employed for radiation-induced polymerisation. For such doses, the enzyme activity of the BAS hardly changes.

Glass-forming alkyl acrylates and methacrylates of the type $\text{CH}_2=\text{CXCOO}(\text{CH}_2)_n\text{OH}$ and $\text{CH}_2=\text{CXCOO}(\text{CH}_2\text{CH}_2\text{O})_m-\text{OCXC}=\text{CH}_2$, where $\text{X}=\text{H}$ or CH_3 , are usually employed as the monomers. 2-Hydroxyethyl methacrylate is widely used. The presence of water and the enzyme accelerates the radiation-induced polymerisation. The immobilisation process consists of the following stages: mixing of the biocomponent with the monomer, preparation of the mould, cooling, and polymerisation. A mixture of the glass-forming monomer with the usual monomers (styrene, methyl methacrylate, vinyl acetate, acrylamide, etc.) is used in some cases. Aqueous solutions of the BAS at specific pH are normally employed for immobilisation. The phase state of the system is altered on freezing the monomer mixed with an aqueous solution of the BAS. Phase analysis showed that an appreciable proportion of the water begins to crystallise at a temperature below -24°C , forming a suspension of ice in the supercooled monomer.

The radiation-induced polymerisation results in the formation of a porous system and the BAS is partly located on the surfaces of the pores. This immobilisation method has been called the adhesion method. The distribution of the BAS between the aqueous phase and the porous polymer (the degree of adhesion of the BAS on the surface) depends on the nature and concentration of the monomer. The rate of freezing also influences in many instances the pore dimensions. The monomer concentration is very important. With its increase (above 30%), the porosity of the matrix begins to diminish and the activity of the BAS falls. At a monomer concentration in excess of 50%, part of the BAS is captured by the polymer and does not participate in the reaction.

Thus the adhesion method requires the optimum (as a rule $\sim 30\%$) monomer concentration.²⁰¹ Under these conditions, 20%–30% of the activity of the BAS is usually retained and changes little on reuse of the BAS. The hydrophilic or hydrophobic properties of the monomer are very important. With increase in the hydrophilicity of the monomer, the rate of liberation of the BAS during use also increases. In certain cases, this rate may be regulated by mixing hydrophilic and hydrophobic monomers and also by employing mixtures of glass-forming monomers with natural polymers (albumin, collagen, etc.). The

addition of various cross-linking agents as well as BAS adsorbents (for example, silica gel) to the monomers has a significant influence on the rate of liberation of the BAS. By selecting glass-forming monomers and the conditions for the radiation-induced polymerisation, it is possible to regulate the rheological properties of polymer matrices with immobilised BAS.

Another method of obtaining biocomposites involves the mixing of the BAS with the polymer (usually in the form of a powder) and pressing under a pressure of $\sim 100\text{ kg cm}^{-2}$ with subsequent cross-linking under the influence of radiation (with a dose of $\sim 10\text{ kGy}$).²⁰⁴ However, this method is used much more rarely. Its main disadvantage is that it is difficult to achieve a uniform mixing of the BAS with polymers.

The immobilisation of glucoamidase, invertase, and β -galactosidase in polymer gels obtained by the radiation-induced polymerisation of acrylamide, *N,N*-dimethylacrylamide, 2-hydroxyethyl methacrylate, and *N*-vinylpyrrolidone and by the radiation-induced cross-linking of poly(vinyl alcohol) has been described.^{225–228} The influence of the irradiation dose on gel formation processes has been investigated. For each monomer, there is a definite dose above which the enzyme ceases to be liberated. If the *N*-vinylpyrrolidone irradiation dose is above 30 kGy, while that for PVA is above 50 kGy, enzymes are not liberated. By selecting the dose, it is possible to regulate the rate of liberation of the enzyme. Satisfactory results have been obtained using acrylamide and *N,N*-dimethylacrylamide (for a dose of 10 kGy). In the case of 2-hydroxyethyl acrylate, gel formation begins at a dose of 2.5 kGy and the enzyme is liberated within a fairly wide dose range. Yoshida and Kaetsu²³⁵ investigated the immobilisation of glucoamylase in polymer matrices obtained by the low-temperature radiation-induced polymerisation of 2-hydroxyethyl methacrylate (hydrophilic monomer) and diethylene glycol dimethacrylate (hydrophobic monomer) in the presence of the enzyme in an aqueous buffer solution (for a dose of 5 kGy). In the case of the hydrophilic matrix, the glucoamylase was in the gap between a thin polymer layer (polymer membrane), formed on radiation-induced polymerisation, and the porous structure of the polymer, as well as partly in the polymer itself, but in the hydrophobic matrix the glucoamylase was present virtually only on the surface of the porous structure of the polymer. The rates of liberation of glucoamylase from the hydrophilic and hydrophobic polymer matrices were compared. Fluorescence photomicrographs were obtained for the distribution of glucoamylase in various polymer matrices. It was established that the diffusion of glucoamylase diminishes appreciably with

increase in the content of the monomer in the mixture. The highest rate of liberation is observed at a monomer concentration of 10%.

The immobilisation of glucoamylase in thin polymer membranes, formed on irradiation of hydrophilic or hydrophobic polymers by a low-energy electron beam in the presence of an aqueous solution of the enzyme, has been investigated.²³³ The polymers employed were poly(ethylene glycol dimethacrylate) or poly(ethylene glycol diacrylate). Thin polymer membranes with a high enzyme activity were obtained. The influence of the irradiation dose, the energy, and the concentration of the polymer on the enzyme activity of the membranes was studied. In the presence of tris(hydroxymethyl)propane triacrylate (a hydrophobic monomer), the activity of the membranes depends to a considerable degree on the irradiation conditions and the monomer concentration.

The immobilisation of glucoamylase in a poly(vinyl alcohol) gel on electron irradiation²³⁶ has been investigated.^{235, 236} Doses ranging from 60 to 360 kGy were used. At 120 kGy, the enzyme activity fell appreciably, while at 360 kGy it vanished completely. A strip which moved under the beam from the accelerator was used for irradiation. The immobilisation of invertase and glucoamylase in a PVA gel obtained on γ -irradiation of the above polymer in the presence of an aqueous enzyme solution was studied in detail. The irradiation dose is very important. The enzyme was liberated only for doses not exceeding 40 kGy. Up to 70 kGy, the dose does not affect the enzyme activity. A disadvantage of the immobilisation of enzymes in the poly(vinyl alcohol) gel was noted — an unduly high (75%–90%) loss of enzyme activity.

The immobilisation of urease on starch with grafted polyacrylamide has been studied.²¹³ The use of low irradiation doses is important. The activity of urease fell to 60% of the initial value after the enzyme had been used seven times.

Kumakura and Kaetsu²³⁸ investigated the immobilisation of lipase by the low-temperature polymerisation of 2-hydroxyethyl methacrylate, tris(hydroxymethyl)propane trimethacrylate, and poly(ethylene glycol diacrylate) in the presence of an aqueous enzyme solution. All the specimens had a porous structure. The enzyme activity was a maximum in 40% solution of the monomer. It was established that the maximum enzyme activity of the lipase is attained for the optimum hydrophobicity of the polymer matrix. When poly(ethylene glycol) is used in the immobilisation the enzyme activity increases with increase in the number of ethylene glycol units in the monomer molecule.

The communication of Guanghui *et al.*²⁴⁶ is devoted to the study of the immobilisation of catalase on acyl azide-modified porous polyacrylamide particles obtained by the radiation-induced polymerisation of acrylamide in the presence of *N,N'*-methylenebisacrylamide at -78°C . The activity of catalase increases appreciably on immobilisation via glycine groups. The immobilised catalase has been used to decompose H_2O_2 in irradiated wines.

Kaetsu *et al.*²⁰¹ studied the immobilisation of α -amylase in polymer matrices produced from the copolymer of 2-hydroxyethyl methacrylate and poly(tetraethylene glycol diacrylate). The immobilisation was carried out by the radiation-induced polymerisation of a mixture of monomers containing an aqueous BAS solution and using a dose of 10 kGy at -24°C . At a certain temperature, the phase state of the system changes and the ice phase is formed. The biologically active substance is concentrated on the surface of the porous polymer matrix. In the case of a hydrophobic polymer matrix, an appreciable proportion of the BAS remains in the ice, so that the activity of the BAS increases with increase in the monomer concentration. However, starting from a certain monomer concentration, the activity of the test substance diminishes owing to occlusion within the polymer. Photomicrographs of the polymeric composite with the immobilised BAS have been published. In the case of the hydrophilic polymer matrix, the reactions of α -amylase take place as a result of the diffusion of the enzyme in the swollen polymer gel.

A method has been developed for the preparation of spherical particles (100–150 μm) in the copolymerisation of hydrophilic and hydrophobic monomers (neopentyl glycol diacrylate or tetraethylene glycol diacrylate). In this case, the activity of the enzyme is independent of the monomer concentration in polymerisation at -78°C and for a dose of 10 kGy. Methods have been developed for the preparation of tubes and filaments containing immobilised BAS. The immobilisation of α -amylase in poly(2-hydroxyethyl methacrylate) matrices has been investigated²⁹⁶ with the aid of radiation-induced polymerisation (dose 5 kGy). The immobilisation of trypsin using low-temperature radiation-induced polymerisation has been investigated in detail.²¹⁶ The enzyme activity was studied in the hydrolysis of casein (substrate). 2-Hydroxyethyl methacrylate, poly(ethylene glycol diacrylate), and methoxypoly(ethylene glycol methacrylate) were used as the components for the immobilisation of trypsin.

The irradiation of the monomers mixed with an aqueous enzyme solution was carried out at -78°C with a dose of 10 kGy. If the monomers are hydrophilic, the enzyme activity falls with increase in their concentration, whereas in the case where they are hydrophobic the activity passes through a maximum. When 2-hydroxyethyl methacrylate is used, a porous polymer matrix with a pore size of 1 μm at a monomer concentration of 50%–70% is formed. With increase in this concentration, the pore size diminishes. When tris(hydroxymethyl)propane triacrylate (a hydrophobic monomer) is used for immobilisation, a polymer is formed in the form of a suspension with a particle size of 50–200 μm and the enzyme is immobilised on the polymer surface. In the case of poly(ethylene glycol diacrylate), the degree of hydration and the enzyme activity increase with increase in the number of oxyethylene units $-\text{CH}_2\text{CH}_2\text{O}-$ (n). For $n \leq 4$, large formations 100–200 μm in diameter are produced, whereas for $n \geq 9$ a continuous porous structure is formed. If methoxypoly(ethylene glycol methacrylate) is used, a cross-linked structure appears. Such a matrix is soft and hydrophilic and the enzyme is readily trapped in it. The study of the influence of the nature of the polymer matrix on the thermal stability of the immobilised enzyme showed that the highest thermal stability occurs when 2-hydroxyethyl acrylate and 2-hydroxyethyl methacrylate are used. The thermal stability of the enzyme depends on the hydrophilicity of the polymer matrix; the maximum stability is attained on increase in the degree of hydration, which is associated with the influence of the latter on the rigidity of the matrix.

The immobilisation of trypsin in the radiation-induced polymerisation of crystalline monomers (acrylamide, methylenebisacrylamide, and acrylic acid salts) has been investigated.^{212, 229} A deficiency of the polymer matrix was discovered — an unduly high hydrophilicity.

The communication of Carenza *et al.*²³⁰ was devoted to the study of the influence of the molecular mass of proteins and peptides on the rate of liberation of these compounds from hydrogels obtained by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate. It was established that the rate of liberation diminishes linearly with increase in $\log M_w$. The rate of decrease may be regulated by adding poly(ethylene glycol) with different M_w to 2-hydroxyethyl methacrylate. The immobilisation of glucose oxidase, glucose peroxidase, and urokinase on the inner surfaces of poly(vinyl chloride) tubes and on LDPE films has been described.²⁴⁹ The immobilisation method consists in the preliminary radiation-induced polymerisation of 2-hydroxyethyl methacrylate and the subsequent decomposition on the grafted surface of a mixture of the monomer with an aqueous solution of the enzyme. The tube is frozen and irradiated at -78°C (dose 5 kGy).

The structure of the surface depends on the polymerisation conditions and the nature of the monomer. These factors influence the uniformity of the coating. The thinnest and most uniform coatings are obtained when a 1:1 mixture of 2-hydroxyethyl methacrylate and tetraethylene glycol diacrylate is used. A high

stability of the immobilised enzymes was established, which can be partly accounted for by the employment of cross-linked systems. Glucose oxidase and glucose peroxidase have been used to assay glucose in blood.^{234,248} The immobilisation was carried out in such investigations by irradiating the monomers mixed with an aqueous enzyme solution. The mixture was deposited on a nylon net or filter paper in a thin layer and was irradiated in an accelerator (dose 10 kGy). Poly(ethylene glycol diacrylate) and tris(hydroxymethyl)propane triacrylate were used as the components for the immobilisation. The maximum activity of the enzymes was attained at a concentration of the components of 20%–30% and the highest enzyme activity was observed when poly(ethylene glycol diacrylate), deposited on a nylon net, was employed. Polymer sheets with immobilised enzymes were obtained as a result.

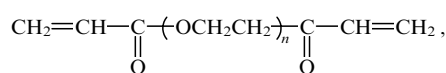
The immobilisation of fumarase in a polyacrylamide gel has been described (dose 5–10 kGy).²⁸⁹ A high activity of fumarase was achieved under the conditions of the enzymic synthesis of malic acid from fumaric acid.

The results of the study of the immobilisation of penicillin acylase in polymer matrices of different hydrophilicity (2-hydroxyethyl acrylate, 2-hydroxyethyl methacrylate, *N*-vinylpyrrolidone, *etc.*) by means of low-temperature radiation-induced polymerisation have been described.²⁵⁰ The influence of the monomer:enzyme ratio on the immobilisation was investigated. It was established that the rate of liberation of the enzyme is independent of the nature of the monomer, the degree of polymerisation, and the porosity, but does depend strongly on the presence in the system of the cross-linking agent tris(hydroxymethyl)propane trimethacrylate even in small amounts (~0.03%–0.04%). The enzyme is retained in the polymer matrix as a result of hydrophobic interactions. The activity of penicillin acylase is preserved for a long time in the presence of the cross-linking agent.

A series of publications^{239–244,251,270} have been devoted to questions concerning the immobilisation of cellulase. The immobilisation of cellulase and cellobiase in polymer matrices obtained by the low-temperature polymerisation of 2-hydroxyethyl methacrylate in the presence of an aqueous enzyme solution has been studied in detail.²³⁹ The enzyme activity was determined from the yield of glucose in the decomposition of cellulose. It was noted that in the presence of additives in the monomer [silica gel and poly(ethylene glycol)] the enzyme activity is retained for a longer time. The effectiveness of the additive depends on the monomer concentration. The maximum activity is attained at a monomer concentration of 60%. Discs 12 mm thick containing the immobilised enzyme were obtained.

Kumakura and Kaetsu²⁴⁰ studied the immobilisation of cellulase in polymer membranes prepared from hydroxylated acrylates. The maximum activity of cellulase was attained at a monomer concentration of 20% and for a membrane thickness of 1 mm, which is associated with the formation of the most porous structure of the polymer under these conditions. The dependence of the enzyme activity on the water content in the polymer has a maximum. In the immobilisation of cellulase in the porous polymer matrix formed by the radiation-induced polymerisation of poly(ethylene glycol diacrylate), the pore structure is determined to a large extent by the polymer concentration and temperature.²⁴¹

The enzyme activity depends on the pore size, the degree of hydration, and the particle size of the composite. The degree of hydration of the polymer increases with increase in the number of oxyethylene groups in the monomer.



$$n = 2, 3, 4, 9, 14.$$

Continuous changes in the porous structure associated with the change of the polymerisation phase have been noted in the temperature range from –10 to –40 °C. With increase in pore size, the enzyme activity falls.

Yoshida *et al.*²⁴² achieved the immobilisation of cellulase in polymer microspheres. The latter were formed as a result of the radiation-induced polymerisation of glycidyl methacrylate in the presence of polystyrene and the enzyme with subsequent immersion of the mixture in cooled methanol. The influence of various conditions on the number and diameter of the microspheres was investigated. Soft and hard microspheres with different diameters were obtained. The enzyme activity of cellulase in the soft microspheres was 4.6 times higher than in the hard ones.

The communication of Kumakura and Kaetsu²⁴³ was devoted to the study of the immobilisation of *Streptomyces phalochromogenes* cells (which produce cellulase) using the 2-hydroxyethyl methacrylate + methoxytetraethylene glycol methacrylate mixture. The mixture together with the cells was deposited on paper and irradiated. Paper sheets with immobilised cells were obtained.

The immobilisation of cellulase in poly(2-hydroxyethyl methacrylate) polymer matrices has been described.²⁴⁴ The immobilisation was carried out by the low-temperature polymerisation of 2-hydroxyethyl methacrylate in the presence of an aqueous enzyme solution. The specimens were prepared in the form of discs. The enzyme activity is a maximum at a monomer concentration of 50% and the optimum thickness of the disc is 1 mm. With increase in cellulase concentration, the specific enzyme activity diminishes. Photomicrographs of the specimens with the immobilised cellulase were published. The immobilised cellulase preparation may be used repeatedly. In another study, Kumakura and Kaetsu²⁵¹ immobilised cellulase on the inner surfaces of polyethylene tubes by the low-temperature radiation-induced polymerisation of a mixture of 2-hydroxyethyl methacrylate and tetraethylene glycols diacrylate. The mixture of the monomers with the enzyme was deposited on the inner surfaces of the tubes, frozen, and irradiated (dose 10 kGy). The thickness of the layer of coating was 300 μm, the optimum monomer concentration was 60%–70%, and the enzyme concentration was 0.5%. This immobilisation method can be used to create enzyme reactors. The immobilisation of yeast cells in various hydrogels has been studied and the conditions for the maximum yield of ethanol in the enzyme hydrolysis of a cellulose-containing raw material were discovered.²⁷⁰ Immobilised cellulase has been used for the enzymic hydrolysis of a cellulose-containing raw material: paper waste,^{270,297,298} starch,^{299,300} biomass (wood chips, sugar beet waste, rice straw),^{299,300} and lignin-containing waste.²⁴⁵ After the preliminary irradiation of the cellulose-containing waste (paper, sawdust, *etc.*) with a dose up to 1 MGy, the yield of glucose in the hydrolysis of the raw material increases appreciably (by a factor of ~3),^{297–301} which is associated with the appreciable decrease in the degree of polymerisation of cellulose and the partial breakdown of its structure. The yield of ethanol in the hydrolysis of plant waste after preliminary irradiation has been studied in detail.²⁷⁰ For the successful enzyme hydrolysis of lignin-containing waste, it is desirable to subject it to preliminary irradiation (dose 1 MGy) and grinding. The influence of preliminary irradiation up to different doses on the subsequent hydrolysis of cellulose (from rice, straw, *etc.*) has been described.³⁰¹ The results of the employment of the radiation technique for the conversion of biomass into sugar and its fermentation in order to obtain ethanol have been surveyed in a review.³⁰⁰ The possibility of the reuse of the immobilised enzymes has been studied.

Functional polymers, obtained by radiation-induced graft polymerisation, have been used in a series of studies for the immobilisation of enzymes. A method for the covalent binding of enzymes, based on the grafting of *p*-nitrostyrene to polymers (mainly polyolefins), the reduction of the nitro groups to amino groups, and the conversion of the latter into isocyanate groups, which readily react with enzymes, has been devised.^{210,219,220} In

the case of amino groups, glutaric dialdehyde was used for the covalent binding of enzymes. Another procedure consists in the radiation-induced grafting of styrene with subsequent nitration of the graft copolymer. Trypsin was used as the enzyme.

A method for the immobilisation of asparaginase on porous polypropylene fibres, an ethene-propene copolymer, and a polypropylene film has been created.^{257,258} The first stage is the radiation-induced grafting of acrylic acid, after which asparaginase is attached covalently to the carboxy groups by the carbodiimide method. An enzyme reactor was developed and was tested *in vitro* and *in vivo*. The immobilisation of enzymes and subcellular organisms in polyethylene has also been described.²⁹⁰ The activity and stability of the enzymes were investigated.

The immobilisation of papain, trypsin, glucose oxidase, and α -chymotrypsin on powdered polyethylene with grafted poly(methacrylic acid) and poly(2-hydroxyethyl methacrylate) has been studied.²⁵⁹ The covalent binding of the enzyme was achieved with the aid of the carbodiimide method. It was established that each enzyme requires its own microenvironment. α -Chymotrypsin proved to be the most active. The best results were obtained in the grafting of poly(2-hydroxyethyl methacrylate) with subsequent partial hydrolysis. The covalent immobilisation of invertase, phosphatase, albumin, trypsin, and galactosidase on polyethylene modified by the grafting of poly(acrylic acid) has been described.²⁶² The enzyme was attached by means of the carbodiimide method. The influence of the methods used for grafting and activation of poly(acrylic acid) on the activity of the enzymes was examined.

The immobilisation of horseradish peroxidase on segmented polyesterurethane films has been described.²⁶¹ The immobilisation of glucose oxidase on polyethylene films has been investigated.²⁴² A study has been made of the influence of the degree of grafting, the hydrophilicity, and the electrical properties on the enzyme activity.

The radiation-induced grafting of 2-hydroxymethyl methacrylate has been used to bind trypsin and glucose oxidase to natural rubber.^{221,222}

Cyanuric chloride and toluene-*p*-sulfonyl chloride were used for the covalent binding. The immobilisation conditions and the activity of trypsin have been examined in detail. The immobilisation of enzymes on polyamide materials (with the aid of radiation-induced graft polymerisation of acrylic acid or acrylonitrile) has been described.^{260,264,265} The immobilisation of protease with the aid of radiation-induced grafting of acrylic acid has been investigated.²¹⁴

The reactivity of α -chymotrypsin immobilised on radiation-grafted hydrogels obtained by the grafting of 2-hydroxyethyl methacrylate and methacrylic acid on silicone rubber has been studied.^{302,303} α -Chymotrypsin was bound covalently using *N*-hydroxysuccinimide. The influence of pH and the content of acrylic acid on the enzyme activity was investigated (hydrolysis of *N*-acetyl-L-tyrosine). The rate of hydrolysis is greatly influenced by the negative charge of the hydrogel. The immobilisation of trypsin on a wide range of polymers modified by the radiation-induced grafting of poly(acrylic acid), polyacrylonitrile, poly(2-hydroxyethyl methacrylate), poly(*N*-vinylpyrrolidone), polyacrylamide, *etc.* has been studied in detail.^{213,214} The covalent binding of trypsin was achieved by means of the carbodiimide method or glutaric dialdehyde. The polymer membranes obtained were designed for use in the milk industry.

Methods for the covalent immobilisation of enzymes with the aid of aldehyde groups, which readily react with amines, have been devised.^{198,199,304,305} The methods involve the radiation-induced graft polymerisation of acrolein. The reactivity of the aldehyde groups was studied.

Radiation-induced graft polymerisation is used for the modification of agarose (by grafting a complex of *N*-acryloylsuccinimide and BSA) in order to obtain a material for the chromatographic separation of biomacromolecules.³⁰⁶

Novel methods for the immobilisation of enzymes on polymeric materials have been developed by Platé and Valuev.²¹⁵ This is a new aspect of the use of radiation-chemical methods for the immobilisation of BAS, because it concerns the radiation-induced graft polymerisation of macromonomers formed by the introduction of a reactive double bond into BAS macromolecules.

Thus the nature of the monomer and in the first place its hydrophilic and hydrophobic properties as well as the monomer concentration are important in the immobilisation of BAS with the aid of radiation-induced polymerisation. These factors influence most significantly the activity of the enzyme, the duration of its use, and its thermal stability. Cross-linking agents and BAS adsorbents can be usefully added at a low concentration in a number of instances in order to regulate the rate of liberation of the enzyme. The radiation dose should not exceed 10 kGy in most cases.

The modification of various polymers by the radiation-induced grafting of acrylic acids or 2-hydroxyethyl methacrylate with subsequent binding of the enzymes by the carbodiimide method is employed most frequently for the covalent binding of enzymes. The specific activities of the enzymes fall with increase in their content in the modified layer (a 5%–10% graft is optimal). The method for the covalent binding of the enzyme is very important. Radiation-induced graft polymerisation makes it possible to employ polymers of virtually any nature and form (powders, fibres, films, *etc.*) for the binding of enzymes. The possibility of creating enzyme reactors has been demonstrated.

2. Immobilisation of medicinal preparations

In the employment of radiation-induced polymerisation for the immobilisation of medicinal substances, the greatest advances have been achieved in the immobilisation of antitumour compositions in polymer matrices. The antitumour substances employed have been adriamycin, mitomycin C, and 5-fluorouracil. In many cases, treatment with immobilised antitumour preparations is combined with hormone therapy. The immobilised antitumour substances are used as a rule in the form of polymer tablets or needles which are inserted in the tumour. The application of immobilised antitumour preparations has the following advantages compared with their introduction in the form of injections or orally: a low concentration of medicinal preparations in the blood, the medicine spreads from the administered preparation into a small region. This reduces to a minimum the side effects of the medicines. The duration of the use of the immobilised antitumour preparations is several months. These preparations have undergone extensive tests in many Japanese clinics.²⁰⁴ In the vicinity of the preparation introduced into the tumour, the cancer cells undergo necrosis and the diffusion of the antitumour preparations terminates in the necrosed layer. The rate of liberation of medicinal substances does not change in the course of 40 days. The number of specimens introduced into the tumour, their density, and form (needles, tablets) are very important.

The concentration of antitumour substances in the blood is insignificant. A mixture of poly(ethylene glycol dimethacrylate) (20%) and diethylene glycol dimethacrylate (80%) is usually employed for the immobilisation of the antitumour preparation mitomycin C.²⁰⁴ The behaviour of the immobilised antitumour preparations in the organism and the methods for the treatment of cancer have been examined in a number of studies.^{307–312} Methods whereby immobilised antitumour preparations can be produced have been described in detail in a series of studies.^{204,205,249,276,278,313,314} The low-temperature polymerisation of diethylene glycol dimethacrylate mixed with various polymers [polystyrene, polyvinylformal, poly(ethylene glycol), poly(methyl methacrylate)] is used for the immobilisation of mitomycin, 5-fluorouracil, and bleomycin. It is emphasised that irradiation must be carried out in an oxygen-free medium and the dose must not exceed 10 kGy. Otherwise the activity of the antitumour preparations is significantly reduced.²⁷⁷ Specimens

with the immobilised antitumour preparations are made in the form of a powder, tablets, cylinders, membranes, *etc.*²⁷⁷

The immobilisation of multicomponent cytotoxic (antitumour) agents in polymer matrices based on poly(diethylene glycol dimethacrylate) and poly[tris(hydroxymethyl)propane trimethacrylate] has been studied. The cytotoxic agents employed are mitomycin C, adriamycin, and 1-(2-tetrahydrofuryl)-5-fluorouracil. The rate of liberation of the medicinal preparations is regulated by introducing a pore-forming agent or adsorbent (for example, activated charcoal) into the polymer matrix. The surfaces of the polymers obtained with the immobilised cytotoxic agents have been studied by electron microscopy.²⁷⁶

The immobilisation of the antitumour preparations 5-fluorouracil and mitomycin C by dispersing the preparations in polymer matrices obtained by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate, 2-hydroxyethyl acrylate, and methyl methacrylate has been examined.³¹³ A cross-linking agent — ethylene glycol dimethacrylate — is added for the effective control of the rate of liberation of the medicinal preparations. The rate of liberation of medicines from polymer matrices obtained under different conditions has been studied in detail. The rate of liberation increases with increase in the hydrophilicity of the matrix and diminishes significantly with increase in the content of the cross-linking agent. The influence of the porosity of the matrix on the liberation of medicinal substances has been studied and electron micrographs of the porous structure have been published. A study has been made of the therapeutic effect of immobilised preparations placed in the form of tablets in the vicinity of a tumour (sarcoma) in mice. The slow liberation of the medicinal drugs led to a greater therapeutic effect compared with direct injection.

The methods and results of clinical tests of the local chemotherapy of malignant glioma have been examined. The following immobilised antitumour preparations have been used: adriamycin, 5-fluorouracil, and nimustine hydrochloride.³¹⁴

The preparation of poly(ethylene oxide) gels with immobilised hydroxyprogesterone acetate for the treatment of carcinoma has been described.²⁷⁸ The controlled liberation of adriamycin from polymer needles has been investigated.³¹⁵

Summarising the foregoing, one may conclude that the application of antitumour preparations immobilised in polymeric materials is promising. When they are used, the cancer cells undergo necrosis within the limits of 0.5–1 cm² around the specimen and the diffusion of the antitumour preparations ceases in the necrosed layer. The number of specimens in the tumour and the rate of liberation of the preparation, which may be regulated within wide limits are very important. Side effects are not observed when immobilised antitumour preparations are employed. The technology of the use of immobilised antitumour preparations may be improved by varying the hydrophilic-hydrophobic properties of the polymer matrix and also by using biodegradable polymers (polypeptides or polylactides).

Methods have been developed for the immobilisation of the antitumour preparation narciclasine.^{279, 316} Chemical and radiation methods for the initiation of polymerisation with the aim of its immobilisation have been compared. A study has been made²³¹ of the immobilisation of the antitumour preparation Ara-C in hydrophobic matrices obtained by the radiation-induced polymerisation of alkyl acrylates and methacrylates. It was shown that the rate of liberation of Ara-C may be varied widely by altering the composition of the matrices. The prospects for the employment of thin polymer particles, obtained by emulsion polymerisation (0.1–3 µm particles) or suspension polymerisation (10–100 µm particles), for immobilisation have been noted.²⁰⁵ Significant results in therapy have been achieved in the joint study of immobilised antitumour preparations and hormones. The immobilisation and use of the immobilised hormones (testosterone) have been described.^{317–320} The hormones were immobilised in polymer needles. An important feature is that the hormones enter the organism for a long time in small amounts. Definite successes

have been achieved in the treatment of the cancer of digestive organs, the bladder, pancreas, the brain, *etc.*

Radiation-induced polymerisation has been used in a series of studies^{159, 202, 205, 321–325} for the immobilisation of antibodies in order to investigate the antibody–antigen reactions. The sensitivity of the reactions of the immobilised antibody with the antigen depends on the choice of monomer and its concentration needed to create a porous medium. An important problem is the minimisation of nonspecific reactions of the polymeric carrier with the antigen. For this purpose, it is necessary to make the polymer matrix more hydrophobic. The immobilised preparations are usually made in the form of microspheres or microcapsules. Microspheres obtained by the polymerisation of acrolein or its copolymers with 2-hydroxyethyl methacrylate or methacrylic acid are also used for the immobilisation of antibodies.

Within the framework of the program of the International Atomic Energy Agency, studies with immobilised monoclonal antibodies have been carried out at the Pasteur Institute (Paris).^{205, 292} The immobilisation of the latter is achieved by the low-temperature polymerisation of 2-hydroxyethyl methacrylate.

An advantage of radiation-induced polymerisation for the immobilisation of antibodies is the fairly high purity of the product obtained.^{326, 327} These preparations may be used for immunological assay.

The immobilisation of a calcium antagonist in a prepolymerised poly(2-hydroxyethyl methacrylate) gel has been described.²⁸⁵ The rate of liberation of the medicinal preparation can be varied widely by means of the radiation-induced cross-linking of the gel and the added methyl methacrylate and *N*-vinylpyrrolidone.

The immobilisation of hydrocortisone in gels obtained by the radiation-induced polymerisation of acrylic acid has been investigated. The rate of liberation is regulated by the irradiation dose and by treating the gels with zinc acetate.³¹⁷

3. Immobilisation of blood components

Haemoglobin has been immobilised in a poly(2-hydroxyethyl methacrylate) polymer matrix using radiation-induced low-temperature polymerisation.^{271–273} Special attention was devoted to the selection of the optimum immobilisation conditions in order to protect the haemoglobin. Haemoglobin is convenient for the study of the state of the immobilised molecule in a polymer matrix, since it has a characteristic optical absorption. The haemoglobin in the membrane was subjected to reversible oxygenation, which may take place to almost the same extent as in native haemoglobin. A method for the preparation of semisynthetic blood based on immobilised carboxyhaemoglobin has been described.²⁷² Radiation-induced polymerisation has been used for the immobilisation of erythrocytes in the form of cells without haemolysis.

The radiation-induced polymerisation of phospholipids has been used for the immobilisation of haemoglobin.^{274, 275} The phospholipids contained two long polymerisable octadecadienyl groups. Artificial red blood cells were obtained by encapsulating haemoglobin with the aid of the radiation-induced polymerisation of bilayer phospholipids — liposomes. The artificial blood cells proved to be mechanically stable and readily withstood freezing. The oxygen transport is similar to the transport by native haemoglobin. Tests *in vivo* (on mice) were carried out and indicated the biocompatibility of such cells.

Methods have been developed for the preparation of polycationic carriers for red blood cells.⁸⁵ The carriers were formed by the polymerisation and grafting of 2-(*N,N*-dimethylamino)ethyl methacrylate. The grafting was carried out on poly(vinyl chloride) beads by a method involving preliminary irradiation. 2-(*N,N*-Dimethylamino)ethyl methacrylate was polymerised in bulk in the presence of tris(hydroxymethyl)propane trimethacrylate and also in suspension and in emulsion. Cationic immunoadsorbents were obtained. Their adsorption capacity was determined. The density of the positive charges on the adsorbent is important.

4. Immobilisation of yeast cells and microorganisms

In a series of studies,^{202, 266, 269, 328, 329} radiation-induced polymerisation has been used for the immobilisation of yeast cells in order to employ the resulting preparations for the synthesis of ethanol from plant waste.

The nature of the carrier, especially its porosity, plays an important role. The porous matrix is formed as a result of the copolymerisation of methoxypoly(ethylene glycol methacrylate) and 2-hydroxyethyl acrylate. The yeast cells are adsorbed on this matrix, are coated by methoxypoly(ethylene glycol methacrylate), and are polymerised at -78°C (dose 10 kGy).²⁶⁸ The activity of *Saccharomyces formosensis* cells (yeast cells) on polymeric carriers obtained by the radiation-induced polymerisation at -78°C of mixtures of 45% of methoxypoly(ethylene glycol methacrylate) containing 23 ethylene glycol units, 45% of hexane diol methacrylate, and 10% of water (fine pores and a low water content) or 15% of methoxypoly(ethylene glycol methacrylate), 15% of 2-hydroxyethyl methacrylate, and 70% of water (structure with wide pores). In the first case, the immobilised cells had an activity greater by a factor of 6 than in the second case. As a rule, the activity of the immobilised cells increases with increase in the water content.²⁶⁶ The influence of the composition of the monomer mixture and the conditions in the immobilisation of yeast cells on the yield of ethanol has been studied in detail.²⁶⁷ Conditions have been found for the multiplication of the yeast cells and for the manifestation of their high activity. A significant role of water in the activity of the cells was observed. A study has been made²⁶⁹ of the immobilisation of *Trichoderma reesei* (QM 9414) cells. Muslin was used as the carrier, which was coated with a solution of the monomer mixed with the cells and irradiated. It was shown that the concentration of the monomer used for immobilisation exerts a significant influence on the activity of the cells.

The capture of the microorganism producing fumarase in a cross-linked polyacrylamide gel has been investigated. A preparation with a high enzyme activity and an increased thermal stability was obtained.³³⁰ The immobilisation of bacteria in hydrophilic gels based on poly(ethylene glycol) and poly(propylene glycol) led to the creation of a bioreactor.³³¹ The rate of liberation of testosterone was regulated by immobilising it in a thermosensitive gel obtained by the radiation-induced polymerisation of the methyl ester of acryloyl-L-proline.³³²

A method for the covalent immobilisation of luminescent bacteria on the surface of a polyethylene film has been developed with the aid of the radiation-induced graft polymerisation of methacryloyl chloride on the film.^{288, 333}

5. Immobilisation of photosynthetic substances and organelles

Chloroplasts and chlorophyll may be immobilised with the aid of low-temperature radiation-induced polymerisation.^{202, 280, 281} The immobilisation of chloroplasts extracted from spinach was achieved by the radiation-induced polymerisation of 2-hydroxyethyl methacrylate in the presence of special additives which prevent the deactivation of the chloroplasts. The liberation of O_2 and the influence of γ -radiation on this process were investigated. The influence diminishes appreciably on irradiation at reduced temperatures (-24 and -78°C). The chloroplasts immobilised at reduced temperatures in a hydrophilic polymer matrix exhibited a stable long-term liberation of O_2 : more than 700 h at 4°C . The thermal stability of chloroplasts increases appreciably on immobilisation.

The photoreductive activity of chloroplasts falls to zero after 5 min at 50°C , whilst immobilised chloroplasts retain their activity for more than 60 min.²⁸¹ The influence of the nature of the monomer and its concentration on the activity of immobilised chloroplasts was investigated.²⁸⁰ 2-Hydroxyethyl acrylate, poly(ethylene glycol diacrylate), poly(ethylene glycol dimethacrylate), methoxypoly(ethylene glycol methacrylate), glycidyl methacrylate, glycidyl diacrylate, tetraethylene glycol diacrylate, and tetraethylene glycol dimethacrylate were used as the monomers. The

optimum monomer concentration was 10%. The best monomer for immobilisation proved to be a mixture of methoxypoly(ethylene glycol methacrylate) and 2-hydroxyethyl acrylate. The activity of the immobilised chloroplasts (liberation of O_2) was high and was retained for 30 days. When hydrophobic monomers were used, the activity of the chloroplasts decreased rapidly as a function of time.

6. Preparation of polymer implants

Technical procedures and methods used for the immobilisation of BAS (radiation-induced polymerisation) may be employed for the preparation of implants of various kinds, mainly for the therapy of damaged sections of the skin and also for the creation of prostheses. Methods have been developed for the preparation of collagen implants by irradiating mixtures of monomers or polymers with collagen.^{334–336} The implants are satisfactorily compatible with blood and do not give rise to inflammation. The implants are used in surgery and can be employed as substrates in biotechnology.³³⁴ Prostheses based on polyesterurethane with a radiation-modified inner surface have been investigated. The modification was achieved by the radiation-induced grafting of 2-hydroxymethyl acrylate or acrylamide on the inner surfaces of the tubes. The prostheses were studied *in vivo*. The histological and mechanical properties were investigated. Their improved thromboresistance was established.³³⁷ A method has been developed for the modification of polymer fillers used in dental technology. The fillers based on glass or quartz fibres were modified by the radiation-induced grafting of acrylic acid from the vapour phase. The physicochemical properties of resins containing different amounts of the modified filler were studied in detail. The advantages of the modified filler employed compared with the filler modified by silanes were noted.³³⁸ Polymeric-ceramic materials for dentistry have been created by irradiating mixtures of alumina and acrylic acid.³³⁹ Implants for the therapy of the skin on sections of the human body damaged by burns have been created with the aid of radiation-induced graft polymerisation.^{340, 341} Silicone rubber modified by the grafting of hydrophilic monomers or natural rubber modified by vulcanisation are normally employed for this purpose.³⁴¹ A method for the hydrophilisation of silicone contact lenses has been created with the aid of radiation technology. As a result of hydrophilisation, the wetting angle decreases from 150° to 20° and the hydrophilic effect persists for a long time.³⁴²

Radiation-modified polymers have been used for the initiation of the growth of various cells.^{147, 343, 344}

7. Preparation of 'smart' polymers and their use for the immobilisation of biologically active substances

'Smart' polymers have acquired in recent years an increasing importance for medicine and biotechnology. This is the term given to polymers capable of responding to small changes in the environment (temperature, pH, electric field, *etc.*).³⁴⁵ 'Smart' polymers with immobilised BAS are used for the liberation of medicinal substances under certain conditions, usually at a specified temperature or pH. 'Smart' polymers are normally obtained by traditional methods, but radiation-induced polymerisation has also come to be employed recently for this purpose.^{165, 247, 332, 346} Among the 'smart' polymers, the greatest number of publications have been devoted to poly(*N*-isopropylacrylamide) (poly-*N*-IPAA).^{345, 347} This polymer has a lower consolute temperature (LCT) of $\sim 32^{\circ}\text{C}$ in water, *i.e.* close to the temperature of the human body. Phase separation, caused by the conformational transition of the poly-*N*-IPAA macromolecule from a loose globule to a compact coil,^{345, 348, 349} which is accompanied by a sharp decrease in the size of the macromolecule, takes place above 32°C .³⁵⁰

The radiation-induced polymerisation of *N*-isopropylacrylamide has been investigated.^{351–353} Poly-*N*-IPAA gels have been obtained by irradiating aqueous solutions of the monomer. The gel formation dose is 71 Gy (dose rate 1 kGy h^{-1}). The temper-

ature dependence of the swelling in water of these gels, obtained for different doses, has been studied. It was established that the degree of collapse of the gels beyond the phase transition point depends significantly on the dose, which was explained by the structure of the polymer network. An important factor is that by selecting the dose it is possible to achieve a fairly fine regulation of the degree of collapse of the gels.

The radiation-induced copolymerisation of *N*-isopropylacrylamide in water and the cross-linking of the resulting gels have been investigated³⁵² by nuclear magnetic resonance. The influence of solvents on the radiation-induced polymerisation of *N*-isopropylacrylamide and the molecular mass of the resulting polymers have been studied.³⁵³ The lower consolute temperature of the resulting polymers is in the range 30.5–31.50 °C and depends little on the polymerisation conditions.³⁵³

The radiation-induced copolymerisation of *N*-isopropylacrylamide with *N*-acryloyloxysuccinimide has been investigated.³⁵⁴ The resulting copolymer was used for the immobilisation of bovine serum albumin, horseradish peroxidase, and monoclonal antibodies. It was shown that the dose at which the copolymer was obtained influences significantly the immobilisation process. The lower consolute temperature of the copolymers is in the range 30–35 °C and depends little on the concentration of the comonomers and the chain length. Asparaginase was immobilised in the gel obtained. The influence of temperature and the pH on the activity of the immobilised BAS was studied.

Radiation-induced copolymerisation led to the formation of copolymers of *N*-isopropylacrylamide and methacrylic acid.³⁵⁵ pH-Sensitive hydrogels were obtained by the radiation-induced copolymerisation of polydimethylsiloxane, containing vinyl groups, with *N*-isopropylacrylamide and acrylic acid. The lower consolute temperatures of the copolymers depend on the pH. The immobilisation of indomethacin³⁵⁶ and amylase³⁵⁷ in gels has been investigated and it has been established that indomethacin and amylase are slowly liberated from the hydrogels at 37 °C and pH 1.4 (the conditions in the stomach), but at pH 7.4 (conditions in the intestine) the liberation of the medicinal substances is appreciably accelerated. The copolymers of *N*-isopropylacrylamide with polydimethylsiloxane containing vinyl groups have been used for the immobilisation of progesterone. These copolymers were obtained for a dose of 10 kGy (dose rate 5 kGy h⁻¹). They have the same LCT as pure poly-*N*-IPAA. The gels contract rapidly on passing through the LCT. The microdomain structure of the gels was established.³⁵⁸ Thermosensitive gels based on alanine derivatives have been obtained.³⁵⁹ Radiation-induced graft polymerisation of *N*-isopropylacrylamide on silicone rubber has been studied.³⁶⁰ The hydration of the resulting graft copolymers has been investigated as a function of temperature and the copolymer composition. The unusual character of the hydration, influenced by the phase transitions in the grafted chains, was established.⁷⁹

The preparation of another 'smart' polymer — the methyl ester of poly(acryloyl-L-proline), which is synthesised by the radiation-induced polymerisation of the methyl ester of acryloyl-L-proline — has been described.^{352, 361} This polymer has a LCT of 14 °C.³⁶¹ The LCT of the polymer may be regulated either by the radiation-induced copolymerisation with 2-hydroxypropyl methacrylate³⁶¹ or by adding sodium dodecyl sulfate.³⁶² The coil–globule transitions and the cross-linking of the methyl ester of poly(acryloyl-L-proline), obtained by radiation-induced polymerisation, have been investigated.³⁶³

Testosterone was introduced into the gel of the methyl ester of poly(acryloyl-L-proline) by means of radiation-induced polymerisation. It was established that testosterone is uniformly liberated from the gel (30 mg per day) in the course of 54 weeks (tests on rats). The gel shrinks on the surface during dehydration, forming a rigid membrane barrier lacking micropores. Compact clusters are formed above the LCT.

A gel of the methyl ester of poly(methacryloyl-D,L-alanine) has been obtained by the radiation-induced polymerisation of the

methyl ester of methacryloyl-D,L-alanine.^{364, 365} The kinetics of the swelling and dehydration of the gel were investigated. It was established that, on dehydration at 40 °C, a bark (skin) is formed on the surface of the gel, closing the pores. The gel was studied by scanning electron microscopy. The gel contracts rapidly on heating.³⁶⁴ The radiation-induced grafting of the methyl ester of acryloyl-L-proline on polymeric materials irradiated by heavy ions has been studied.^{365, 366} The influence of surfactants on the phase transitions in polymers with amino acid side groups has been investigated.³⁶⁷

The antitumour preparation 9-β-D-arabinofuranosyladenine (Ara-A) was immobilised in a thermosensitive gel based on the copolymer of 2-hydroxyethyl methacrylate, styrene, and the methyl ester of acryloyl-L-proline cross-linked by nonaethylene glycol dimethacrylate. The gel was obtained by radiation-induced copolymerisation. The phase transition occurs at 14 °C. The gel shrinks rapidly on passing through the phase transition point. The liberation of Ara-A was investigated at 10–37 °C. The gel operates *via* a pulsating mechanism resembling a pump. Rapid shrinkage and liberation of Ara-A take place at 37 °C.³⁶⁸ Thermosensitive gels, obtained by the radiation-induced cross-linking of poly(methyl vinyl ether) (PMVE) dissolved in water, have been described.^{369–372} The phase transition is at 38 °C. Porous and fibrous gels were obtained and their swelling was studied under various conditions. Artificial muscles and fingers have been created on the basis on the PMVE gels.³⁶⁹ According to the data of Kobra *et al.*,³⁷⁰ the LCT for aqueous PMVE solutions is in the range 34–38 °C. By selecting the irradiation conditions, it is possible to obtain PMVE gels with high rates of swelling and dehydration.^{370–371} Aqueous 50% solutions of PMVE and doses of 60–110 kGy are used. A characteristic feature of the PMVE gels is larger volume changes compared with other thermosensitive gels. On heating, the gels contract rapidly and a microporous structure develops.^{372, 373} The transitions in the PMVE gels have been investigated.³⁷⁴ The immobilisation of exo-1,4-α-D-glucosidase in the PMVE gel has been described.³⁷⁵ The formation of glucose from maltose with the aid of this enzyme has been investigated and a marked influence of temperature on the activity of the enzyme has been established, this being associated with a phase transition in the gel.³⁷⁴

A series of data on the application of radiation-induced polymerisation and cross-linking for the creation of 'smart' polymers and their employment for the immobilisation of various medicinal preparations have been presented in reviews.^{346, 376–378} The problems of the employment of radiation-induced polymerisation for the creation of signal-sensitive systems consisting of a biosensor, an activator, and a reservoir have been considered.^{346, 378} Special systems with a biosensor for glucose are being developed. They are switched on in accordance with the on–off principle for the liberation of specific portions of insulin immobilised in gels.^{377, 378} New thermosensitive hydrogels have been obtained by the radiation-induced copolymerisation of vinyl ethers of glycols with various alkyl vinyl ethers.³⁷⁹ Certain theoretical problems associated with 'smart' polymers have been considered in a review.³⁸⁰

VI. The use of radiation-induced cross-linking for the preparation of polymeric biomaterials

The interest in the preparation of polymeric biomaterials by radiation-induced cross-linking has grown significantly at the present time. Such cross-linking is most frequently used to prepare hydrogels, mainly based on polyacrylamide poly(vinyl alcohol), poly(ethylene oxide), and poly(*N*-vinylpyrrolidone).^{381–383} An advantage of the radiation-induced cross-linking is the comparative simplicity of its implementation, the possibility of the wide scale regulation of the network density by selecting irradiation conditions (dose rate, dose), the possibility of using reduced temperatures, the purity of the product obtained (the absence of initiators), and simultaneous sterilisation. The radiation-cross-

linked hydrogels are used as BAS (enzymes, medicinal substances, *etc.*) carriers, implants, prostheses, eye lenses, medical membranes, dressings, and biological media for the study and culturing of microorganisms.

The methods of preparation and properties of hydrogels based on radiation-cross-linked polyacrylamide have been studied in greatest detail.^{384–401} The formation of gels of this compound on irradiation of aqueous acrylamide solutions over a wide range of conditions (monomer concentration, dose, and dose rate) has been investigated.^{282, 384, 388, 398}

The dose for gel formation is in the range 0.1–2.5 kGy. It falls rapidly with increase in the monomer concentration and increases with increase in dose rate. On irradiation of aqueous acrylamide solutions up to high doses, decomposition with formation of aldehydes and carboxylic acids takes place.³⁸⁸ The mechanism of the cross-linking of polyacrylamides is associated with the abstraction of a hydrogen atom from a tertiary carbon atom.³⁸⁷ Various procedures for the preparation of gels based on polyacrylamide have been studied.³⁹⁵ Using radiation-induced polymerisation, it is possible to obtain readily hydrogels of this polymer with a wide range of properties (hydrophilicity, modulus of elasticity, swellability, *etc.*). The hydrogels formed as a result of the radiation-induced copolymerisation of acrylamide and maleic acid exhibit a satisfactory biocompatibility with the serum prepared from human blood.³⁹¹

Methods have been developed for the preparation of dressings based on radiation-cross-linked polyacrylamide gels^{282, 385} as well as polymer eye lenses.²⁸² A three-stage radiation technology for the manufacture of dressing hydrogels to achieve the healing of extensive areas of burns and its advantages over other technologies have been described.⁴⁰¹ Polyacrylamide, obtained by radiation-induced polymerisation, has been used as the coating agent in X-ray films in order to economise on silver.³⁸⁶

A series of studies^{397, 402–420} have been devoted to the preparation of hydrogels by the radiation-induced cross-linking of poly(vinyl alcohol). The mechanism of the formation of its gel on irradiation in water and the properties of the gels,^{402, 403} in particular their swelling,³⁹⁷ have been studied in detail. The hydration of poly(vinyl alcohol) gels leads to crystallisation. Biomembranes for the selective transport of macromolecules as well as materials used as cartilage for joints have been obtained from radiation-cross-linked poly(vinyl alcohol).⁴⁰⁶ Radiation methods for the immobilisation of heparin,⁴⁰⁷ cellulase, urease,⁴⁰⁹ glucoamylase, and invertase⁴⁰⁵ as well as other BAS in poly(vinyl alcohol) hydrogels have been developed. Data on the use of radiation-cross-linked poly(vinyl alcohol) hydrogels for the fixation and controlled liberation of BAS have been presented in a review.⁴¹¹ A disadvantage of such gels is their low mechanical strength. The use of poly(vinyl alcohol) hydrogels as dressings has been described⁴¹⁸ and its advantage over muslin has been noted: homogeneous adhesion to the entire wound and easy removal without damaging the skin. Schemes for the preparation of heat-resistant hydrogels have been described^{418, 419} and methods have been proposed for the improvement of their mechanical properties.⁴¹⁸

Radiation-cross-linked poly(ethylene oxide) hydrogels have been investigated in fair detail.^{397, 421–431} A characteristic feature of such gels is an anomalous decrease in swelling and an increase in the modulus of elasticity on drying, caused by the formation of additional units as a result of crystallisation. The possibility of obtaining porous gels in which the pore size can be varied widely as a function of the irradiation dose is very important. The structure of the ultrahigh-molecular poly(ethylene oxide) after γ -irradiation has been investigated.^{430, 431} It has been suggested that radiation-cross-linked hydrogels of this polymer be used as the medium for the culturing of microorganisms.⁴²⁹ The preparation of biocompatible materials based on radiation-cross-linked poly(ethylene oxide),⁴²⁰ the hydrophobic properties of which may be enhanced by the radiation-induced grafting of butadiene, styrene, or ethene,⁴²⁰ has been described.⁴²⁰

Hydrogels based on poly(*N*-vinylpyrrolidone) are highly hydrophilic and are satisfactorily biocompatible.^{432–442} The methods of preparation of such gels by the irradiation of aqueous *N*-vinylpyrrolidone solutions have been studied in detail.^{438, 443} The radiation-induced cross-linking and degradation of poly(*N*-vinylpyrrolidone) have been studied.⁴³⁵ The radiation technology for the preparation of gels of this polymer, used as a material for the treatment of burns and trophic ulcers, has been described in detail.^{436, 440} These materials are sold in Poland under the commercial names HDR^R and AQUA-Gel^R. A therapeutic system based on the poly(*N*-vinylpyrrolidone) gel has been developed for use in obstetric practice to accelerate births and to induce abortions. In this case, the gel consists of a thin rod containing prostaglandin. The methods for the preparation of such gels have been described in detail.^{432, 436} Data on the biological and physical properties of the hydrogels used as dressings have been described and compared with the usual muslin bandages.⁴⁴¹ The influence of the irradiation dose on the mechanical properties of poly(*N*-vinylpyrrolidone) gels filled with agar and poly(ethylene glycol) has been studied (Fig. 1).⁴⁴²

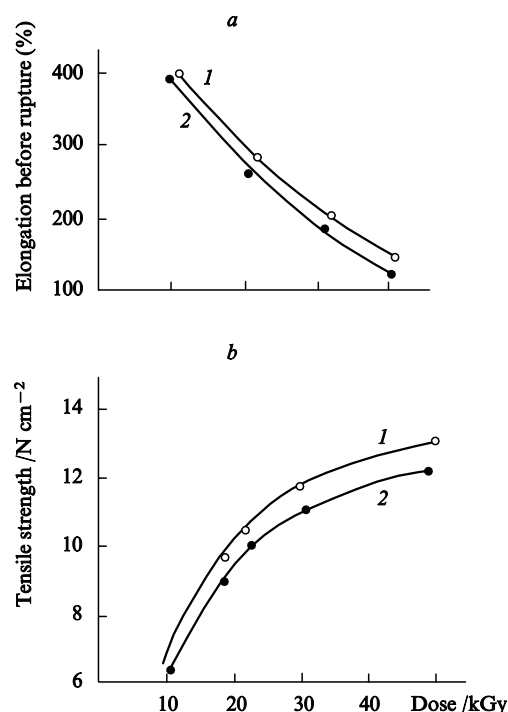


Figure 1. Dependence of the elongation before rupture (*a*) and of the tensile strength (*b*) on the irradiation dose for poly(*N*-vinylpyrrolidone) gels 2.5±0.5 mm thick. (1) Gels filled with agar and poly(ethylene glycol); (2) gels filled with agar.

The technology for the preparation of hydrogels for dressings has now been developed in fair detail and they have undergone extensive clinical tests.⁴³⁹ An important factor is the possibility of obtaining gels for dressings containing medicinal preparations (for example, chloramphenicol).⁴⁴⁰ In the case of large wounds, such a hydrogel is significantly more effective than the usual dressings. Radiation-cross-linked hydrogels based on poly(*N*-vinylimidazole), the properties of which are close to poly(*N*-vinylpyrrolidone) gels,^{444, 445} as well as radiation-cross-linked gels based on microbial poly- γ -glutamic acid with a high moisture-absorbing capacity⁴⁴⁶ and hyaluronic acid gels with a high biocompatibility⁴⁴⁷ have been obtained. Practical advice concerning the preparation of various hydrogels — optically homogeneous and with a minimal content of the residual monomer — has been given.⁴⁴⁸

Interesting studies have been carried out in order to obtain polymeric materials based on collagen.^{334–336, 449–454} The formation of gels on irradiation of collagen solutions has been studied in detail.^{449, 454} These solutions have been used for the creation of radiation-modified medical implants.^{449–451, 454} Collagen coatings on silicone rubber, subsequently radiation-cross-linked and sterilised, are used in medicine.⁴⁵³ Another natural product employed for the preparation of biomaterials is gelatin.^{454–457} The radiolysis of gelatin has been studied and the conditions for the formation of three-dimensional structures on irradiation of its solutions have been discovered.⁴⁵⁴ It has been suggested that a radiation-cross-linked composition comprising poly(vinyl alcohol) and gelatin be used as a dressing.⁴⁵⁷

Gels based on polyphosphazenes have been investigated.⁴⁵⁸ A new method has been proposed⁴⁵⁹ for the preparation of hydrogels using natural polymers: gelatin, dextran, and albumin. The method consists in the functionalisation of natural polymers by introducing into them double bonds with subsequent cross-linking by γ -irradiation. The method makes it possible to introduce a large amount of a BAS into the hydrogels.

Radiation-induced cross-linking has been used for the preparation of medical articles made from polysiloxanes: biologically inert porous cord, syringe tubes, capillaries,⁴⁶⁰ and various implants.^{461–463} In the radiation-induced cross-linking of polydimethylsiloxane under specially pure conditions, its haemocompatibility increases significantly.⁴⁶² The radiation-cross-linked polyvinylmethylsiloxane has been used to prepare thin membranes for the making of medicinal preparations (for example, levonorgestrel).⁴⁶³

The radiation-induced cross-linking of trans-1,4-polyisoprene has been used to create thermoshrinking materials for the tying of large blood vessels. The materials have undergone extensive tests *in vitro* and *in vivo* (on dogs).^{464, 465} Radiation modification makes it possible to improve the properties of medical prostheses based on polyolefins.⁴⁶⁶ Polymeric biomaterials with enhanced adhesion to human skin have also been obtained with the aid of radiation-induced cross-linking.^{466, 467}

The manufacture of a synthetic dressing, obtained by the radiation-induced grafting of hydrophilic monomers on polyurethane, has been initiated in Israel. The material is water-impermeable and transparent, is readily attached to the skin, and is permeable to medicinal drugs. The material is manufactured under the name Omiderm.⁴⁶⁸

A pilot plant has been created for the manufacture of radiation-cross-linked natural rubber latexes.⁴⁶⁹ The production of the plant is 1000 tonnes of the product per year (Malaysia). These materials are used to manufacture high-quality medical gloves, thin-walled articles, *etc.*^{469–471} Radiation-induced cross-linking polymerisation is particularly important in the manufacture of polymeric biomaterials for ophthalmology. Procedures for the hydrophilisation of contact lenses by the radiation-induced graft polymerisation of *N*-vinylpyrrolidone^{472–476} or hydroxyethyl methacrylate^{477, 478} have been described. Methods have been developed for the preparation of an artificial cornea and contact lenses with a high swellability in water from radiation-cross-linked poly(vinyl alcohol) with added sodium chondroitin sulfate.⁴⁷⁹

Ionising radiation has been used to ensure complete hardening and to minimise the amount of residual monomer in the preparation of contact lenses.^{480–482} In order to increase significantly the permeability of the contact lenses to oxygen, it is suggested that they be irradiated with accelerated heavy ions having a mass of 2–100.⁴⁸³ Hydrogel materials for soft contact lenses have been created with the aid of radiation-induced polymerisation.^{484, 485} These materials are produced in China.⁴⁸⁵

Radiation-cross-linked collagen, isolated from the sclera of animal eyes, has found an application in the manufacture of ophthalmological materials. This material has been used for the creation of temporary allodrainages in antiglaucoma operations.⁴⁸⁶

Thus the use of ionising radiation for the preparation of polymer hydrogels is promising. Considerable progress has been achieved in the study of the mechanisms of the radiation-induced cross-linking of hydrogels and their practical applications have expanded, particularly in the preparation of polymeric materials used for the rapid healing of various wounds.

An advantage of the radiation-induced cross-linking is the possibility of regulating comparatively easily not only the network density but also the nature of the radiation-induced cross-linking itself by varying the dose rate and the polymer concentration. It has been established that, at a low polymer concentration and at a high dose rate, intramolecular cross-linking predominates over intermolecular cross-linking.^{487, 488}

VII. Conclusion

The scale and level of studies on the employment of radiation-chemical methods for the preparation of polymeric biomaterials designed for application in medicine and biotechnology has expanded significantly in recent years. Certain advantages of these methods compared with traditional ones have been clearly established. The use of ionising radiation for the preparation of polymeric biomaterials is one of the examples of the application of atomic energy for the benefit of humanity.

Considerable advances have been achieved in the employment of low-temperature radiation-induced polymerisation for the immobilisation of various BAS. The immobilisation of antitumour preparations has been studied in greatest detail and extensive investigations of their application in clinics have been performed.

Low-temperature radiation-induced polymerisation has been applied in the immobilisation of enzymes designed for the enzymic hydrolysis of plant waste (Japan). Extensive studies on the use of the radiation-chemical technology for the processing of plant raw material have been carried out in Russia.

Sorbents which have increased significantly the effectiveness of the chromatographic separation of mixtures of certain BAS have been created with the aid of radiation-induced graft polymerisation. Much work has been done on the application of radiation-induced graft polymerisation for the modification of polymeric materials in order to increase their haemocompatibility.

A whole series of novel methods for the immobilisation of BAS using radiation chemistry have been developed in our country.¹

Studies on the employment of radiation-chemical methods for the preparation of a wide variety of polymer hydrogels have been developed very successfully. Some of them (in the form of dressings and polymer eye lenses) have been introduced into clinical practice (Poland, Israel, China). Immunodiagnostic sets employing the radiation-induced polymerisation of 2-hydroxyethyl methacrylate are being manufactured on an industrial scale [K Vacek (Czech Republic), private communication]. The immunodiagnostic sets are used to determine the activity of phagocytes. The radiation-induced graft polymerisation of organotin monomers has been used to prepare modified polymers with fungicidal properties.⁴⁸⁹

New extremely promising aspects of the application of radiation-chemical methods for the preparation of 'smart' polymers designed to be used in biotechnology and medicine have appeared in recent years. They are designed in particular for the deliberate introduction of medicinal substances at the required site in the human organism and also for the preparation of polymer membranes responding to changes in the environment (pH, temperature, *etc.*), which may find an important application in medicine and biotechnology. In all probability, there is a great future for this aspect of the application of radiation-chemical methods.

Studies on the use of ionising radiation for the creation of polymeric biomaterials are being coordinated by the International Atomic Energy Agency (IAEA) and are being prosecuted most vigorously in the USA and Japan.⁴⁹⁰

Significant advances have been achieved by specialists in Poland.^{491, 492}

Hydrogels are being developed most vigorously at the Institute of Applied Radiation Chemistry at the Technical University of Lodz in Poland. Two of the polymer hydrogels developed for the treatment of bed sores, burns, wounds, and transplanted skin tissues and also in the therapy of ulcers have become commercially available in a number of European countries.⁴⁹² The development of materials for an artificial pancreas (it produces insulin), graft tissues for blood and other vessels, and materials for employment in ophthalmology and dentistry is in the completion stage.⁴⁹²

There is no doubt that one may expect in the immediate future the appearance in the market place of new polymeric biomaterials obtained with the aid of radiation-chemical methods.

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^c — *Colloid. J. (Engl. Transl.)*

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

^e — *Mendeleev Chem. J. (Engl. Transl.)*

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

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

^h — *Physics-Uspokhi (Engl. Transl.)*

Alkynylcarbenium ions and related unsaturated cations

S M Lukyanov, A V Koblik, L A Muradyan

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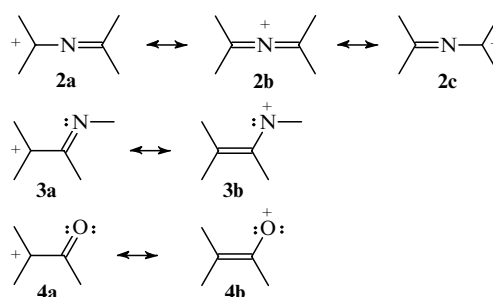
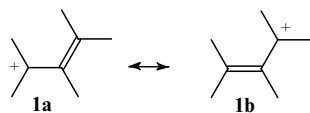
Abstract. Published data on carbenium ions containing $C \equiv C$ bonds both directly conjugated with the carbenium centre and separated from it are surveyed and described systematically. Ammonium, diazonium, iminium, phosphonium and iodonium cations containing alkynyl groups, which can be regarded as heteroanalogues of alkynylcarbenium ions, are also considered. The bibliography includes 283 references.

I. Introduction

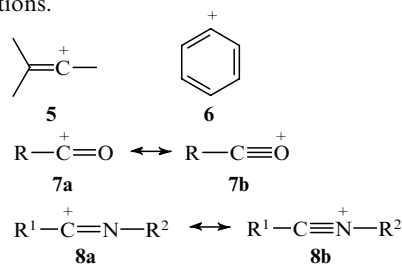
The chemistry of unsaturated carbenium ions is constantly attracting the attention of researchers. The range of objects containing unsaturated carbenium ions is fairly broad: they vary from stable salts used as reagents with unique properties to extremely reactive intermediates the stability of which is comparable to that of the methyl cation.

Unsaturated carbocations with a variety of structures are known. However, all of them can be classified as two main types: (1) cations with a tricoordinated carbenium centre (trisubstituted ions) and (2) cations with a dicoordinated carbenium centre (disubstituted ions). In the former type of cations, the multiple bond is located in the α -position in relation to the positively charged atom (or is farther removed from it along the chain), whereas in the latter type of cations, an atom forming the multiple bond acts as the carbenium centre.

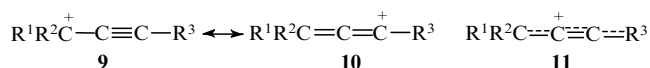
The first type of unsaturated cations comprises allyl cations **1**^{1–7} including functionally substituted ones^{8,9} and their hetero-analogues — 2-azaallenium ions **2**,^{10–15} iminocarbenium ions **3**^{16,17} and α -oxocarbenium ions **4**.^{17–21}



The second type includes vinyl (**5**)^{22–27} and phenyl (**6**)^{17,26–29} cations as well as acylium (**7**)^{2,26,30} and nitrilium (**8**)^{26,31,32} cations.



The species, which arise when a carbenium centre is generated near a triple carbon–carbon bond, occupy a special place among unsaturated carbocations. They can be related to either of the two types mentioned above, because in some cases, these species behave as destabilised (compared to the dimethylvinyl- and even ethyldimethyl-carbenium) tertiary cations (alkynylcarbenium ions **9**),¹⁷ whereas in some other cases, they behave as vinyl ions stabilised by conjugation (allenyl ions **10**).²³



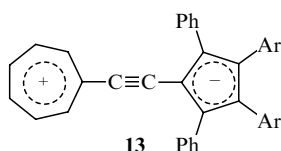
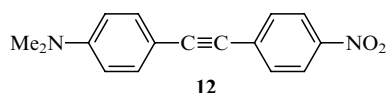
It is obvious that in reality, the charge in the three-carbon chain is substantially delocalised, the degree of delocalisation and, hence, the structure and the behaviour of the cations **11** being dependent on the nature of the substituents R^1 , R^2 and R^3 and the reaction medium. These cations have been considered in numerous studies, the results of which have not yet been surveyed. The stabilised species **10** are discussed in several reviews devoted to vinyl cations.^{22,23,26,33} However, in our opinion, it is more correct

S M Lukyanov, A V Koblik, L A Muradyan Institute of Physical and Organic Chemistry, Rostov State University, pr. Stachki 194/2, 344104 Rostov-on-Don, Russian Federation. Fax (7-863) 228 56 67

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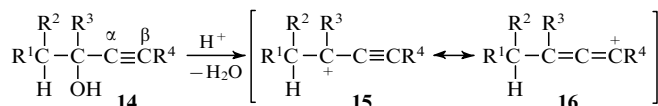
to regard them as acetylene derivatives in which the triple bond is activated by a cationic substituent. This approach has been proposed in studies^{34,35} dealing with the reactions of acetylene derivatives with nucleophiles. The use of acetylene derivatives with cationic substituents proved to be more efficient than the introduction of neutral electron-withdrawing groups^{36–38} or the use of acetylene derivatives of the push–pull type (for example, compounds **12** and **13**^{39,40}).



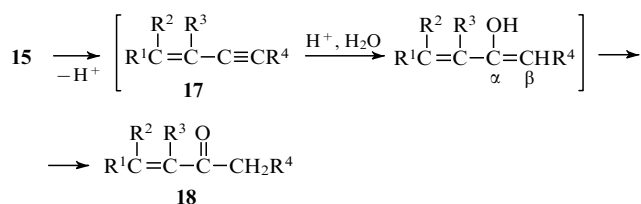
In this review we consider the ions **11** as alkynylcarbenium ions the properties of which are determined by the degree to which the multiple bond in these species retains the nature of a triple carbon–carbon bond.

II. Alkynyl carbocations in transformations of acetylene derivatives

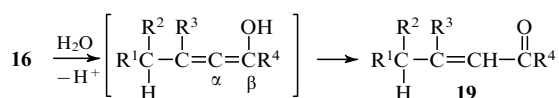
Alkynylcarbenium ions have been postulated as intermediates in acid-catalysed transformations of functionally substituted acetylene derivatives. First of all, this refers to the Meyer–Schuster and Rupe rearrangements (see a review⁴¹ and studies^{42–44}). Long before alkynylcarbocations were detected experimentally (see Section III), it had been concluded that acid-catalysed propargyl rearrangements^{45–47} can occur *via* the intermediate formation of carbocations the structure of which allows realisation of two reaction pathways.⁴⁸ These pathways usually compete, the predominance of either of them being determined by the structure of the initial α -hydroxyacetylene **14**.



the Rupe rearrangement



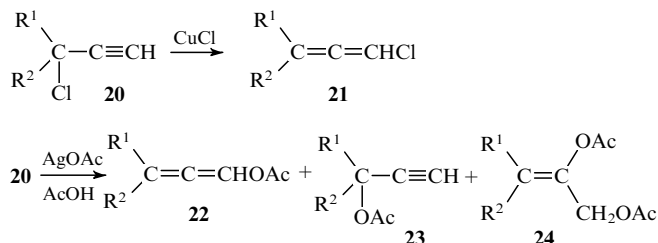
the Meyer–Schuster rearrangement



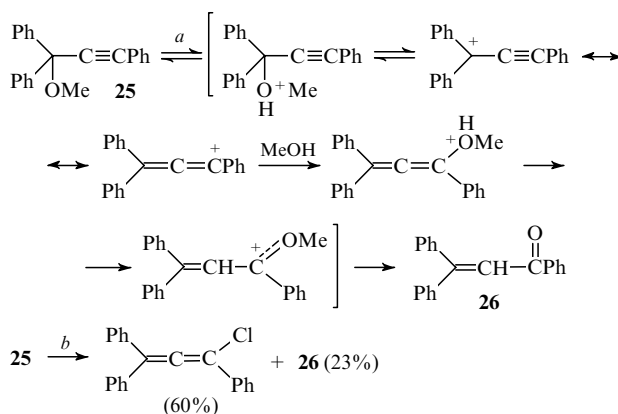
In both cases, α,β -unsaturated carbonyl compounds **18** and **19** are formed. The main difference between these two routes is determined by the carbon atom in the acetylenic fragment which is hydrated and, hence, forms the carbonyl group. The Rupe rearrangement occurs *via* alkynylcarbenium intermediates **15**, which are capable of being deprotonated to enynes **17**. Protonation of the β -carbon atom in the enyne **17** with the addition of water to the α -carbon atom is energetically the most favourable route. However, when the cationic intermediate is stabilised by, for example, aryl groups, participation of the allenyl cation **16** in the reaction becomes more favourable. This cation is hydrated at

the β -carbon atom of the acetylenic fragment (the Meyer–Schuster rearrangement).

Other functional derivatives of acetylene also can enter into this type of rearrangement. α -Chlorinated alkynes **20** are converted into allene compounds **21** or **22**, depending on the reaction conditions.^{48,49} In the latter case, the reaction also gives products **23** and **24**.⁴⁹

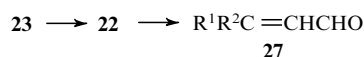


3-Methoxy-1,3,3-triphenylprop-1-yne **25** rearranges under various conditions, and the structure of the rearrangement products implies that the reaction occurs predominantly *via* the most stable cationic intermediates.⁵⁰



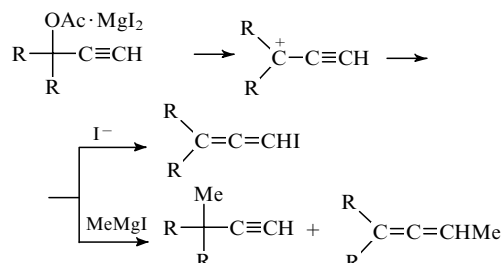
(a) MeOH, 100% H₂SO₄; (b) HCl.

In the presence of copper and silver salts, the acetates of tertiary alkynols **23** are converted exclusively into α,β -unsaturated aldehydes **27**.⁴⁶

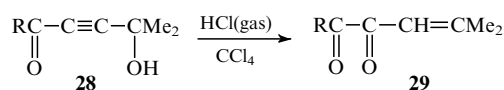


R¹ = Me; R² = (CH₂)₂CH = CMe₂, (CH₂)₂C(Me) = CMe₂;
R¹, R² = (CH₂)₄, (CH₂)₅.

It has been suggested that alkynyl carbocations can arise even under Grignard reaction conditions.⁵¹

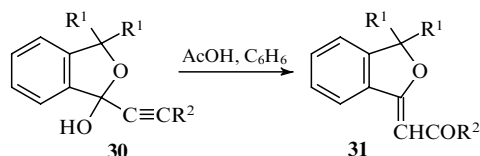


When hydroxy ketones of the acetylene series **28** react with dry HCl in CCl₄, they undergo an unusual rearrangement to give vinyl-substituted α,β -diketones **29**.⁵²



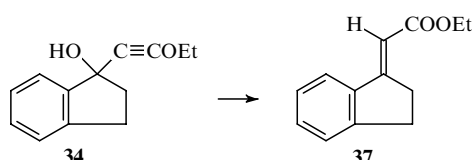
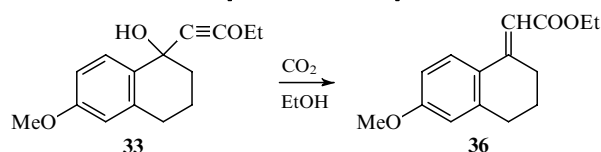
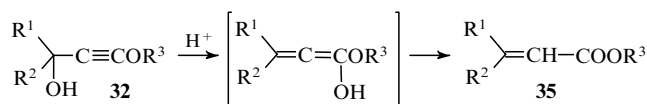
R = Me, Et, Prⁱ.

A series of studies describe^{53–57} the transformations of 1-ethynyl-1-hydroxyphthalans **30** yielding the corresponding α,β -unsaturated ketones **31**.



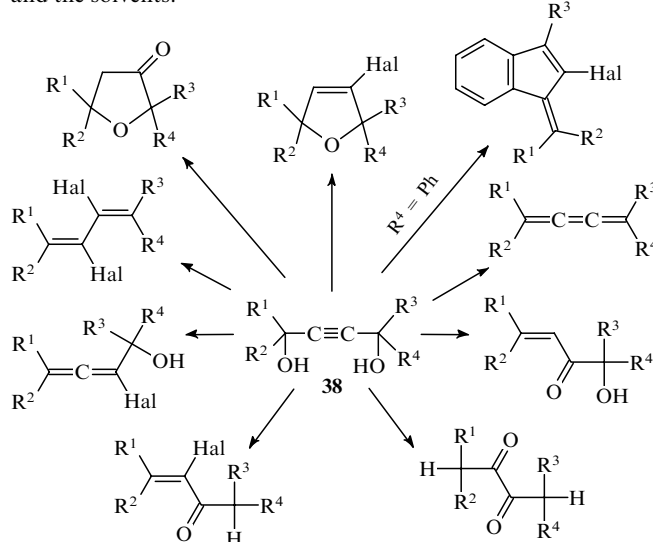
$\text{R}^1 = \text{Me, Ph; R}^2 = \text{Me, Bu}^t, \text{Ph, 4-MeC}_6\text{H}_4$.

Alkoxyalkynols **32–34** are converted into α,β -unsaturated esters **35–37** under mild conditions.^{58–60}



Four possible mechanisms, including those involving alkynylcarbenium ions, have been discussed for these transformations.⁵⁹ It has been noted that none of the schemes provides a satisfactory explanation for the formation of the *cis*-isomers of the compounds **36** and **37**, which possess higher energies than the corresponding *trans*-isomers.

Acid-catalysed transformations of a large series of symmetrical and asymmetrical alkynediols **38** have been described in detail.⁶¹ The pathway of these reactions, which occur presumably with participation of alkynylcarbenium ions, depends on the structure of the substrates and the nature of the acid catalysts and the solvents.

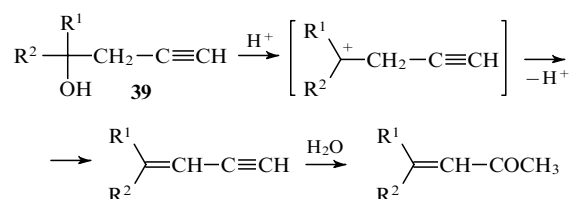


$\text{R}^1 - \text{R}^4 = \text{Me, Et, Pr}^i, \text{Bu}^t, \text{Ph, 4-MeC}_6\text{H}_4, \text{PhCO, 2-pyridyl, (CH}_2\text{)}_5$; Hal = Cl, Br, I;

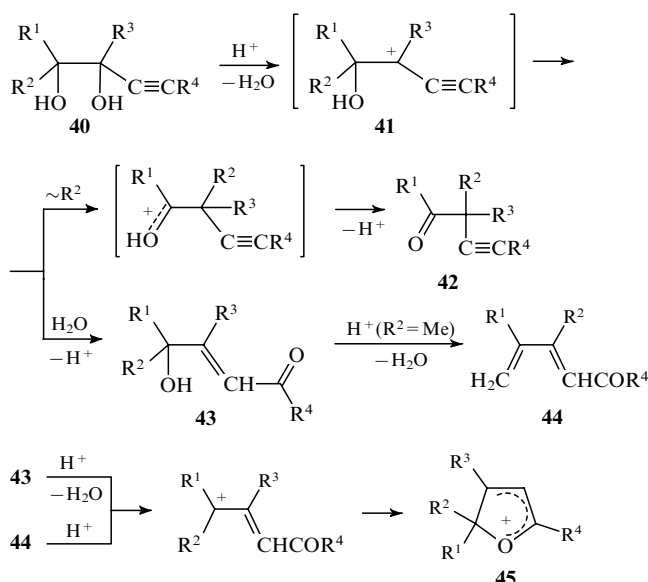
Acid catalyst: $\text{H}_2\text{SO}_4, \text{HCl, HBr, HI, HI-I}_2, \text{AcCl, HCOOH}$;

Solvent: THF, EtOH, AcOH, $\text{Me}_2\text{CO, CCl}_4, \text{AcOH-dioxane}$.

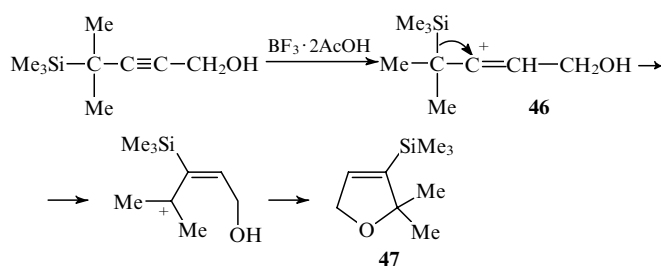
The structures of the products formed in these transformations reflect the typical reactions of carbenium intermediates,² namely, deprotonation, addition of nucleophiles, alkyl migrations and electrophilic aromatic substitution.⁶¹ The same typical reactions are observed in many other cases. Thus tertiary β -alkynols **39** undergo the Rupe rearrangement.⁴¹



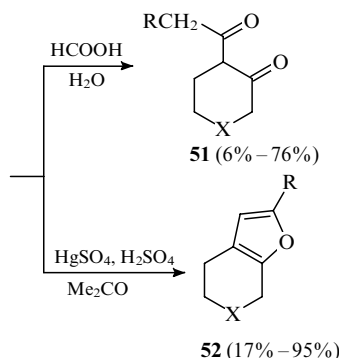
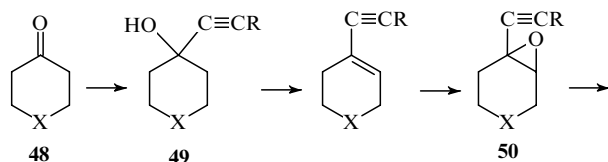
On treatment with dilute H_2SO_4 , bitertiary 1,2-diols of the acetylene series **40** undergo not only the Meyer–Schuster rearrangement yielding enones **43** (or subsequent dehydration to dienones **44**) but also the pinacolic rearrangement to give alkynones **42**. Undoubtedly, this process occurs *via* the alkynyl carbocations **41**. The transformation of the compounds **40** affords as well stable dihydrofurylium salts **45**.^{62,63}



The use of the Meyer–Schuster and Rupe rearrangements, accompanied by sextet rearrangements with group migrations and ring transformations, for the synthesis of compounds that are difficult to prepare by other methods has been described in a review.⁴¹ These transformations are possible when tertiary or, at least, secondary alkynyl carbocationic intermediates are fairly stable. In this connection, the formation of the vinylic cation **46**, which rearranges to give dihydrofuran **47**, deserves attention.⁶⁴

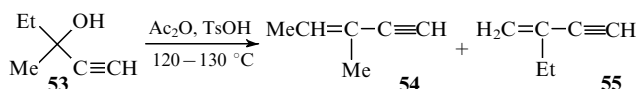


Based on dehydration of hydroxyacetylenes **49**, an interesting preparative approach has been developed for the transformation of alicyclic ketones **48** into diketones **51** and furans **52**.^{65,66}

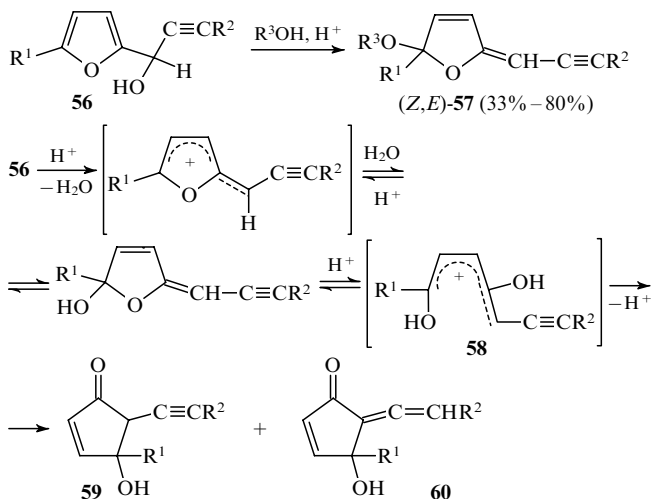


R = Me, Ph, 3,4-(MeO)₂C₆H₃, 4-NO₂C₆H₄; X = CH₂, CHMe, CHPh, CPh₂ (**51**, **52**);
 R = 4-MeOC₆H₄, 2,4-(NO₂)₂C₆H₃; X = SO₂, NTs, NCO₂Et (**52**).

Tertiary alcohols of the acetylene series **53** have been used to synthesise enynes **54** and **55**.⁶⁷



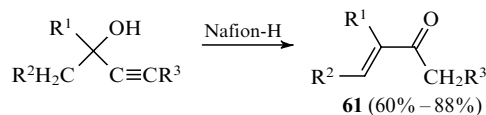
Dehydration of secondary alkynols of the general formula **56** occurring on treatment with various acidic reagents (HCl, CF₃COOH, polyphosphoric acid) affords unusual enyne furan derivatives **57**.^{68–72}



R¹ = H, Me; R² = H, Pr, Bu, C₅H₁₁, C₆H₁₃, CH₂OMe, C≡CPh, Ph;
 R³ = Et, Bu^t.

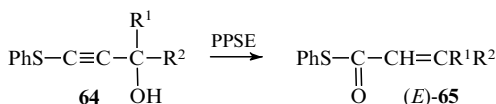
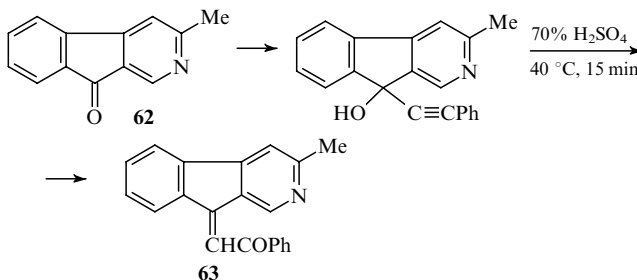
On heating in aqueous dioxane (60 °C) in the presence of toluene-*p*-sulfonic acid, the alcohols **56** recycle to cyclopentenones **59**, **60**, which can serve as valuable starting compounds for the synthesis of prostanoids.⁷² In early experiments, the yields of these products were very low (~10%), due to substantial resinification of the reaction mixtures; however, later, the yields were brought to 80% as a result of stabilisation of the intermediate alkynyl carbocations by complex formation (see Section V).

The Rupe rearrangement in the presence of the solid superacid 'Nafion-H' has been proposed as an improved method for the synthesis of alicyclic and linear α,β-unsaturated ketones **61** (⁷³ (see also Ref. 74).



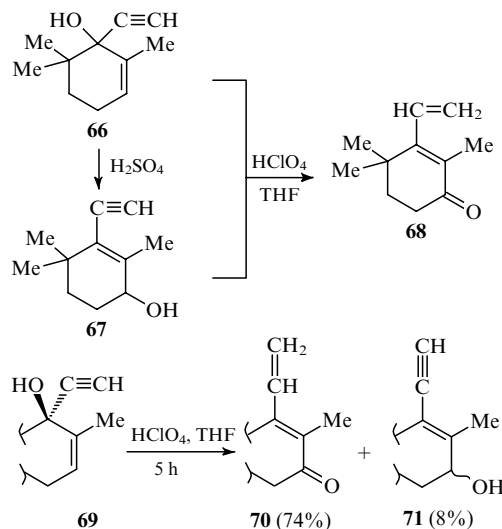
R¹ = Me, Et; R² = Me; R¹, R² = (CH₂)_n, n = 3–6; R³ = H, Me.

The Meyer–Schuster rearrangement has been used to prepare fulvenes **63** (which are intermediates in the synthesis of spiro compounds) based on 3-methyl-2-azafluorenone **62**.⁷⁵ A new method for the preparation of *S*-phenyl thioesters **65** consists in the reaction of phenylthio-substituted alkynols **64** with the trimethylsilyl ester of polyphosphoric acid.⁷⁶

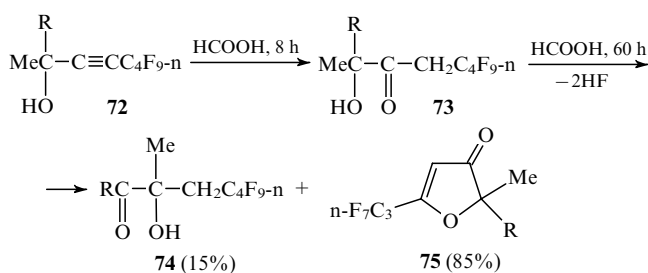


R¹ = Et, Prⁱ, Bu, Bu^t, PhCH₂CH₂, BuCH₂, PrCH=CH,
 PhCH=CH, BuC≡C; R² = Bu; R¹, R² = (CH₂)_n, n = 4–6.
 PPSE is the trimethylsilyl ester of polyphosphoric acid.

The specific structure of the initial hydroxyacetylene may result in an unusual route of the propargyl rearrangement. Thus treatment of ethynyl-containing alcohols **66**, **67** and **69** with a 35% solution of HClO₄ in THF gave rise to dienones **68** and **70**, which are difficult to prepare by other methods and which are used in the synthesis of di- and tri-terpenoids.⁷⁷

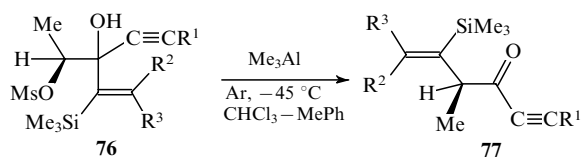


Perfluorobutyl-substituted alkynols **72** have been found⁷⁸ to behave unusually under the Rupe reaction conditions: dehydration does not occur at all; nevertheless, a carbonyl group appears at the α-carbon atom of the multiple bond. The α-hydroxy ketones **73** thus formed are converted into a mixture of hydroxy ketones **74** and furanones **75** upon prolonged (60 h) refluxing in HCOOH as a result of the acyloin rearrangement involving the perfluorobutyl group.



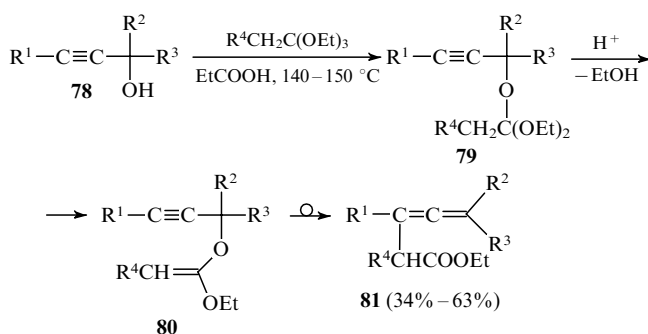
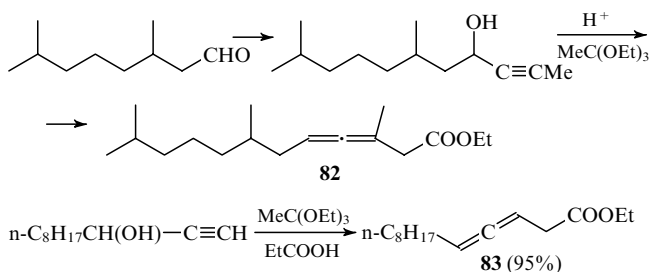
R = Me, Et.

Mention should be made of the unusual pinacolic rearrangement of 1,2-glycol derivatives of the acetylene series **76**, which gives rise to α,β -unsaturated alkynones **77**. These compounds are used as chiral synthons in syntheses of biologically active compounds.⁷⁹

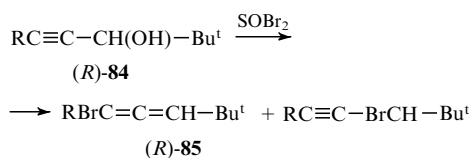

$$R^1 = \text{Ph, Bu}^t\text{Me}_2\text{Si, Ph}(\text{CH}_2)_3; R^2 = \text{H, Bu, PhCH}_2\text{OCH}_2; R^3 = \text{H, Bu.}$$

This stereospecific 1,2-rearrangement occurs due to the fact that the ability of the ethynyl substituent for migration to the carbenium centre is much lower than that of the alkenyl substituent activated by the Me₃Si group.⁷⁹

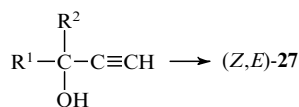
Acid-catalysed esterification of alcohols **78** resulting in the formation of mixed orthoesters **79** and the subsequent Claisen rearrangement of ketene acetal **80** afford allene esters **81**.⁸⁰ This type of transformation of orthoesters is known⁸¹ to involve cationic intermediates. These reactions have been used to synthesise compounds **82** and **83**, analogues of juvenile hormones⁸² and sex pheromones⁸³ of insects.


$$R^1 = \text{H, Me}; R^2, R^3 = \text{H, Me, Pr, (CH}_2)_5; R^4 = \text{H, Me.}$$


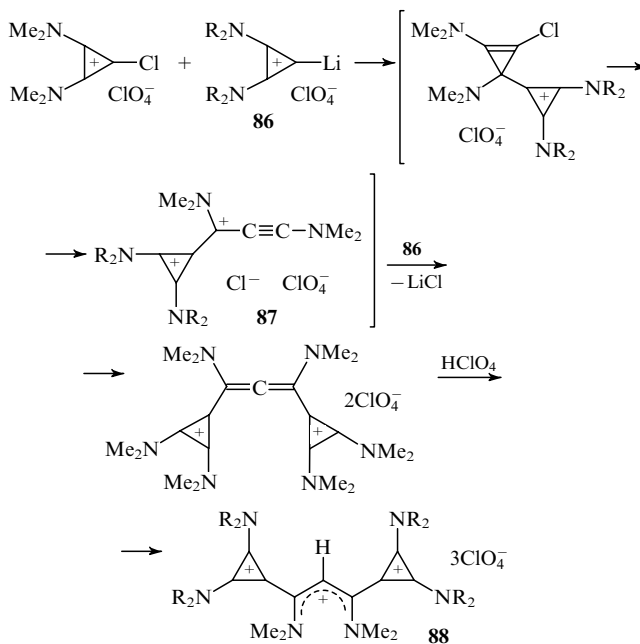
The Meyer–Schuster rearrangement initiated by SOBr_2 has been used to carry out stereospecific synthesis of chiral 1,3-disubstituted bromoallenes (*R*)-**85** from alkynols (*R*)-**84**⁸⁴ and to synthesise the α,β -unsaturated aldehydes **27** in the presence of polyanadiummorganosiloxanes.^{85, 86}



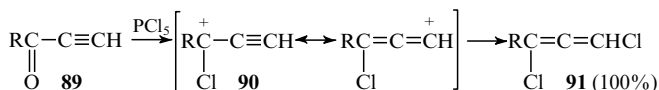
R = Me, Bu^t.


$$R^1 = H, Me; R^2 = 4-Pr^iC_6H_4, 4-Bu^iC_6H_4, 4-MeOC_6H_4, 4-MeC_6H_4, 2,4-Me_2C_6H_3.$$

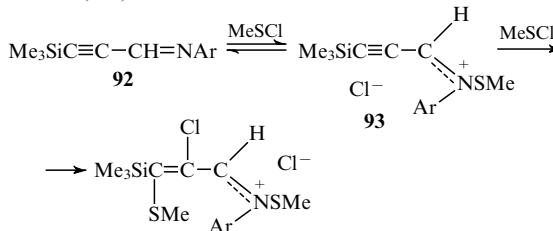
A reaction of cyclopropenylum salts which is accompanied by rearrangement with cyclopropene ring opening and gives alkynyl-carbenium dications **87** has been described;⁸⁷ the dications **87** were converted into tricarbenium ions **88** stabilised by electron-donating substituents. The principle of coupling of positively charged building blocks used here seems promising for the synthesis of extended polycationic systems consisting of allyl-cationic and/or cyclopropenylum fragments stabilised by electron-donating groups.



Treatment of ethynyl ketones **89** with PCl_5 affords 1,3-dichloroallenes **91** *via* intermediate chloro(ethynyl)carbenium ions **90**.⁸⁸ Participation of ethynyliminium ions **93** has also been assumed in the transformations of azomethines of the acetylene series **92**.⁸⁹

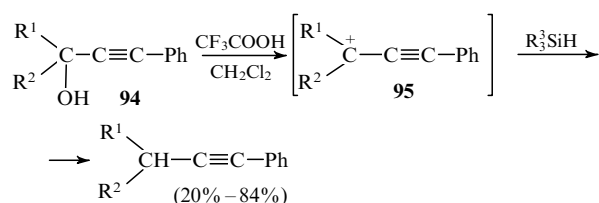


R = Me, Prⁱ, Ph.



Ar = 2-MeC₆H₄, 4-ClC₆H₄.

Ionic hydrogenation of alkynols **94** (treatment with trialkylsilanes in the presence of trifluoroacetic acid) involves reduction of the hydroxyl group.⁹⁰ The mechanism proposed for this reaction includes transformation of the alcohol into carbocation **95**, which adds the hydride ion detached from the silane.⁹¹

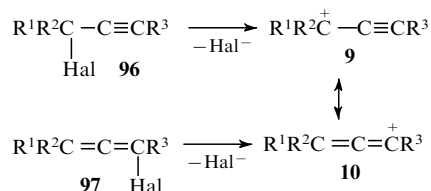


R¹ = Me, Et, Ph; R² = H, Me, Et, Prⁱ, Bu^t; R³ = Me, Et, Bu, Ph.

In the greater part of the publications listed above, the formation of alkynylcarbenium ions was merely postulated based on the general considerations about the mechanisms of acid-catalysed propargyl rearrangements and transformations of functional derivatives. However, alkynylcarbenium ions have ceased to be hypothetical species long ago. They have been repeatedly detected by spectroscopy (Section III); numerous reliable examples of stable alkynylcarbenium salts have now been described (Section V).

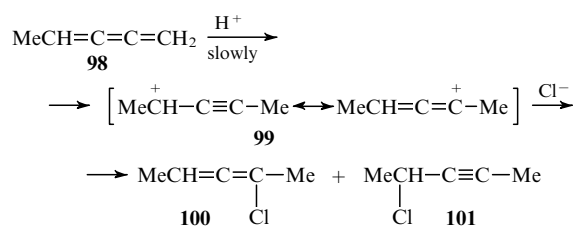
III. Spectroscopic studies of alkynyl carbocations

The first attempts to detect experimentally alkynylcarbenium ions were based on the study of the kinetics of solvolysis. The few studies devoted to this topic are surveyed in several publications.^{33, 92, 93} However, they provided only kinetic evidence for the participation of carbocationic intermediates in solvolysis but gave no information about the structure of these species. It has been noted that the allenyl cations **10** are contributing structures in relation to the propargyl cations **9** and that the ions in question can be generated by solvolysis of both haloalkynes **96** and haloallenes **97**.



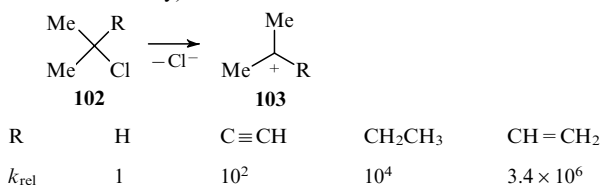
In general, the experimental data obtained for the solvolysis of both series of derivatives under a variety of conditions indicate that these reactions follow the S_N1 mechanism and that the halides **96** react much faster than the corresponding allenyl isomers **97**.⁹²⁻⁹⁵

Attempts to elucidate the nature of unsaturated cationic intermediates have also been made in studies dealing with electrophilic addition to cumulenes. Thus, it has been found that hydrochlorination of penta-1,2,3-triene **98** in aqueous ethanol gives 1,2- and 1,4-addition products (**100** and **101**, respectively) in 1 : 4 ratio, whereas in a 4 : 1 sulfolane-CH₂Cl₂ mixture, the ratio of these products is 1 : 1.⁹³

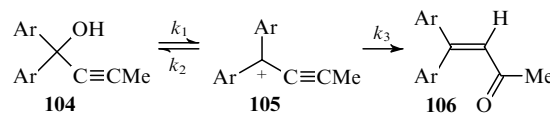


The relative stability of the ethynyl carbocations with respect to the stabilities of secondary, tertiary and allylic cations can be derived based on the rates of solvolysis of the series of derivatives

102. The results obtained indicate that substituents R can stabilise the cationic intermediate **103** (the rate of solvolysis for R = H was taken to be unity).¹⁷



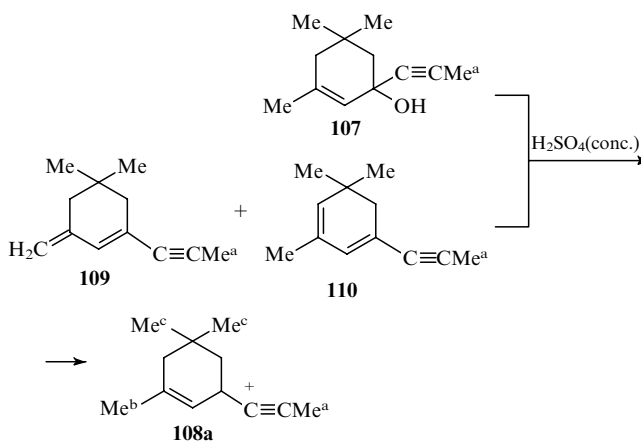
More definite information about the structure of the unsaturated cations in question can be obtained by NMR spectroscopy. The first direct observation of alkynyl carbocations **105** was reported by Richey *et al.*⁹⁵ in 1965. These cations aroused particular interest due to the fact that they could be regarded as a sort of vinylic cations (see Section I). The ¹H NMR spectrum of the solution resulting from extraction with CCl₄ of the product formed upon careful addition of 1,1-di(*p*-methoxyphenyl)but-2-yn-1-ol **104** to concentrated H₂SO₄ proved the formation of the cations **105** under these conditions.



Ar = 4-MeOC₆H₄.

Dilution of this solution by water or aqueous alkali results in the recovered initial alcohol **104** together with a minor amount of the rearranged product **106** (*i.e.* $k_2 \gg k_3$). The signal for the methyl protons of the propynyl fragment ($\delta = 2.6$ ppm) in the cation **105** is substantially shifted downfield in relation to this signal for the initial alcohol **104** ($\delta = 1.87$ ppm); this is due to the substantial charge delocalisation between the tertiary carbenium centre and the multiple bond.

It was shown in the same study⁹⁵ that the cation **108a** is generated both from alcohol **107** and from a mixture of dienyne **109** and **110**; this was proved by the data of ¹H NMR spectra in which the signals for the methyl protons at the ends of the unsaturated chain (Me^a, Me^b) almost coincide.



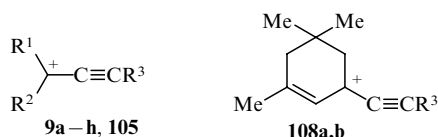
Compound	Chemical shift, δ /ppm		
	Me ^a	Me ^b	Me ^c
107	1.78		
108a	2.65	2.76	1.10
109	1.93		
110	1.93		

A large series of ethynyl- and propynyl-carbenium ions **9a-h**, **105** and **108a,b** have been obtained by mixing solutions of the corresponding tertiary alcohols in liquid SO₂ with a solution of

Table 1. Chemical shifts of the protons of substituent R³ in the ¹H NMR spectra of ethynyl- and propenylcarbenium ions.⁹⁶

Compo- und	R ¹	R ²	R ³	δ(R ³) /ppm	Δδ
9a			Me	2.47	0.63
9b	Ph	Ph	Me	2.88	1.06
9c	Ph	Me	Me	2.94	1.12
9d	MeC≡C–	MeC≡C–	Me	2.76	0.89
9e			H	5.58	3.35
9f	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	H	5.70	3.05
9g	Ph	Ph	H	6.96	4.35
9h	Ph	Me	H	7.24	4.76
105	4-MeOC ₆ H ₄	4-MeOC ₆ H ₄	Me	2.60	0.73
108a	–	–	Me	2.63	0.85
108b	–	–	H	6.32	4.00

antimony pentafluoride in fluorosulfonic acid (the ratio SbF₅:FSO₃H = 1:3 by volume) at –78 °C. Table 1 presents the ¹H NMR spectra of these mixtures recorded at –60 °C.⁹⁶



The chemical shifts of the methyl group protons in the compounds **9a–d**, **105** and **108a** and the ethyne protons in **9e–h**, **108b** as well as the downfield shifts of these signals (Δδ) with respect to the signals of the corresponding protons in the initial alcohols point to substantial deficiency of the electron density on the carbon atoms of the acetylenic fragment. This deficiency becomes more pronounced as the carbenium ions become less stable, *i.e.* the ability of the substituents at the tertiary carbenium centre to delocalise the charge decreases.

More comprehensive data on the ¹H NMR spectra of the above cations and some other alkynyl carbocations can be found in reviews.^{33,97}

Olah *et al.*⁹⁸ attempted to generate alkynylcarbenium ions by treating tertiary alkynyl chlorides with SbF₅ or a solution of SbF₅ in SO₂. However, these experiments were unsuccessful due to the large amount of side products. Therefore, the researchers⁹⁸ used again the corresponding tertiary alcohols, which were treated as described in the study cited above.⁹⁶ As a result, they recorded the ¹H NMR spectra of the cations **9b** and **9i–n** (Table 2).

Table 2. Chemical shifts of methyl group protons in the cations **9b**, **i–n**.⁹⁸

Compound	R ¹	R ²	R ³	δ/ ppm
9b	Ph	Ph	Me	2.88
9i	Ph	Ph	Ph	–
9j	Ph	Me	Ph	3.14
9k	Me	Me	Ph	3.39
9l	Me ^a	Me ^a	Me ^b	3.67(a), 3.13(b)
9m	Me ^a	4-Me ^b C ₆ H ₄	Me ^c	3.05(a), 2.45(b), 2.59(c)
9n	Me ^b	Me ^a	Ph	3.11(a), 2.82–3.00(b, c)

Several conclusions were drawn from analysis of the ¹H NMR spectra of these cations.⁹⁸ Thus the downfield shift of the signal of the protons of the methyl group bound to the tertiary carbenium centre increases in the sequence **9m** < **9n** < **9j** < **9k** < **9l**, *i.e.* following the decrease in charge delocalisation by the other two substituents. The positive charge in the ion **9l** (δ^{Me} = 3.67 ppm) is markedly redistributed, with respect to that in the *tert*-butyl cation (δ^{Me} = 4.35 ppm),⁹⁹ with participation of the propynyl fragment;

this is also manifested as a downfield shift of the signal of the methyl protons in the cation **9l**. Nevertheless, an alkynyl group is unable to delocalise the charge efficiently (at least, as efficiently as does the vinyl group), because the attempts to generate alkynyl carbocations from the secondary alcohols RCH(OH)C≡CPh (R = Ph, Me) failed.⁹⁹ Under the conditions reported, instantaneous polymerisation occurred even at –60 °C.

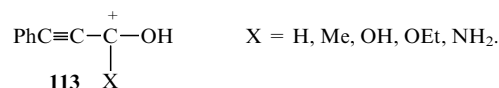
The alkynoyl cations RC≡C–C⁺=O (R = H, Me, Ph) are quite stable; for these species, ¹H and ¹³C NMR spectra have been recorded¹⁰⁰ and substantial charge delocalisation over the conjugation chain has been demonstrated. Tris(*tert*-butylethynyl)methanol **111** readily reacts with strong acids even at room temperature. However, a satisfactory ¹H NMR spectrum of cation **112** was obtained only upon cooling a solution of the alcohol **111** in chlorosulfonic acid below 3 °C. The spectrum exhibits a singlet with δ = 1.86 ppm due to the *tert*-butyl group protons (note for comparison that the protons of the alkyl group in the initial alcohol **111** are responsible for a signal with δ = 1.70 ppm).¹⁰¹



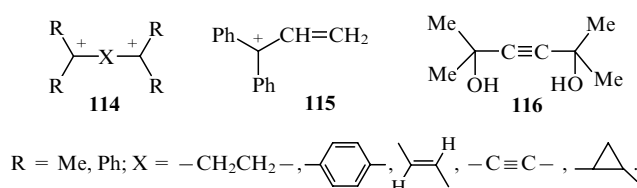
It is of interest that bright colouring of acidic solutions of tris(alkynyl)methanols was mentioned in publications back in the 1920s (see Ref. 101 and references therein).

The alkynyldihydroxycarbenium ions RC≡C–C⁺(OH)₂ (R = H, Me, Ph) arising upon protonation of the corresponding propiolic acids by FSO₃H in liquid SO₂ (–78 °C) or in SO₂ClF (–120 °C) have been detected by NMR spectroscopy.¹⁰²

A fairly comprehensive study of the ¹³C NMR spectra of a series of phenylethynylcarbenium ions (together with benzyl- and naphthylcarbenium cations) has been reported by Olah *et al.*¹⁰³ They analysed in detail the degree of positive charge delocalisation as a function of the nature of the substituents at the carbenium centre. In particular, the ¹³C NMR spectra of protonated carbonyl compounds **113** were discussed.



Olah *et al.*¹⁰⁴ have analysed the ability of an alkynyl group to delocalise positive charge in comparison with this property of other groups. This was done using a series of carbenium dications **114** generated from the corresponding diols or dihalo-derivatives on treatment with FSO₃H, SbF₅–FSO₃H or SbF₅–SO₂ClF.

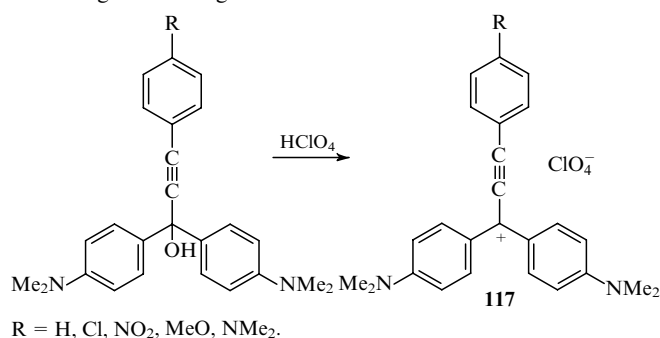


According to the data of ¹H and ¹³C NMR spectra, *para*-phenylene and cyclopropyl groups possess the best capacity for charge delocalisation. The –CH=CH– group occupies an intermediate position, and the –C≡C– group exhibits the poorest charge delocalisation capacity. In the tetraphenyl-substituted dications **114** (R = Ph), the charge is mainly concentrated on the carbenium centres and also in the *ortho*- and *para*-positions of the terminal phenyl groups.¹⁰⁴

The ¹³C NMR spectra of dications of the type **114** were compared with those of the diphenylpropynylcarbenium (**9b**) and diphenylallyl (**115**) cations.^{100, 104} The relationship between the chemical shifts of the carbon atoms implies that in symmetrical dications **114** (R = Ph, X = –CH=CH–, –C≡C–), the charge is delocalised to a lesser extent than in the corresponding ions **115** and **9b**. When the initial alcohol molecule contains no electron-

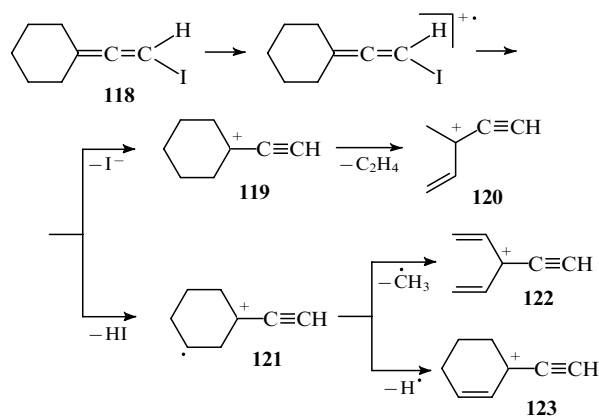
releasing groups attached to the potential carbenium centre and capable of charge delocalisation, dications of the type **114** ($R = \text{Me}$) are not formed. Attempts to ionise 2,5-dimethylhex-3-yne-2,5-diol **116** result in a complex mixture of carbocations. As has already been mentioned, systems of this sort (**38**, Section II) readily undergo various types of isomerisation such as the Rupe and Meyer–Schuster rearrangements.

Other spectroscopic methods have also been used to study alkynylcarbenium ions. Stable alkynylcarbenium salts have been characterised by IR spectroscopy (Section V). Electronic spectroscopy has been used to detect cationic intermediates and to measure their lifetimes.^{33,95} The dependence of the electronic spectra of cations **117** on the nature of the substituent in the arylolefinyl fragment has been studied in order to develop new ethynyl analogues of triphenylmethane dyes, which intensely absorb light in the region 700–800 nm.¹⁰⁵



It has been found that introduction of a triple carbon–carbon bond in the structure of a triarylmethane dye makes this cationic species planar, because one of the aryl groups moves away from the trigonal unit; this is accompanied by a strong bathochromic shift of the absorption band to the visible region of the spectrum. In addition to the decrease in the steric strain between the *ortho*-hydrogen atoms in the aryl groups, it becomes possible to influence the electron density distribution over the whole cation by varying the nature of substituent R .

Degradation of the molecular ions of allene hydrocarbons has been proposed to give the propargyl cation ($\text{HC}\equiv\text{C}-\text{CH}_2^+$).⁷ The most intense peaks (about 100%) in the mass spectrum of iodoallene **118** are the peaks of fragment ions with m/z 107, 91, 79 to which structures of the ethynylcarbenium ions **119**, **122** and **120**, respectively, were assigned.¹⁰⁶

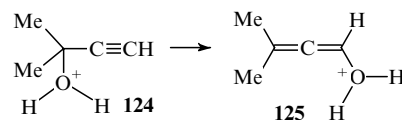


The use of various spectroscopic techniques for identification of alkynylcarbenium ions is discussed in Section V using particular synthetic examples.

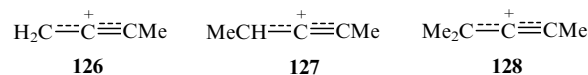
IV. Quantum-chemical calculations

The mechanism of the Meyer–Schuster rearrangement has been studied theoretically using *ab initio* calculations for *O*-protonated 3-methylbut-1-yn-3-ol **124** and the product of its rearrangement, 3-methylbuta-1,2-dien-1-ol **125**. Based on the results of these

calculations, it was concluded that the transition state of the **124** → **125** rearrangement is a complex consisting of a carbocation and a water molecule acting as the migrating species.¹⁰⁷

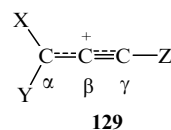


To rationalise the predominant 1,4-addition to penta-1,2,3-triene **98**, which could not be explained based merely on the data of ^1H and ^{13}C NMR spectra of alkynyl carbocations (Section III), *ab initio* calculations of the charge distribution in three cations (**126**–**128**) have been performed.⁹³



The calculations showed that in these three cations, the charge is mostly concentrated on the propargyl sp^2 -hybridised centre. As the number of methyl groups in the cations **126**–**128** increases, nucleophilic attack at this position becomes more favourable.⁹³ Since the stability of alkynyl carbocations is insufficient for them to be directly observed by spectroscopic methods (Section III), it is difficult to follow the variation of the stability of these species over a wide range of structures starting from the simplest one and to estimate the contributions of the resonance structures **9** and **10** as functions of the degree of substitution.

Valuable information on the geometrical parameters of a series of alkynylcarbenium ions **129** and charge distribution in these species found by *ab initio* calculations has been reported by Dorado *et al.*¹⁰⁸



$X, Y, Z = \text{H, Me, F, NH}_2.$

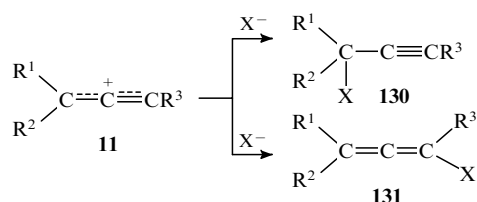
For cations **129**, the lengths of the $\text{C}_\alpha-\text{C}_\beta$, $\text{C}_\beta-\text{C}_\gamma$, $\text{C}_\alpha-\text{X}$, $\text{C}_\alpha-\text{Y}$ and $\text{C}_\gamma-\text{Z}$ bonds, bond angles and the relative energies have been calculated. In general, it was noted that the propargyl form **9** predominates in those cases where the substituent X , substituent Y or both of them either withdraw σ -electrons from the C_α atom or donate π -electrons to the unsaturated fragment. Conversely, the same effects of the substituent Z increase the contribution of the allenyl structure **10**. These effects are especially pronounced for fluorinated cations.

The change in the ratio of the $\text{C}_\alpha-\text{C}_\beta$ and $\text{C}_\beta-\text{C}_\gamma$ bond lengths (and, correspondingly, in the bond orders) depending on the number and positions of substituents in cations **129** presents particular interest. Upon introduction of any substituent other than hydrogen (Me, F, NH_2) to the C_γ atom, the $\text{C}_\alpha-\text{C}_\beta$ bond becomes shorter, while the $\text{C}_\beta-\text{C}_\gamma$ bond becomes longer than the corresponding bonds in the cation **129** in which $X = Y = Z = \text{H}$. Conversely, accumulation of substituents at C_α causes the opposite tendency. The average $\text{C}_\alpha-\text{C}_\beta$ and $\text{C}_\beta-\text{C}_\gamma$ bond lengths for trisubstituted cations have been determined. For $X = Y = Z = \text{Me}$, these values are 1.381 and 1.204 Å, and for $X = Y = Z = \text{F}$, they are 1.399 and 1.196 Å, respectively. Thus, introduction of substituents into the C_α position makes the $\text{C}_\alpha-\text{C}_\beta$ bond 'more single' and the $\text{C}_\beta-\text{C}_\gamma$ bond 'more triple'. The values for charge distribution determined in the study cited¹⁰⁸ are consistent with the fact found by Olah *et al.*¹⁰⁰ that the positive charge on the C_α atom is approximately twice as large as that on the C_γ atom.

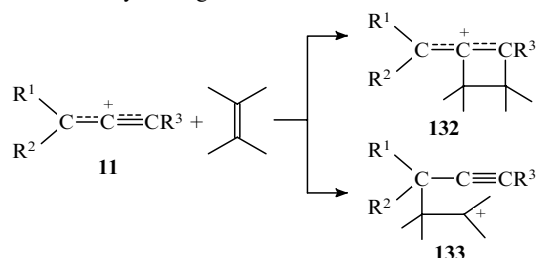
A detailed theoretical study of a series of alkynylcarbenium ions including the unsubstituted propargyl cation and methyl- and phenyl-substituted ions of the type **129** has been reported by Mayr *et al.*¹⁰⁹ As in the previous publication,¹⁰⁸ *ab initio* calculations for

the bond lengths, charge distributions and stabilisation energies for methyl- and phenyl-substituted allenyl cations were carried out. The bond lengths calculated by the two groups of researchers^{108,109} and the conclusions based on them virtually coincide. Thus the C_α – C_β bond in the nonsubstituted propargyl cation (**129**, $X = Y = Z = H$) (1.360 Å) is somewhat shorter than the length of the single C–C bond in propyne (1.484 Å) but longer than the double C=C bond in allene (1.288 Å); at the same time, the C_β – C_γ bond in this cation (1.215 Å) is longer than the triple bond in propyne (1.170 Å) but shorter than the double bond in allene. Phenyl substituents at the tertiary C_α atom elongate the C_α – C_β bond and simultaneously shorten the C_β – C_γ bond more substantially than methyl substituents.

The calculations performed¹⁰⁹ made it possible to predict the reactivity of the alkynyl carbocations **11** with respect to nucleophilic reagents. The propargyl structure **9** is responsible for the addition to C_α and the allenyl form **10** provides the attack at C_γ . Hard nucleophiles add predominantly to the C_α position, because the positive charge on this atom is always greater than that on the C_γ atom; therefore, under conditions of kinetic control, propargyl derivatives **130** are mostly formed. The formation of allenyl derivatives **131** can be explained by assuming thermodynamic control of the addition.



Soft π -nucleophiles should also add predominantly to the C_α atom, because, according to the results of calculations, this site is characterised by the highest LUMO coefficients.¹⁰⁹



However, as substituents R^1 – R^3 stabilising the cations **11** are introduced in the molecule, the addition to the C_β – C_γ moiety becomes more and more pronounced, because these substituents stabilise intermediate **132** but not **133**. The formation of the allylic cations **132** can be demonstrated by reactions of alkynylcarbenium ions with alkenes and dienes (the Diels–Alder reaction).

V. Synthetic applications of alkynyl carbocations

The first systematic studies on the possibility of practical application of alkynylcarbenium ions as reactive intermediates for building various cyclic and polyfunctional systems were carried out in the late 1970s and the early 1980s by a group of German scientists headed by Mayr.¹¹⁰ Alkenes and dienes of various structures were used as nucleophilic substrates.

1. Reactions of alkynyl carbocations with unsaturated compounds

The alkynylcarbenium (allenyl) cations **11** are ambident electrophilic species. Five variants of the addition of unsaturated substrates (alkenes **134** and 1,3-dienes **135** both linear and cyclic) can be conceived theoretically. Figure 1 shows the structures of cationic adducts **A**–**Q** arising upon the reaction of the ions **11** with unsaturated substrates. The carbon atoms of the substrates **11**, **134** and **135** participating in the formation of new covalent bonds are designated by letters. The alkenes **134** and the 1,3-dienes

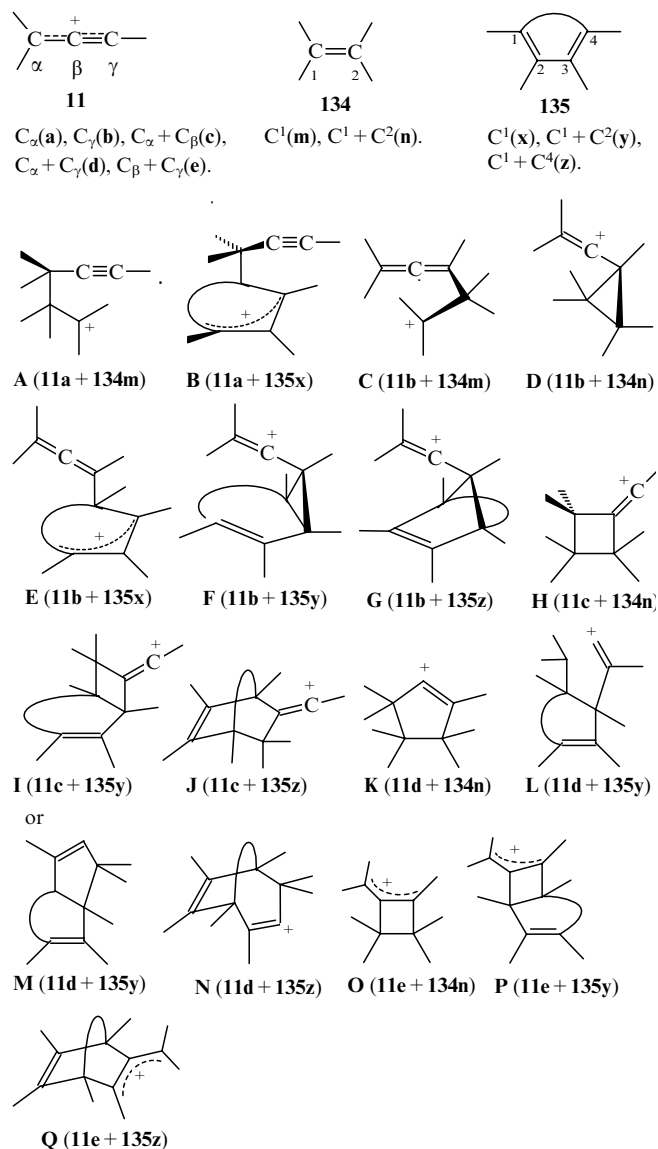
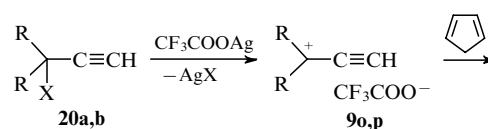


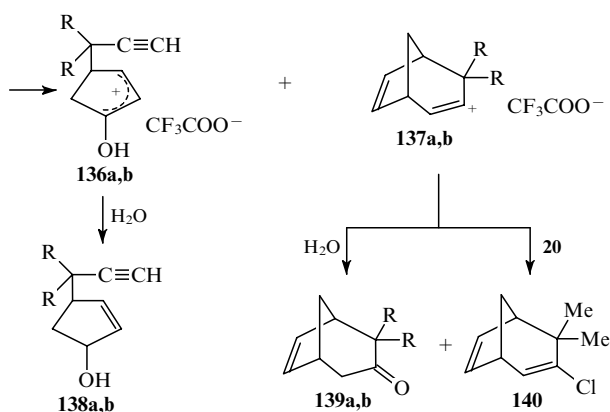
Figure 1. Variants of cycloaddition of alkynylcarbenium ions to alkenes and dienes. The letters designate the fragments of molecules formed upon the reaction.

135 are considered to be symmetrical, *i.e.* positions C(1) and C(2) in the substrate **134** and positions C(1) and C(4), C(2) and C(3) in the substrate **135** are equivalent.

The addition of alkynyl carbocations of the type **11** to the alkenes **134** and the dienes **135** can yield linear carbenium ions (**A**, **C**) or allylic (**B**, **E**, **O**, **P**, **Q**) or vinylic (**D**, **F**, **G**, **H**, **I**–**N**) cations.

The reactions of alkynyl carbocations with cyclopentadiene (CPD) have been studied most comprehensively.^{110–116} The ions were generated by treatment of the corresponding halides with silver trifluoroacetate in pentane in the presence of CPD.¹¹⁰ After hydrolysis of the reaction mixture, obtained from 3-bromopropyne **20a**, with aqueous ammonia, 4-(prop-2-ynyl)cyclopent-2-en-1-ol **138a** was isolated as the major product containing a slight amount of bicyclic ketone **139a**. Under the same conditions, the transformation of 3-chloro-3-methylbut-1-yne **20b** gave three products **138b**, **139b** and **140** in nearly equal amounts.^{110,113}

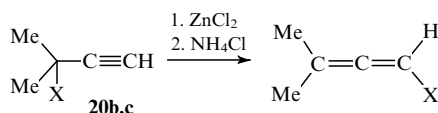




R = H(**9o**, **20a**), Me(**9p**, **20b**); X = Cl, Br.

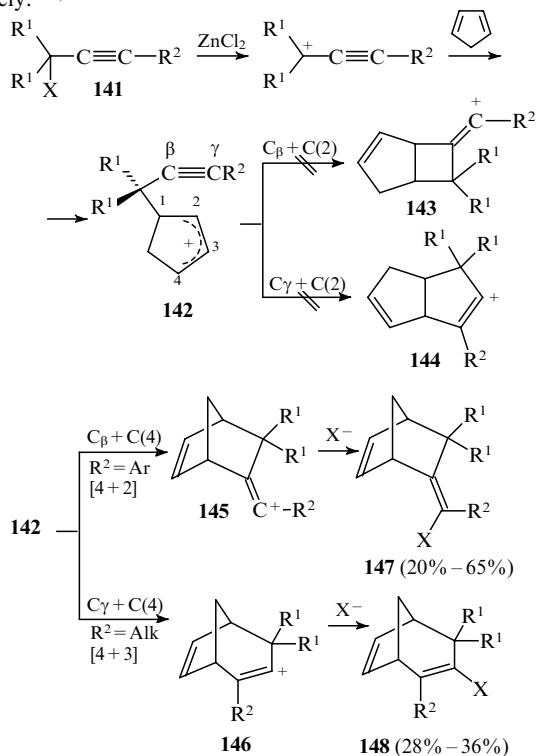
Since cyclopentadiene is highly sensitive to acidic reagents, in more recent studies,^{111,112} the researchers employed a milder catalyst, namely, the efficient homogeneous catalytic system $\text{ZnCl}_2\text{--Et}_2\text{O--CH}_2\text{Cl}_2$, which is formed upon dissolution of zinc chloride (1 mole) in diethyl ether (1.5 moles) and dilution of the resulting solution with dichloromethane.¹¹³

It has been noted¹¹⁰ that the reaction route depends on the structure of the alkynylcarbenium ion. The reaction conditions are also fairly significant. In the presence of an ethereal solution of ZnCl_2 , the halides **20b,c** mentioned above do not react with CPD but instead, they are converted into allenyl halides.¹¹³



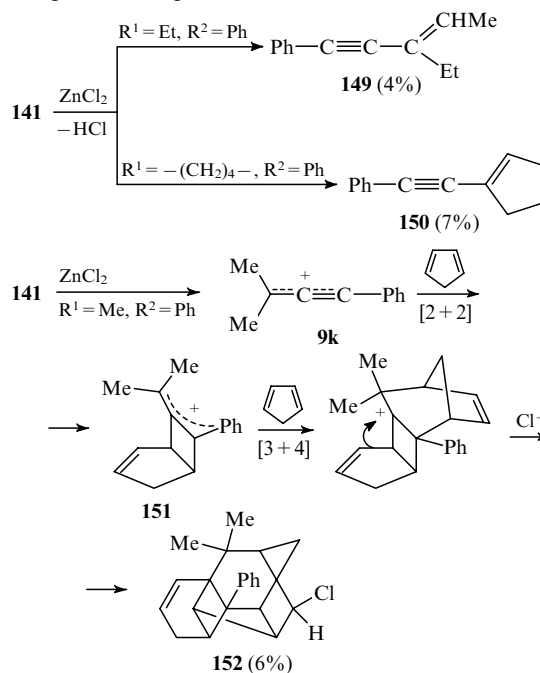
X = Cl (**20b**), Br (**20c**).

Trisubstituted haloalkynes **141** react with CPD to give products of [4 + 2]- and [4 + 3]-cycloaddition **147** and **148**, respectively.^{111,113}

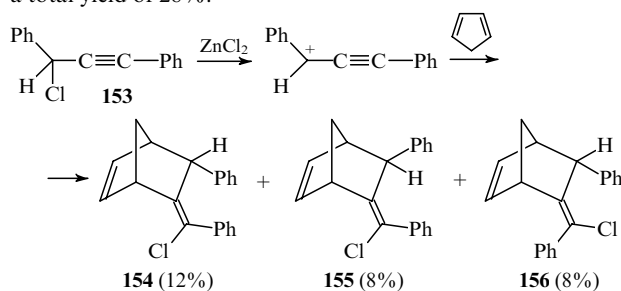


R¹ = Me, Et, (CH₂)₄; R² = Me, Et, Ph, 4-MeOC₆H₄, 4-BrC₆H₄; X = Cl, Br.

In some cases, side products, enynes **149** and **150**, have been isolated from the reaction mixtures. Apparently, these compounds result from dehydrochlorination of the initial haloalkynes **141**. Another side product, compound **152**, forms upon the addition of two CPD molecules to the dimethyl-(phenylethynyl)carbenium ion **9k**.^{112,113} It is assumed that [2 + 2]-cycloaddition of the ethynyl fragment of the ion **9k** to one of the C = C bonds in CPD giving allylic cation **151** also occurs to a small extent. This cation is sufficiently stable, so that it has time to add one more CPD molecule. The subsequent rearrangements of the cations give the compound **152**.

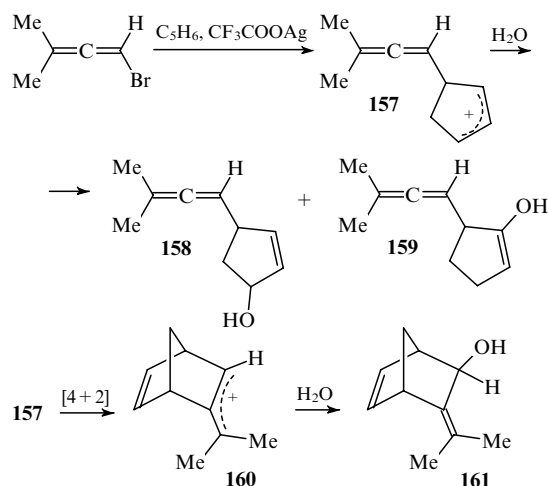


The reaction of 3-chloro-1,3-diphenylpropyne **153** with CPD gives three isomeric products of [4 + 2]-cycloaddition **154–156** in a total yield of 28%.¹¹³



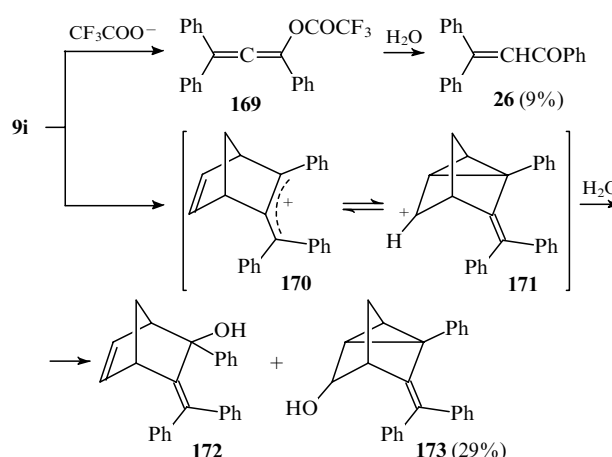
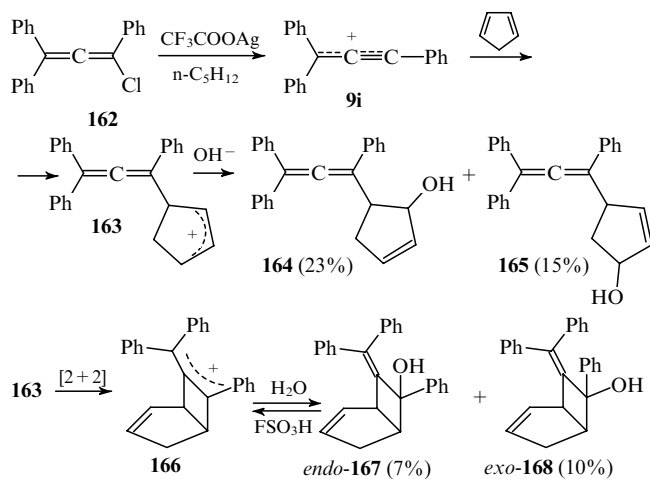
The structures of the products **147**, **148** and **154–156** formed in these transformations indicate that the addition of CPD to alkynyl carbocations having geminal substituents (or a phenyl group at the secondary carbenium centre) involves the sp^2 carbon atom (C_α) and one of the sp atoms (C_β or C_γ). This can give only the vinylic cations **143–146** (Fig. 1, ions I, J, L, N). Allylic cations of the types P and Q (Fig. 1), which are energetically more favourable, are not formed. Of the four possible routes of transformation of the cations **142**, only two are realised, namely those in which the ions **145** and **146** are formed intermediately. This is due to the fact that, according to calculations,¹¹³ the bicyclic vinylic cations **143** and **144** are characterised by much higher energies. It is noteworthy that the alternative pathway to the vinylic halides **147** consisting in the isomerisation of the initial haloalkynes **141** to haloallenes followed by their reaction with CPD has been rejected,¹¹³ because it was found that 1-halo-3-methylbuta-1,2-dienes do not react with CPD under these conditions.

As has already been noted (Section III), not only functional acetylene derivatives but also the corresponding allene derivatives can serve as the precursors of the alkynyl carbocations **11**. In fact, the reaction of cyclopentadiene with 1-bromo-3-methylbuta-1,2-diene in the presence of silver trifluoroacetate affords a mixture of polymers from which allenylcyclopentenols **158** and **159** (ratio 83:17, total yield ~15%) and traces of the compounds **138b** and **161** were isolated.¹¹³



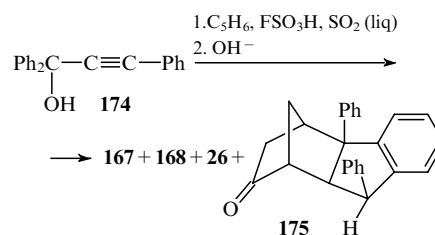
Thus, 3-chloro-3-methylbut-1-yne **20** and isomeric bromoallene react with CPD under the same conditions to give absolutely different products. Although in the latter case, the yields of the reaction products are too low for reliable conclusions to be made, it should be noted that the CPD molecule adds to that carbon atom in the alkynylcarbenium ion precursor from which the halogen atom is eliminated. In all probability, this situation is due to the very low stability of ethynylmethyl carbocations of the type **9** with a terminal triple bond.

Alkynyl carbocations with three aryl substituents are much more stable (see also Sections III and IV). The attempts to generate triphenylethynyl carbocations by treatment of chlorotriphenylallene **162** with the $\text{ZnCl}_2 - \text{Et}_2\text{O} - \text{CH}_2\text{Cl}_2$ catalytic system resulted in complex product mixtures of an unknown composition. Therefore, silver trifluoroacetate was used, which ensured that transformations of the cationic intermediates were irreversible, because the cations were bound by the trifluoroacetate anions.^{114,115} Treatment of a mixture of chlorotriphenylallene **162**, CPD and CF_3COOAg in pentane with an alcoholic solution of KOH gave a mixture of the compounds **26**, **164**, **166**, **167**, **172** and **173** in a total yield of 95%.

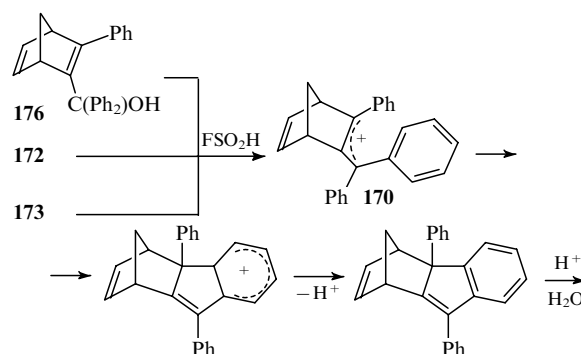


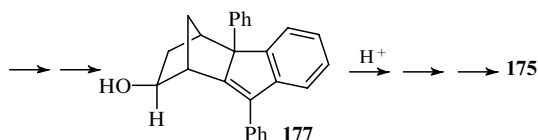
However, it can be seen from the above scheme that only 9% of the alkynyl carbocations **9i** are bound by trifluoroacetate anions yielding the α,β -unsaturated ketone **26** as the final product. The prevailing process is addition of CPD to the cation **9i**. It was shown in special experiments^{114,115} that the tertiary alcohol **172** rearranges to the secondary alcohol **173** on treatment with toluene-*p*-sulfonic acid. Nevertheless, according to ^1H NMR spectroscopy, dissolution of allenylcyclopentenol **164** and the tertiary alcohol **167** in a mixture of FSO_3H and liquid SO_2 at -70°C affords only the bicyclic vinylic cation **166**. Thus, the allylic cations **170** are intermediates on the pathway to the alcohols **172** and **173**, while the cations **163** react with CPD to give the ions **166**. These results led the investigators to the conclusion that the [2+2]-cycloadditions $9i \rightarrow 163$, $9i \rightarrow 166$ are stepwise processes, whereas the [4+2]-cycloaddition $9i \rightarrow 170$ is a concerted process.

The addition of CPD to the terminal *sp*-hybridised carbon atom in the cation **9i** might be a result of the structure of the initial chloroallene **162**. However, when phenyl-substituted alkynol **174** was made to react with CPD in the presence of fluorosulfonic acid, compounds **167** and **168** were obtained as the major products after hydrolysis of the reaction mixture (the ratio **167**:**168**:**26**:**175** = 9:4:4:3, total yield ~35%).^{114,116}

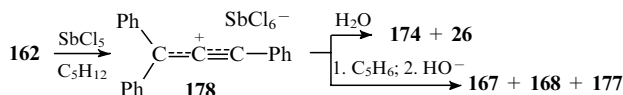


The tricyclic ketone **175** is formed in a high yield on treatment of the alcohols **172** and **173** or specially synthesised compound **176** with acids. A mechanism for this process was proposed, which includes electrocyclic ring closure in the cationic intermediate **170** and acid-catalysed rearrangements of compound **177**.^{114,116}



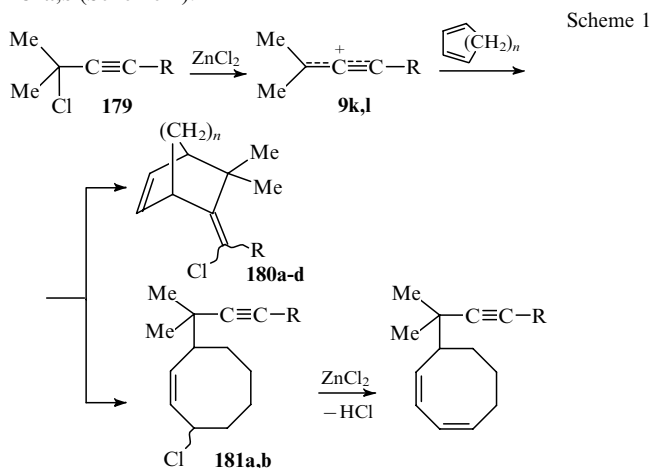


Treatment of chlorotriphenylallene **162** with SbCl_5 affords dark-red crystals of hexachloroantimonate **178**. Hydrolysis of this salt gives rise to a mixture of the alcohol **174** and the ketone **26** in 11 : 14 ratio. The reaction of the salt **178** with CPD (liquid SO_2 , -30°C) and subsequent alkaline hydrolysis yields the products **167**, **168** and **177** described above in a ratio of 4 : 5 : 1 (total yield $\sim 30\%$).¹¹⁶



Thus, the data presented here permit the conclusion that the triphenyl-substituted ethynyl carbocation **9i** always adds a CPD molecule at the terminal sp -hybridised carbon atom, irrespective of the nature of the preceding compound. The cycloaddition involves only the C_β and C_γ atoms, *i.e.* only allylic cations **166** and **170** (type **P** and **Q** cations, see Fig. 1) are generated.

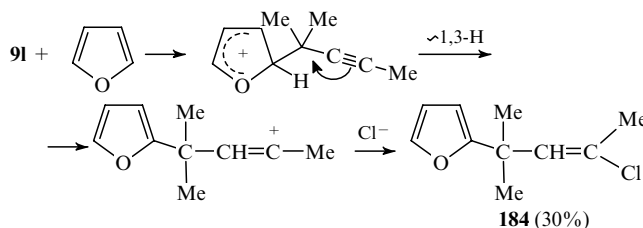
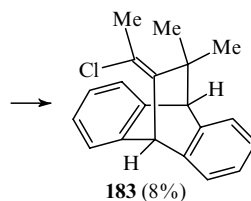
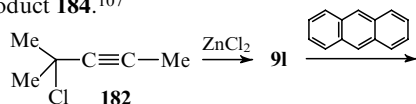
Unlike cyclopentadiene, which enters into both [2+4]- and [3+4]-cycloaddition reactions with dialkyl-substituted alkynyl carbocations,^{111,113} cyclohexadiene and cycloheptadiene react only according to the [2+4]-cycloaddition pattern in the presence of ZnCl_2 , and cyclooctadiene gives only 1,4-addition products **181a,b** (Scheme 1).^{117,118}



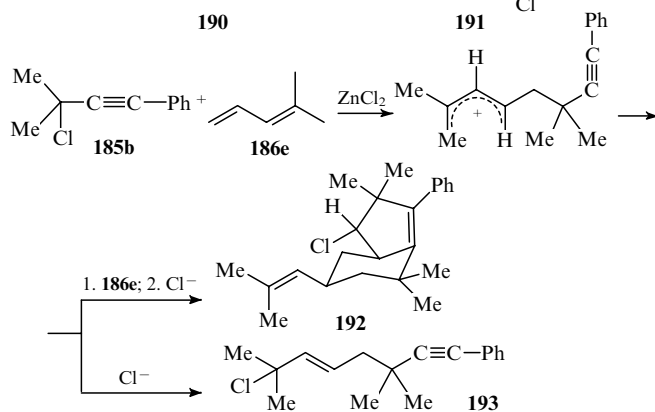
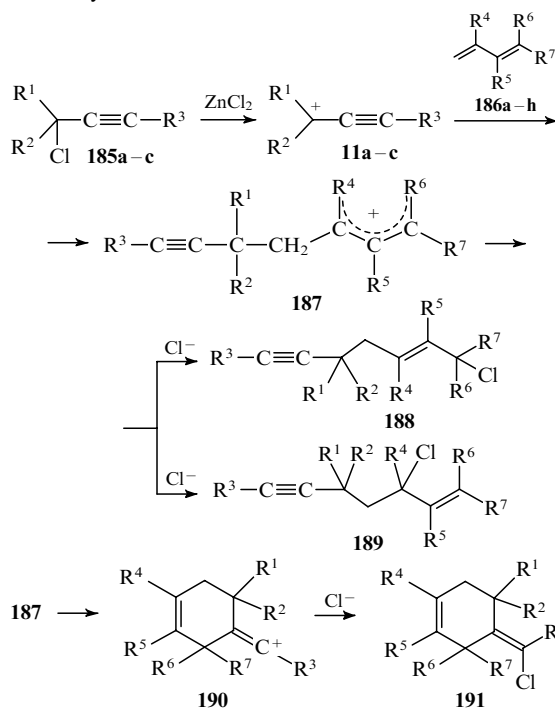
Compound	R	n	E/Z	Yield (%)
180a	Me	2	1 : 1	22
180b	Ph	2	only <i>E</i>	54
180c	Me	3	1 : 1	22
180d	Ph	3	only <i>E</i>	50
181a	Me	4	—	10
181b	Ph	4	—	29

This difference in the behaviour of alicyclic 1,3-dienes is due to different energies of both the corresponding cationic intermediates and the final products, which result from different degrees of strain in the rings.

The reaction of 4-chloro-4-methylbut-2-yne **182** with anthracene in the presence of ZnCl_2 gives rise to the product resulting formally from [4+2]-cycloaddition to the isomeric chloroallene **183**.¹⁰⁷ The reaction of furan with the same cation yields acyclic product **184**.¹⁰⁷



The addition of linear 1,3-dienes **186a–g** and 1,2-dimethylenecyclohexane **186h** to the propynylcarbocation **11a–c** in the presence of the $\text{ZnCl}_2\text{–Et}_2\text{O–CH}_2\text{Cl}_2$ system occurs only at the sp^2 -hybridised carbon atom and gives linear allylic cations **187**. Subsequent transformations of the cations **187** are largely determined by the structures of both reactants.^{119,120}

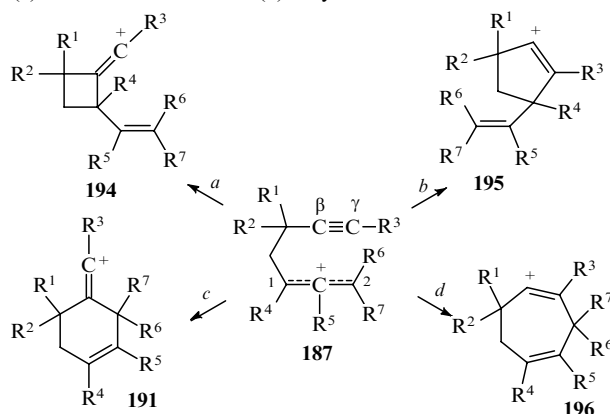


$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}$ (**185a**, **11a**); $\text{R}^1 = \text{R}^2 = \text{Me}$, $\text{R}^3 = \text{Ph}$ (**185b**, **11b**); $\text{R}^1 = \text{R}^3 = \text{Ph}$; $\text{R}^2 = \text{H}$ (**185c**, **11c**); $\text{R}^4 = \text{R}^5 = \text{R}^6 = \text{R}^7$ (**186a**); $\text{R}^4 = \text{Me}$, $\text{R}^5 = \text{R}^6 = \text{R}^7 = \text{H}$ (**186b**); $\text{R}^4 = \text{R}^5 = \text{R}^6 = \text{H}$, $\text{R}^7 = \text{Me}$ (**186c**); $\text{R}^4 = \text{R}^5 = \text{Me}$, $\text{R}^6 = \text{R}^7 = \text{H}$ (**186d**); $\text{R}^4 = \text{R}^5 = \text{H}$, $\text{R}^6 = \text{R}^7 = \text{Me}$ (**186e**); $\text{R}^4 = \text{R}^7 = \text{Me}$, $\text{R}^5 = \text{R}^6 = \text{H}$ (**186f**); $\text{R}^4 = \text{R}^6 = \text{R}^7 = \text{Me}$, $\text{R}^5 = \text{H}$ (**186g**); $\text{R}^4\text{–R}^5 = (\text{CH}_2)_4$, $\text{R}^6 = \text{R}^7 = \text{H}$ (**186h**).

Most often, allyl chlorides **188**, which are thermodynamically more stable than their isomers **189**, are formed as the major products of these reactions. Upon the reactions of the chlorides **185a,b** with buta-1,3-diene **186a** and the reaction of chloride **185c** with penta-1,3-diene **186c**, isomeric allyl chlorides **189** were also isolated (the **188** : **189** ratios were 4 : 1, 1 : 1 or 2 : 1, respectively). Cyclic vinyl chlorides **191** were the only products formed upon the reaction of the chloride **185b** with 1,2-dimethylenecyclohexane **186h** and the reaction of **185c** with the diene **186f**. It should be noted that the formation of six-membered cyclic vinyl halides **191** is of special interest, because the allyl-cation intermediates **187** are alkynylcarbenium ions in which the triple carbon-carbon bond is separated from the carbenium centre by one methylene unit (see Section VI).

It was shown^{119,120} that dimethylpropargyl chloride **185c** does not add to buta-1,3-diene **186a** or isoprene **186b**. When the chloride **185a** is made to react with the diene **186e** or the chloride **185b** reacts with the dienes **186e,f,g**, the reaction mixtures polymerise. Only the reaction of the chloride **185b** with the diene **186e** did give bicyclic diene **192** (yield 23%) which resulted from the addition of two molecules of the diene **186e** to the cation **11b**.

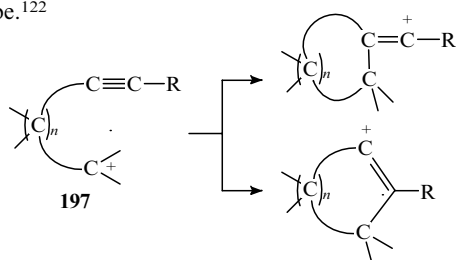
Four cyclisation pathways can, in principle, be conceived for the alkynylallylic cations **187**: those leading to four- (*a*), five- (*b*), six- (*c*) and seven-membered (*d*) vinylic cations.



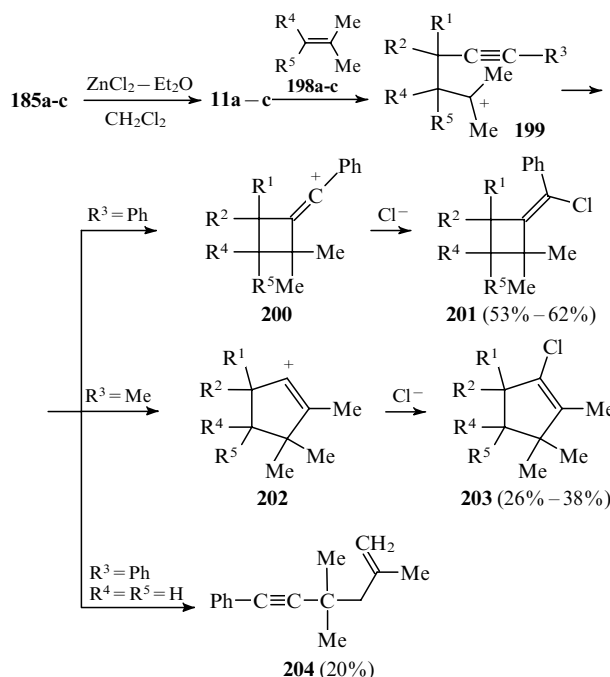
(*a*) $C_\beta + C_1$; (*b*) $C_\gamma + C_1$; (*c*) $C_\beta + C_2$; (*d*) $C_\gamma + C_2$.

Obviously, pathways *a* and *b* are energetically unfavourable, because **194** contains a strained four-membered ring, and in **195**, the geometry of the vinyl cationic fragment differs substantially from the linear geometry inherent to it.¹²⁰ The latter statement is also true for the isomer **196**. Only the cation **191** in which the carbenium centre is exocyclic and is stabilised by the neighbouring phenyl substituent is energetically favourable. This is especially clearly seen for the diene **186h**, which reacts with the chloride **185b** yielding the species **187** [$R^4, R^5 = (CH_2)_4$] the geometry of which is rigidly fixed by the cyclohexane ring.

Considerable synthetic and theoretical interest is aroused by rearrangements of alkynylcarbenium ions **197** in which the multiple bond and the carbenium centre are separated by one or more sp^3 -hybridised carbon atoms. π -Cyclisation of cations of the type **197**, where $n = 1$ (homopropargyl rearrangement^{22–24, 26, 27, 121}) and $n = 3$ (see Ref. 22, for more details, see Section VI) is a well-known reaction. The reactions of alkynyl carbocations with dienes described above are examples of cyclisation of cations of the type **197** with $n = 2$; the reactions with alkenes also belong to this type.¹²²



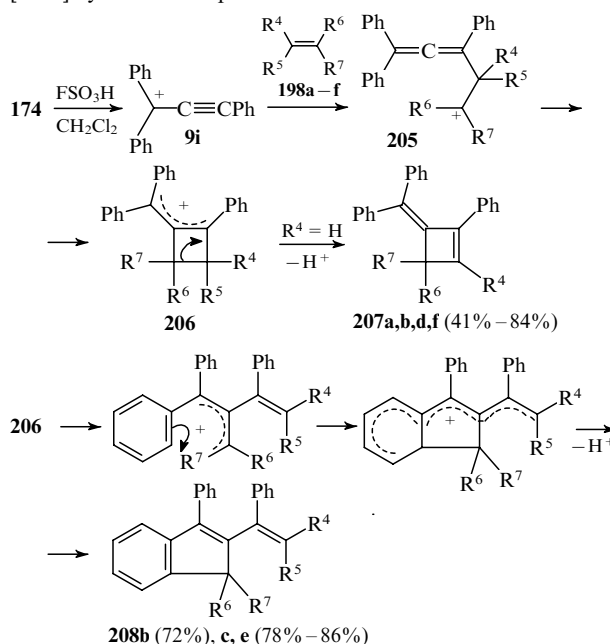
Chlorobenzylidenecyclobutanes **201** and chlorocyclopentenes **203** are formed upon [2 + 4]- or [3 + 4]-cycloaddition of the alkynyl carbocations **11a–e** to alkenes **198a–c**.¹²²



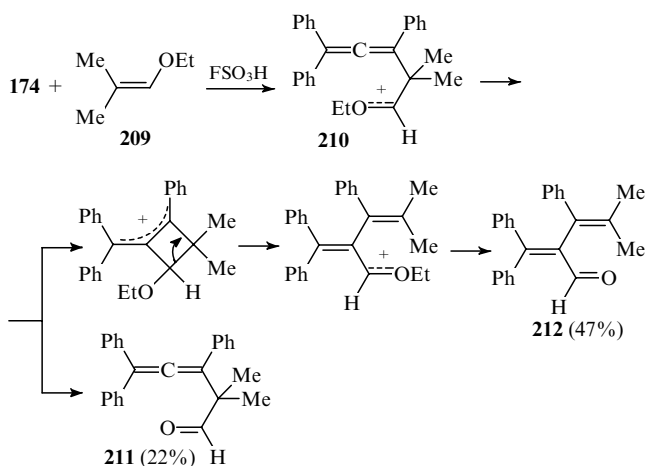
$R^4 = R^5 = H$ (**198a**); $R^4 = H, R^5 = Me$ (**198b**); $R^4 = R^5 = Me$ (**198c**).

A stepwise mechanism with participation of carbocationic intermediate **199** was proposed for this reaction. The formation of this intermediate was proved by the isolation of enynes having mainly structure **204** as side products. The two routes for cyclisation of the intermediates **199** are determined by the stabilising influence of the phenyl substituent, which is attached directly to the vinylcarbenium centre in structure **200**. When the molecule contains no phenyl substituent, the reaction affords product **202** having a less strained structure.¹²²

The reaction of the triphenyl-substituted cation **9i** with alkenes follows a fundamentally different pathway¹²³ leading to [2 + 2]-cycloaddition products.



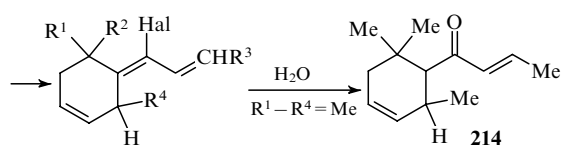
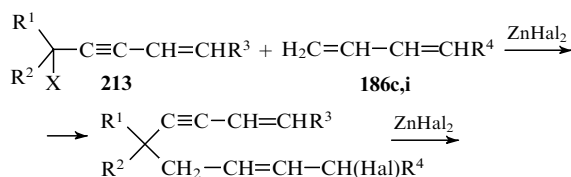
$R^4 = R^5 = H, R^6 = R^7 = Me$ (**a**); $R^4 = H, R^5 = R^6 = R^7 = Me$ (**b**); $R^4 = R^5 = R^6 = R^7 = Me$ (**c**); $R^4 = H, R^5 = R^6 = Me, R^7 = H$ (**d**); $R^4 = R^5 = H, R^6 = Ph, R^7 = Me$ (**e**); $R^6 = Me, R^4 - R^7 = (CH_2)_4$ (**f**).



The alkenes **198a,b,d,f** are converted into methylenecyclobutenes **207a,b,d,f**, while in the case of tetramethylethylene **198c**, α -methylstyrene **198e** and trimethylethylene **198b** (with excess FSO_3H), fast electrocyclic opening of the four-membered ring occurs, resulting in the formation of bicyclic structures **208b,c,e**. When the alcohol **174** reacts with vinyl ether **209**, some of the arising ethoxycarbenium ions **210** undergo dealkylation, typical of this type of species,¹²⁴ to give aldehyde **211**. However, most of the ions **210** have time to cyclise yielding a new ethoxycarbenium ion, which is converted into aldehyde **212**.

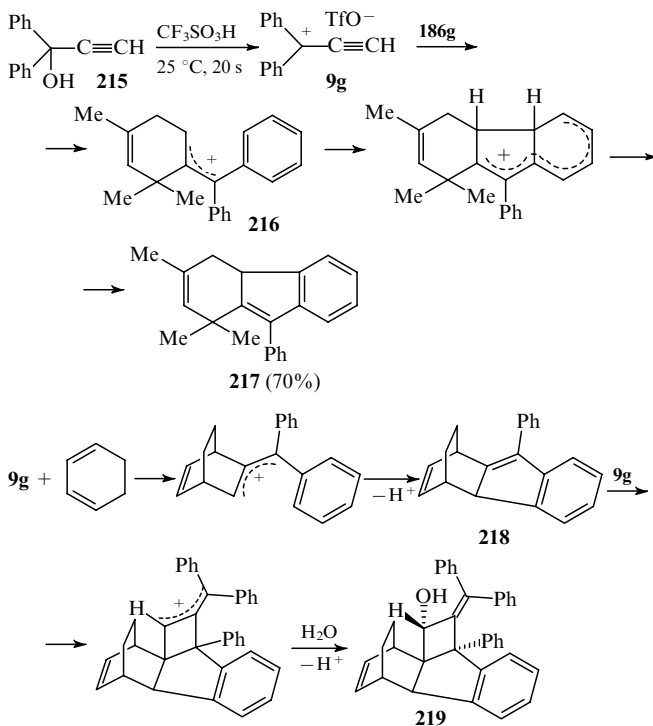
Turning back to Fig. 1, which shows all the possible variants of cationic intermediates, one can conclude that the studies described above have provided experimental evidence for the formation of eleven of these ions, namely, **A** (**199**), **B** (**136**, **142**, **187**), **C** (**205**, **210**), **E** (**157**, **163**), **H** (**200**), **J** (**145**, **191**), **K** (**202**), **N** (**137**, **146**), **O** (**206**), **P** (**166**) and **Q** (**160**, **170**). Cyclopropylvinyl cations (**D**, **F**) have been reported^{22, 23, 97} to be quite stable. As regards structures (**G**, **I**, **L** and **M**), they are energetically so unfavourable that their formation is considered¹¹³ to be doubtful irrespective of the structure of the initial compounds and reaction conditions. It is obvious that the increase in the stability of the ion **11** upon introduction of two aryl substituents to the sp^2 -carbenium centre increases the contribution of the alkynylcarbenium structure **9**. This is consistent with the data obtained by spectroscopy and quantum-chemical calculations (see Sections III, IV), which indicate that the $\text{C}_\alpha\text{--C}_\beta$ bond in the cations **129** is elongated, while the $\text{C}_\beta\text{--C}_\gamma$ bond is shortened. The attack on these cations by nucleophilic agents is mainly directed at the sp -carbon atom remote from the cationic centre, as in acetylene derivatives activated by electron-withdrawing substituents, while cycloaddition follows the $[2+2]$ pattern involving the two sp -carbon atoms.

Conversely, the introduction of substituents, able to delocalise positive charge, into the acetylenic fragments results in the predominance of the allenyl form of the cation **10** and causes the nucleophile to attack the sp^2 -carbon atom. It has been shown above for phenylethynylcarbenium ions (**9i–k**, **n**, **117**, **132**, **142**) that a similar influence can be exerted by the vinyl group. Thus the reaction of halogenated enynes **213** with buta-1,3-dienes **186c,i** in the presence of a homogeneous catalytic system, $\text{ZnHal}_2\text{--Et}_2\text{O--CH}_2\text{Cl}_2$ ($\text{Hal} = \text{Cl}, \text{Br}$), affords alkenyldenecyclohexenes.¹²⁵ A valuable product formed in this reaction is the perfume δ -damascone **214**.



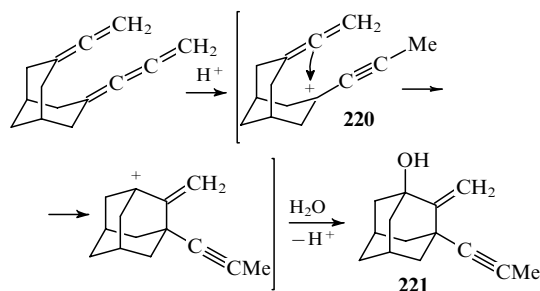
$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{Me}, \text{Et}; \text{Hal} = \text{Cl}, \text{Br}$.

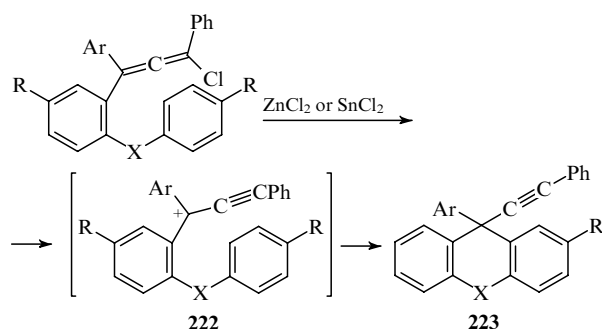
Similarly to allylic cations, alkynylcarbenium ions can act as efficient dienophiles in low-temperature Diels–Alder reactions.¹²⁶ Thus the reaction of 1,1-diphenylprop-2-yn-1-ol **215** with 2,4-dimethylpenta-1,3-diene **186g** gave tricyclic compound **217** in 70% yield.¹²⁶ Presumably, this product is formed in two successive cyclisations *via* the ethynyl carbocation **9g** and the cyclic allylic cation **216** (corresponding to structure **Q**, see Fig. 1). However, the reaction of the cation **9g** with cyclohexadiene does not stop at the stage of formation of the 1 : 1 tricyclic adduct **218**. This adduct undergoes one more $[2+2]$ -cycloaddition to give alcohol **219** (the total yield after 20 s at 25 °C is 80%). The proposed reaction scheme was confirmed by isolation of the compound **218** (yield 62%) from this reaction carried out with a tenfold excess of cyclohexadiene and its subsequent transformation into the final product **219** under the same conditions.¹²⁶



Neither styrene nor the indene derivative **217** reacts with the cation **9g** under the described conditions. The high reactivity of the compound **218** was explained¹²⁶ by the strained character of the double bond in the five-membered ring.¹²⁶

Cyclisation of alkynylcarbenium ions **220** and **222** was used to prepare alkynyl derivatives of adamantane **221**¹²⁷ and fused heterocycles **223**.¹²⁸

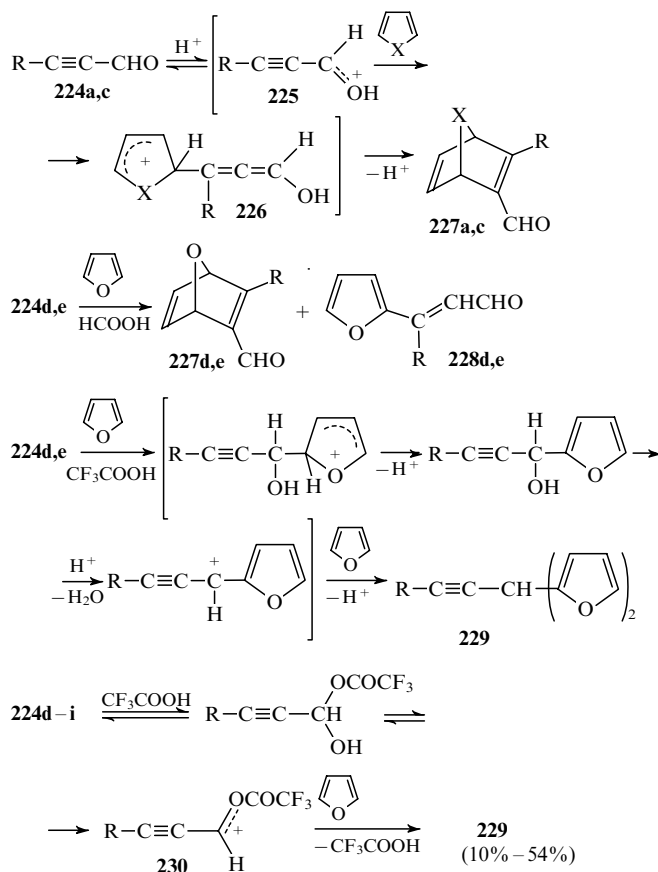




X = O, S, NMe, NPh.

The participation of the sp^2 -hybridised carbenium atom in the cyclisation is due to the fact that the greatest charge is concentrated on this atom and also to the geometry of the intermediate **222**, which hampers the attack of the sp -hybridised carbon atom.

Heteroatoms (O, S, N) adjacent to a carbenium centre are known to exert a stabilising influence on carbocations.¹²⁴ In the presence of acids (HCOOH, CF₃COOH), aldehydes of the acetylene series **224** are converted into alkynylhydroxycarbenium ions **225**, which can react with cyclic dienes according to three pathways: (1) the Diels–Alder reaction giving cycloaddition product **227**, (2) nucleophilic addition of the C≡C bond to the diene molecule giving compounds of the type **228** and (3) the Michael condensation of two furan molecules with one aldehyde molecule^{129, 130} affording alkynes **229**.

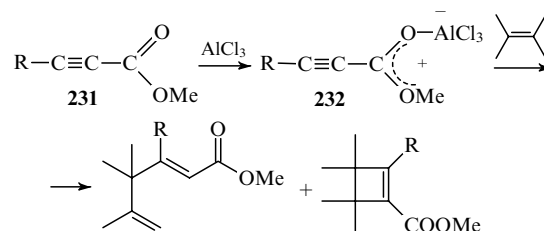


R = CHO (a), (EtO)₂CH (b), COOEt (c), CONMe₂ (d), CN (e), H (f), Bu (g), Ph (h, 54%), 4-ClC₆H₄ (i, 20%).

It has been shown^{129, 130} that cyclopentadiene and cyclohexa-1,3-diene react with the aldehydes **224a,c** to give only cycloaddition products **227a,c** in high yields. The reactions of anthracene and diphenylfulvene with the same aldehydes **224a,c** give rise to mixtures of compounds **227** and **228** in which the Diels–Alder reaction products predominate. The third pathway, which is

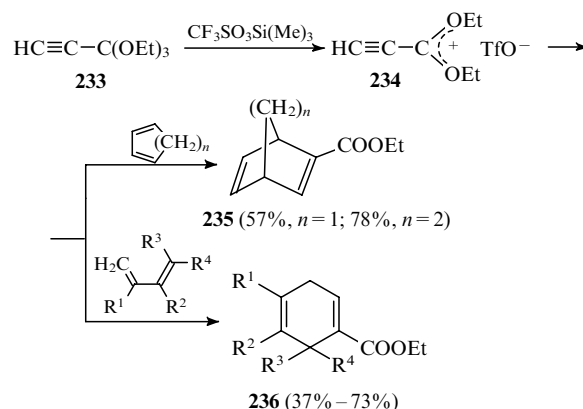
similar to the known reaction of aldehydes with dimerone,¹³¹ occurs only for the aldehydes **224d,e,g–i**. The products **229h,i** were obtained in only moderate yields (20% and 55%, respectively). The route of the reaction of the aldehydes **224** with furan depends on the nature of the acid used. For example, the aldehydes **224d,e** react with furan in the presence of HCOOH giving rise to mixtures of the compounds **227d,e** and **228d,e**. In the presence of CF₃COOH, no cycloaddition products **227** are formed; instead, mixtures of compounds **228** and **229** are produced. This difference in the reaction pathways is due to the fact that in trifluoroacetic acid, which is stronger than formic acid (pK_a 0.23 for CF₃COOH and pK_a 3.75 for HCOOH¹³²), acyloxycarbenium ions **230** can be formed, which are less stable than the hydroxycarbenium ions **225**.³² As a result, the diene adds to the sp^2 -hybridised atom of the alkynyl carbocation.

The addition of acetylenic esters **231** to alkenes is catalysed by Lewis acids and occurs either as nucleophilic addition at the triple bond or as [2 + 2]-cycloaddition.^{133, 134} The reaction presumably involves the intermediate formation of complexes **232**, which can be regarded as stabilised¹²⁴ dialkoxycarbenium ions.

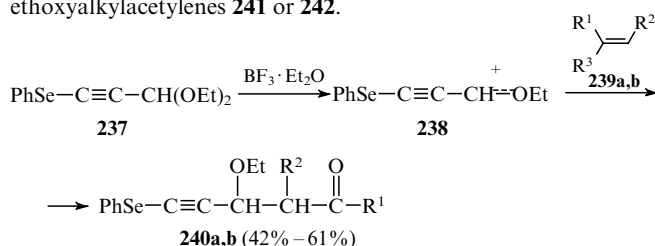


R = H, Cl, COOMe.

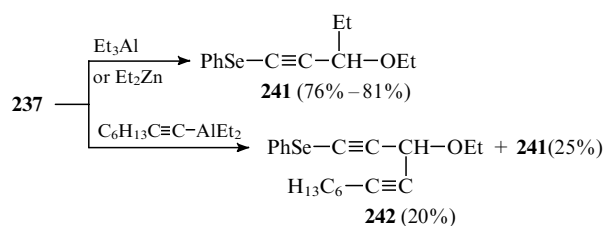
True ethynyldialkoxycarbenium ions **234** generated, for example, from orthoester **233** proved, as expected, to be extremely reactive dienophiles.¹³⁵ They add to dienes at low temperatures (0 to –78 °C) to give cyclic products **235** or **236** in good yields. These examples demonstrate successful application of alkyl propiolates in Diels–Alder reactions.¹³⁵



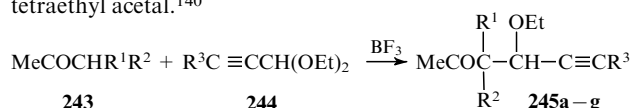
Ionisation of acetals of the acetylene series having a phenylselenenyl substituent (**237**) affords alkoxy-carbenium cations **238**, which add silyl ethers of enols **239a,b** at the carboxonium fragment.¹³⁶ The alkylation of the acetals **237** with organoaluminium or organozinc compounds occurs in a similar way giving rise to ethoxyalkylacetylenes **241** or **242**.



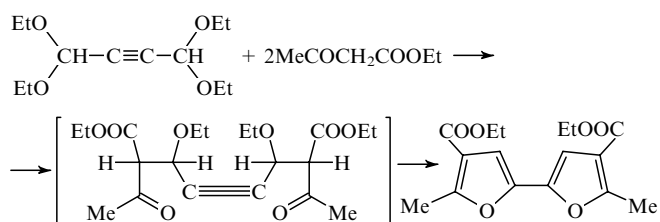
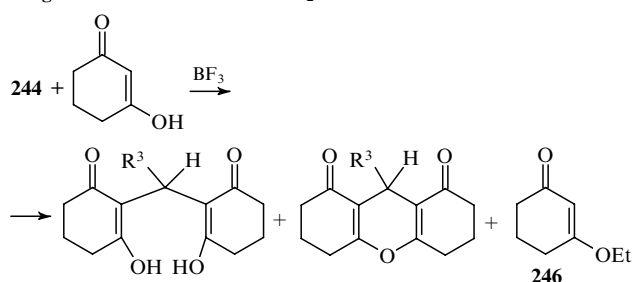
R¹–R² = (CH₂)₄, R³ = OSiMe₃ (a); R¹ = Ph, R² = H, R³ = OSiMe₃ (b).



A series of studies devoted to reactions of acetals of acetylenic aldehydes with CH acids in the presence of boron trifluoride etherate deserve attention.^{137–140} Acetone, methyl ethyl ketone,¹³⁷ ethyl acetoacetate, methyl acetoacetate,^{138, 140} acetylacetone and cyclohexane-1,3-dione¹³⁹ have been used as substrates in the reactions with alkynal acetals **244** and butynedial tetraethyl acetal.¹⁴⁰



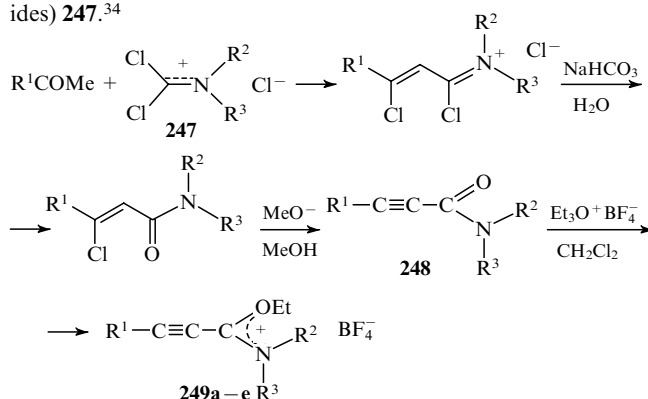
Compound	R ¹	R ²	R ³	Yield (%)
245a	H	H	H	71
245b	H	Me	H	26
245c	H	CO ₂ Et	H	75
245d	H	CO ₂ Et	Ph	75
245e	H	COMe	H	37
245f	Me	CO ₂ Me	H	18
245g	Me	CO ₂ Me	Ph	18



The researchers cited claim^{137–140} that in these reactions, acetals are not converted into alkoxy-carbenium ions like **238** and propose at least six hypothetical schemes with four- and six-centre cyclic transition states. However, none of the schemes consider the role of the catalyst, boron trifluoride etherate. In addition, in our opinion, some of the observations made by the authors rather attest to the participation of alkoxy-carbocations. Thus alkynal diethyl acetals are converted into ethoxycyclohexenone **246**, and dimethyl acetals give the corresponding methoxy derivative. When a mixture of acetals is used, a mixture of methoxy- and ethoxy-cyclohexenones is formed.

The idea of activating acetylene derivatives by cationic substituents attached directly to the triple bond has found synthetic implementation in cycloaddition reactions involving iminium derivatives of the acetylene series. Viehe *et al.*^{34, 141} have developed a method for the synthesis and studied the properties of ethynyl-substituted amidium salts **249** unknown previously. These salts proved to be substantially more efficient dienophiles than other acetylene derivatives activated by electron-withdrawing substituents. The salts **249** were prepared by *O*-alkylation of the amides

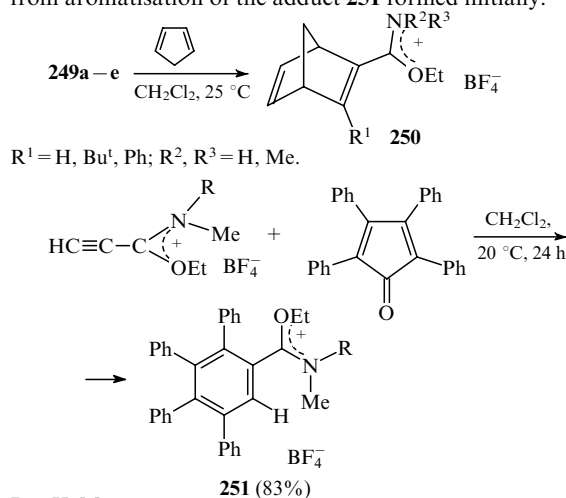
248 synthesised using the Viehe salts (phosgene iminium chlorides) **247**.³⁴



R¹ = Ph, R² = R³ = Me (**a**); R¹ = Bu^t, R² = R³ = Me (**b**);
R¹ = H; R² = R³ = Me (**c**); R² = H, R³ = Me (**d**); R² = R³ = H (**e**).

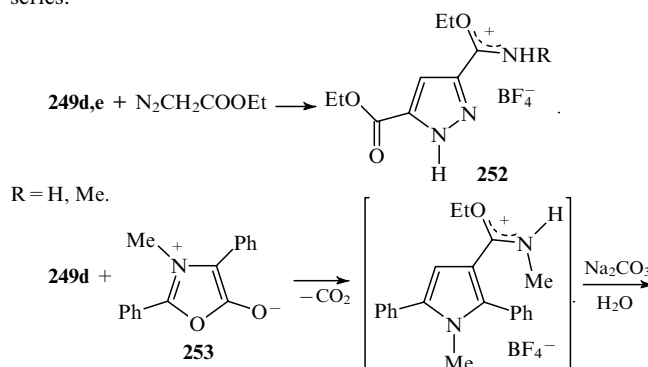
The amidium salts **249** remain unchanged in air and are much more stable than their dialkoxy-carbenium heteroanalogues **234**. A systematic study of their ¹³C NMR spectra showed that the carbon–carbon triple bond is substantially polarised; this decreases the energy demands and considerably facilitates the Diels–Alder and 1,3-dipolar cycloaddition reactions.

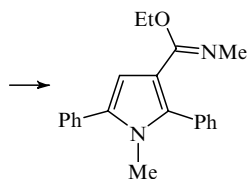
The salts **249a–e** readily react with cyclopentadiene at room temperature according to the [4 + 2]-cycloaddition pattern to give stable salts **250**. The reaction of the ethynyl-substituted salts **249c,d** with tetraphenylcyclopentadienone under the same conditions gives rise to polysubstituted benzene derivatives resulting from aromatisation of the adduct **251** formed initially.³⁴



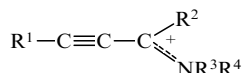
R = H, Me.

The ethynylcarbenium salts **249d,e** readily enter into 1,3-dipolar cycloaddition at room temperature. Thus the reaction with ethyl diazoacetate yields pyrazole derivatives **252**, and the addition of the salt **249d** to the azomethine 1,3-dipolar fragment of munchnnone **253** opens up the way to imidates of the pyrrole series.³⁴



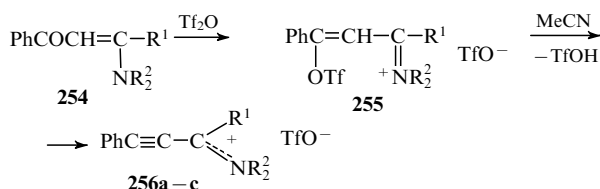


Among the alkynes containing resonance-stabilised cationic substituents, the best known are those containing a propynyliminium fragment of the general formula



$\text{R}^1 = \text{H}, \text{Alk}, \text{Ar}; \text{R}^2 = \text{H}, \text{Alk}, \text{Ar}, \text{NR}^3\text{R}^4, \text{OR}^5, \text{SR}^5, \text{Hal}; \text{R}^3, \text{R}^4 = \text{H}, \text{Alk}, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$.

These are propynyliminium ($\text{R}^2 = \text{H}, \text{Alk}, \text{Ar}$), propynylamminium ($\text{R}^2 = \text{NR}^3\text{R}^4$) and propynylamidium (**249**) ions.¹⁴² The propynyliminium ions **256** can be prepared by treatment of easily accessible enamines **254** with trifluoromethanesulfonic anhydride.¹⁴²

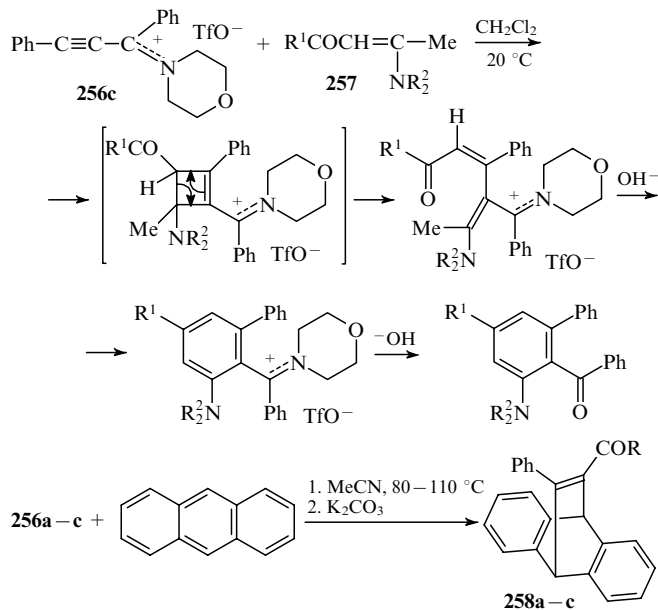


$\text{R}^1 = \text{H}$ (a), Me (b), Ph (c); $\text{R}^2 = \text{Me}, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$; $\text{Tf} = \text{CF}_3\text{SO}_3$.

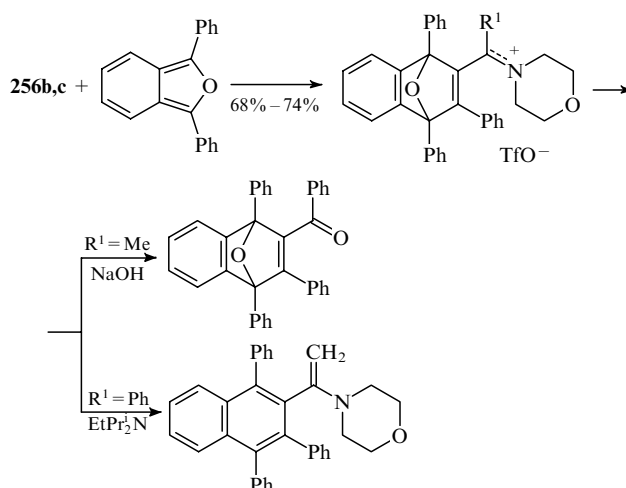
Elimination of TfOH from the iminium triflate **255** is carried out either thermally or in the presence of a tertiary amine. This procedure is suitable only for the aryl-substituted enamines, because enamines containing an aliphatic substituent in the acyl fragment are deprotonated to give diene amines of the type $\text{R}^1\text{C}(\text{NR}_2)=\text{CH}-\text{C}(\text{OTf})=\text{CR}_2$.

The IR spectra of the salts **256** exhibit intense absorption bands in the region of 2190–2200 ($\text{C}\equiv\text{C}$) and 1590–1630 ($\text{C}=\text{N}$) cm^{-1} . The ^{13}C NMR spectra of these triflates have been studied.¹⁴²

Propynyliminium salts similar to **256** react with enamines **257** according to the [2+2]-cycloaddition pattern and with diphenylisobenzofuran and anthracene according to the [2+4]-cycloaddition scheme.¹⁴²



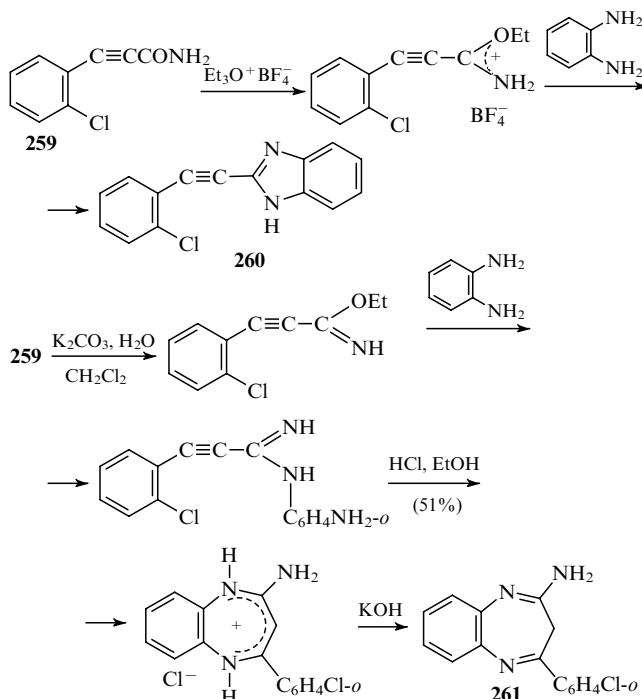
$\text{R} = \text{H}$ (a), Me (b), Ph (c).



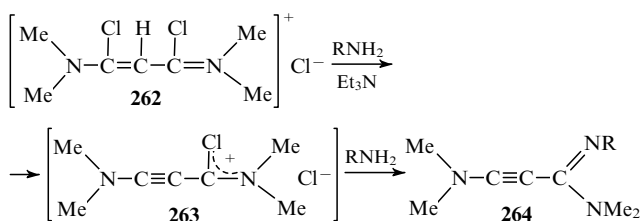
The propynylamidium salts **249** form no cycloaddition products with anthracene.³⁴ In turn, the propynyliminium salts **256** do not react with tetraphenylcyclopentadienone.¹⁴²

2. Reactions of alkynyl carbocations with nucleophiles

The propynylamidium cation arising upon *O*-alkylation of the amide **259** has been used to prepare 2-(2-chlorophenylethynyl)-benzimidazole **260** and 2-amino-3*H*-1,5-benzodiazepine **261**.¹⁴³

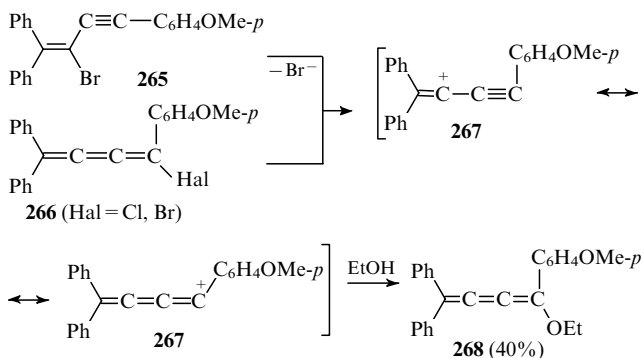


Treatment of 1,3-dichlorotrimethinecyanine **262** with aliphatic amines gives ynamine amidines **264** via unstable chloriminium cations **263**.¹⁴⁴

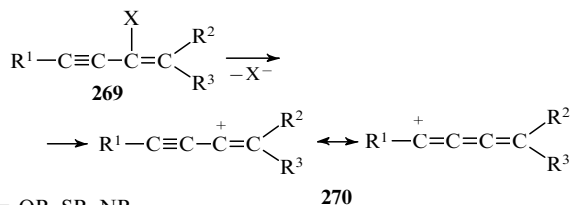


Methods for generation and properties of another type of alkynyl carbocations — alkynylvinyl cations **267** — were simultaneously described by Japanese¹⁴⁵ and German¹⁴⁶ scientists, working independently. The former researchers¹⁴⁵ studied sol-

volysis of 2-bromo enyne **265** and 1-halobuta-1,2,3-triene **266** in aqueous ethanol. Ethoxycumulene **268** was detected in the reaction mixtures.

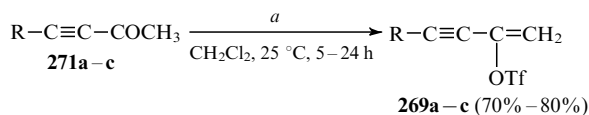


Unlike the well-known ethynylvinyl derivatives with terminal functional groups,¹⁴⁷ the isomeric 1-alkynylvinyl compounds of the type **269** have been little studied.

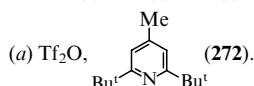


X = OR, SR, NR₂.

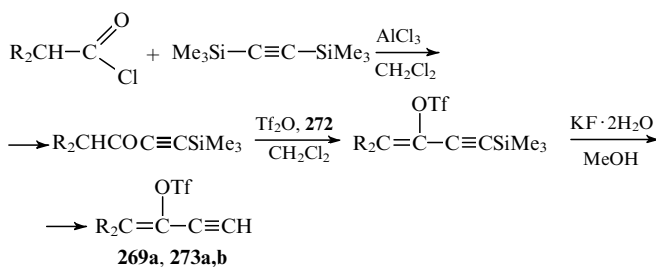
Hanack *et al.*¹⁴⁶ proposed a method for the synthesis of alkynyl triflates **269**, which can serve as the precursors of α -alkynylvinyl cations of the general form **270**. The method consists in treatment of ketones of the acetylene series **271a–c** with trifluoromethanesulfonic anhydride in the presence of a non-nucleophilic sterically hindered base, 2,6-di-*tert*-butyl-4-methylpyridine **272**.



R = H (**a**), Me (**b**), Bu^t (**c**).

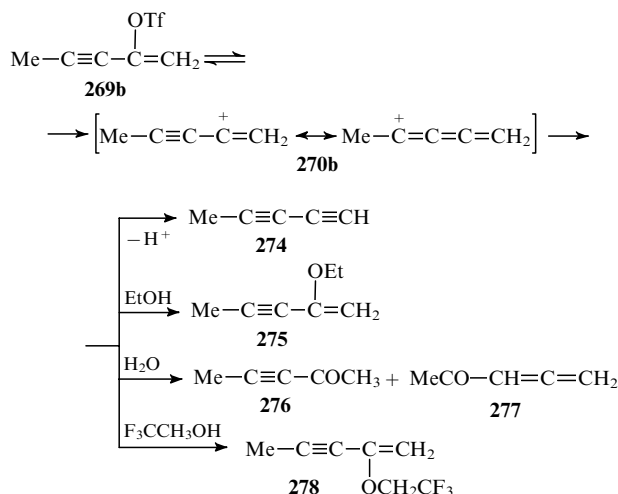


A somewhat different approach, based on silylated ethynyl ketones, has been proposed by Stang *et al.*¹⁴⁸ These compounds are converted into ethynylvinyl triflates **269a** and **273a,b** upon successive treatment with trifluoromethanesulfonic anhydride in the presence of the base (**272**) and with potassium fluoride in methanol.



R = H (**269a**), Me (**273a**), Ph (**273b**).

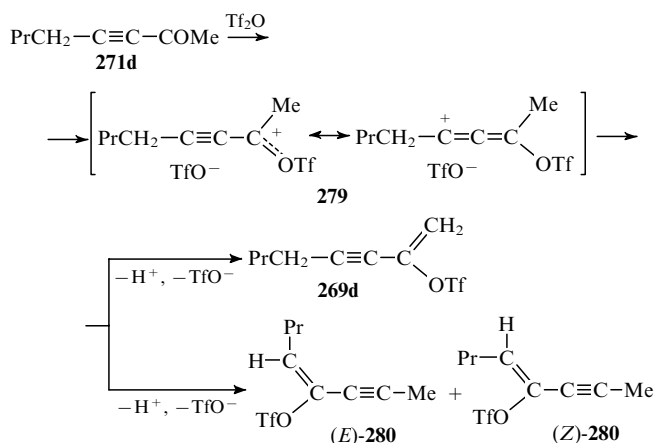
The reaction mixtures resulting from solvolysis of the triflate **269b** in 80% aqueous ethanol and 80% trifluoroethanol have been found to contain products **274–278** the formation of which has been explained by the participation of the cationic intermediate **270b**.¹⁴⁶



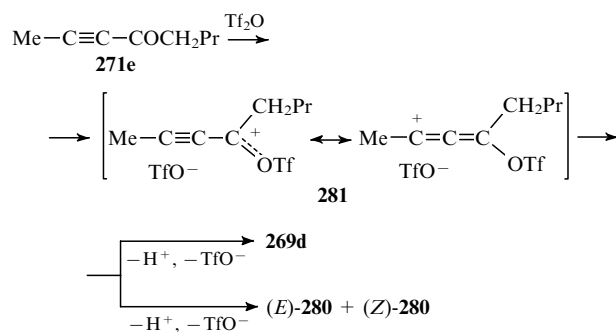
Alcohol	Yields of solvolysis products (%)				
	274	275	276	277	278
EtOH	30	15	4	3	0
CF ₃ CH ₂ OH	24	0	20	0	28

The composition of the products of solvolysis depends on the alcohol used. These results imply that the cation **270b** reacts mainly in the form of the alkynylvinyl cation. This is consistent with kinetic measurements. It was shown¹⁴⁶ that the propynylvinyl triflate **269b** is solvolysed in 50% aqueous ethanol 70 times faster than the triflate MeC(OTf)=CH₂ and 35 times faster than the triflate PrC(OTf)=CH₂;¹⁴⁶ this points to a stabilising influence of the ethynyl fragment on the neighbouring vinyl cationic centre.

The above synthesis of 1-(1-alkynyl)vinyl triflates **269** from ethynyl ketones **271**¹⁴⁶ involves intermediate formation of alkynylacyloxycarbenium cations **279**, **281**. The route of their deprotonation to the final products **269** depends on the nature of the substituents R¹ and R².¹⁴⁹ It was shown that only in the case of the acetylenic ketones **271a–c**, does the reaction occur unambiguously to give the compounds **269a–c**. The alkynyl ketones **271d** and **271e** form complex mixtures of products. Thus the ketone **271d** gave the expected triflate **269d** in 70%–75% yield. In addition, the reaction mixture contained the isomeric triflate **280** (25%–30%, the ratio *E*:*Z* = 1:1).

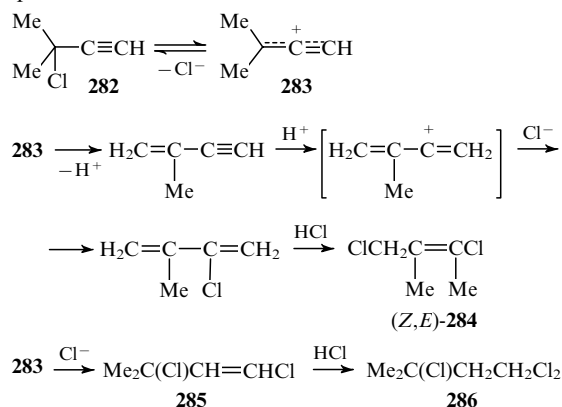


Treatment of the ketone **271e** with trifluoromethanesulfonic anhydride affords mainly the triflate **280** (85%–90%, the ratio *E*:*Z* = 1:1) and only 10%–15% of the triflate **269d**.



It can be seen from the above scheme that in both cases, the major reaction products result from deprotonation of the intermediates in the alkynyl carbocation form **279**, **281**.

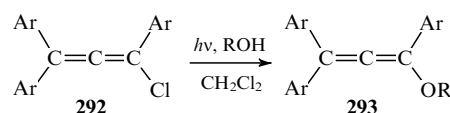
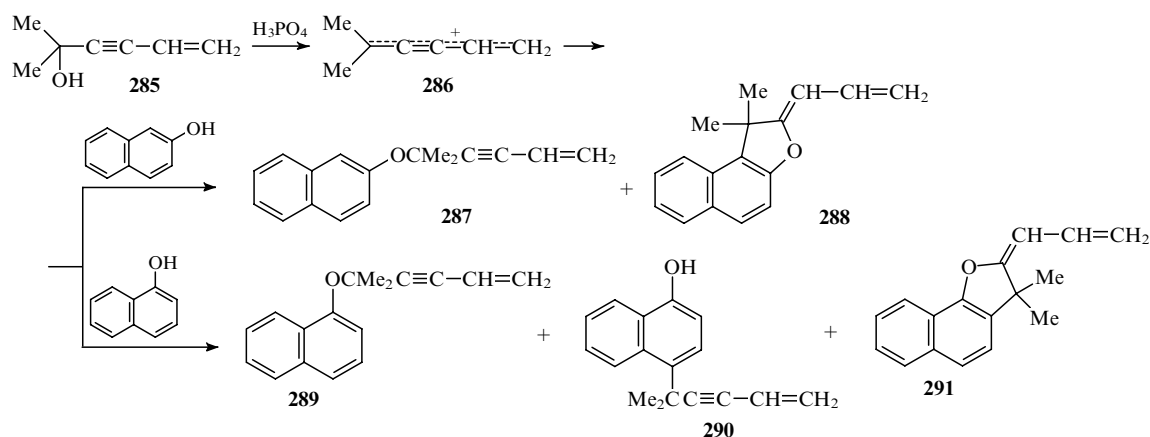
The addition of anhydrous HCl to 3-chloro-3-methylbut-1-yne **282** affords 16 reaction products. The main products are (*E*)-1,3-dichloro-3-methylbut-1-ene **285**, 1,1,3-trichloro-3-methylbutane **286** and (*Z*)- and (*E*)-1,3-dichloro-2-methylbut-2-ene **284**. The intermediate formation of dimethylethynyl carbocation **283** was postulated.¹⁵⁰



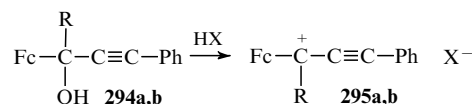
In the presence of H_3PO_4 , the alcohol **285** reacts with 2- and 1-naphthols to give products of *O*-alkylation (**287**, **289**), aromatic electrophilic substitution (**290**) and cyclisation (**288**, **291**) (Scheme 2).¹⁵¹

When the reaction mixture is kept in the presence of an acid, the compound **287** isomerises to **288**, and the compound **289** isomerises to **291**; apparently, isomerisation involves dissociation of the thermodynamically less favourable naphthol ethers under the action of acids.

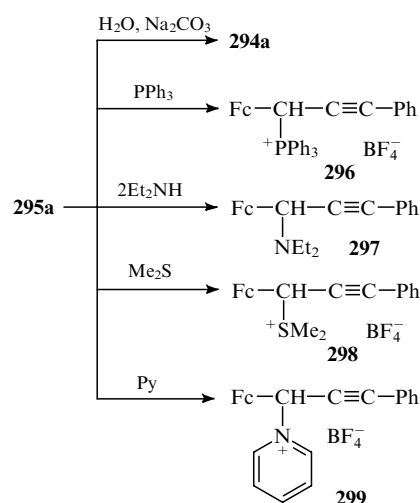
When triarylcycloallenes **292** are irradiated with a mercury lamp at -30°C in CH_2Cl_2 solutions of alcohols, alkoxy-substituted cycloallenes **293** are formed.¹⁵² This reaction is believed to proceed *via* alkynylcarbenium ions.



A ferrocenyl residue is known to stabilise efficiently a carbenium centre adjacent to it.¹⁵³ The treatment of ferrocenyl(phenylethynyl)-methanol **294a** or -ethanol **294b** with acids resulted in the synthesis of stable phenylethynylcarbenium salts **295a,b**. They react with nucleophiles at the sp^2 -hybridised carbon atom to give charged or neutral ferrocenyl derivatives of the type **296–299**.¹⁵⁴ Bis-ferrocenyl cations in which the two ferrocene fragments are linked by one or two acetylene (or butadiyne) bridges have been studied by spectroscopy.¹⁵⁵



R = H (**a**), Me (**b**); X = BF₄, ClO₄.



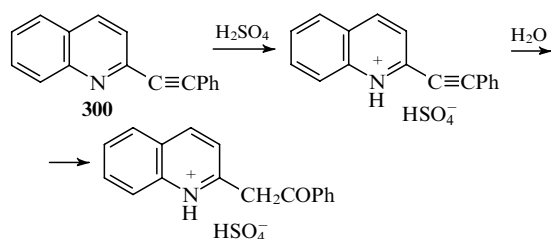
Fc is ferrocenyl, Py is pyridine.

3. Alkynyl-substituted heterocyclic cations

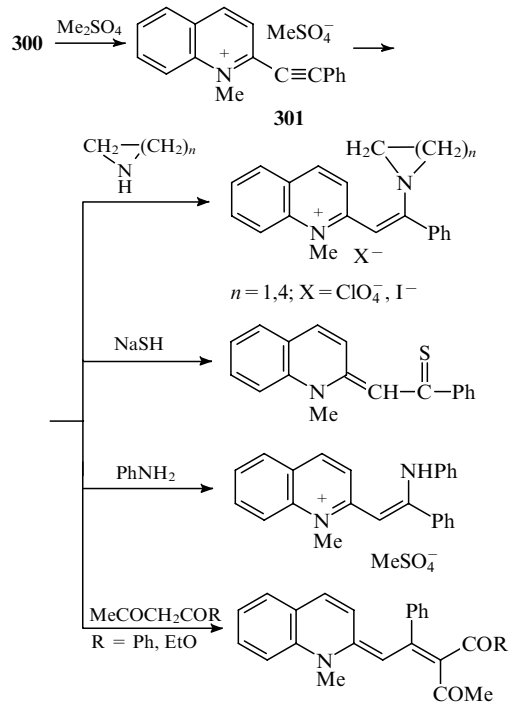
The cationic fragment of the alkynyliminium cations of the type **256** described above can be a part of an aromatic heterocycle. These cations are the most stable due to the charge delocalisation with participation of the aromatic system.

The protonation or alkylation of the nitrogen atom in alkynyl-substituted pyridines and quinolines proved to be an efficient method for activating the acetylene fragment towards reactions with various nucleophiles. Thus 2-phenylethynylquinoline **300** readily adds water in acid media.¹⁵⁶

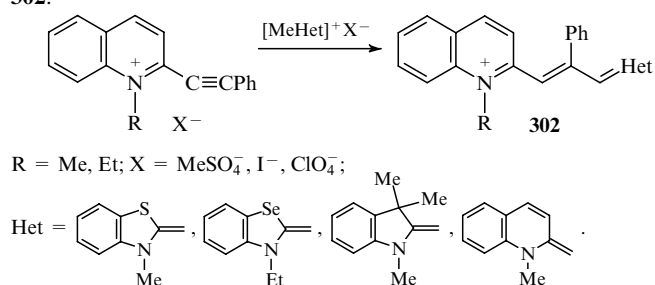
Scheme 2



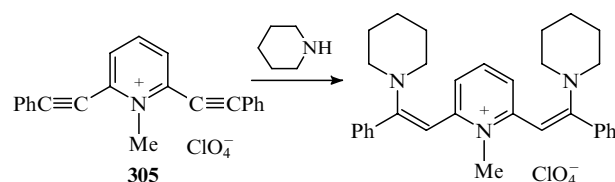
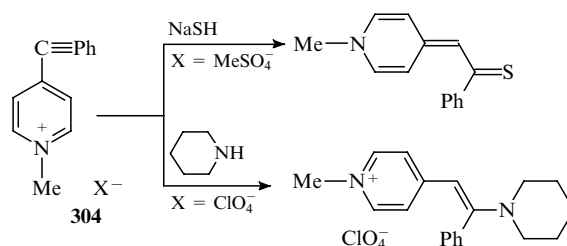
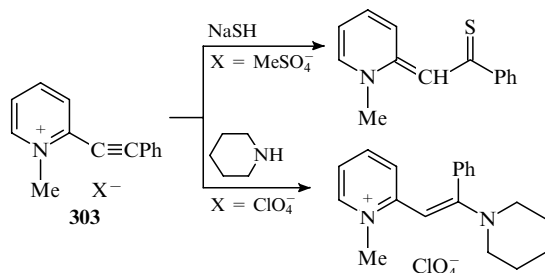
The alkylation of the quinoline **300** with dialkyl sulfates or with esters of toluene-*p*-sulfonic acid yields quaternary salts **301**, which are quite stable in alkaline solutions and are fairly reactive towards S- and N-nucleophiles and CH-acids.¹⁵⁶



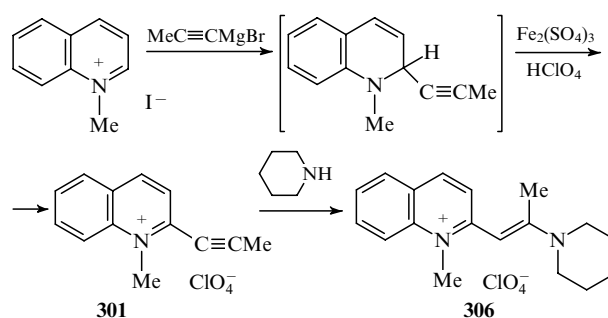
N-Alkylated salts of nitrogen-containing heterocycles readily add to phenylethynylquinolinium salts giving rise to cyanine dyes **302**.¹⁵⁶



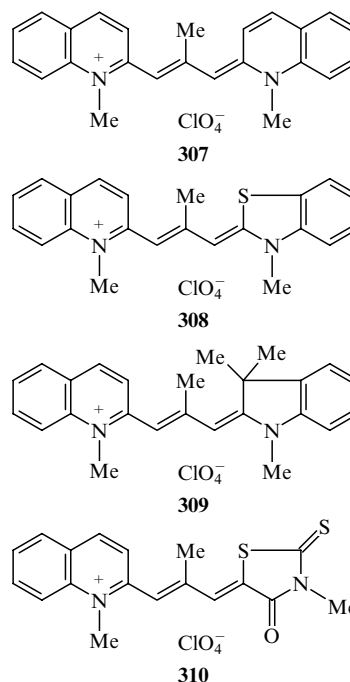
Phenylethynylpyridinium salts **303**–**305**, which add nucleophiles at the C≡C bond, have been obtained by *N*-methylation of the corresponding ethynylpyridines.¹⁵⁷



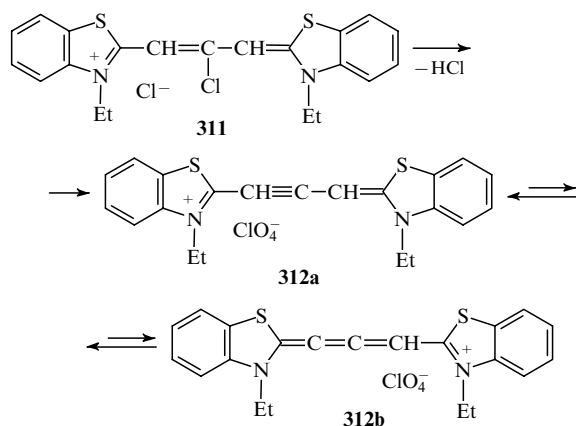
Yet another method for the synthesis of the alkynylquinolinium salt **301** is based on the interaction of *N*-methylquinolinium iodide with propynylmagnesium bromide. The subsequent oxidation in the presence of HClO₄ affords the corresponding perchlorate.¹⁵⁸ The IR spectrum of this salt contains an intense absorption band at about 2230 cm⁻¹ corresponding to the triple carbon–carbon bond; this confirms the salt structure. As in the case of quinolinium salts with a phenylethynyl substituent, the addition to the propynyl group is also directed at the end of the triple bond that is more distant from the heterocycle. This gives enamine **306**.



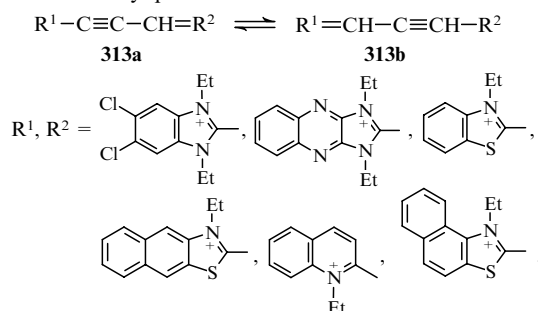
Cyanine dyes containing quinaldine (**307**), 2-methylbenzothiazole (**308**), 2,3,3-trimethylindolenine (**309**) and *N*-methylrhodamine (**310**) residues are synthesised in a similar way.



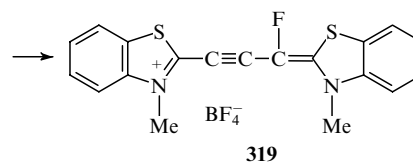
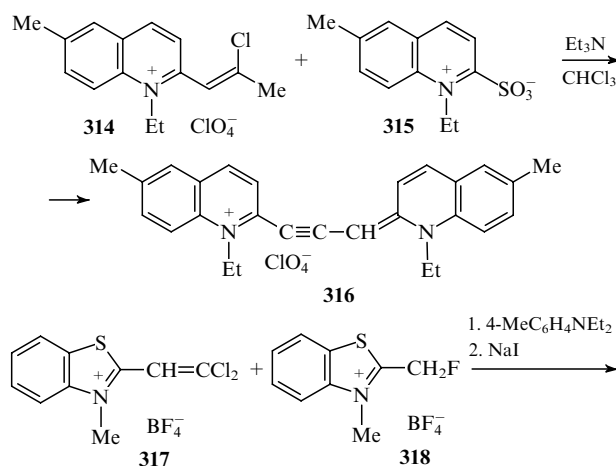
Acetylenic analogues of cyanine dyes containing a carbon–carbon triple bond in the conjugated chain between two heterocycles can be prepared by different methods. Thus perchlorate **312** was synthesised by dehydrochlorination of *meso*-chlorocarbocyanines **311**.^{159, 160}



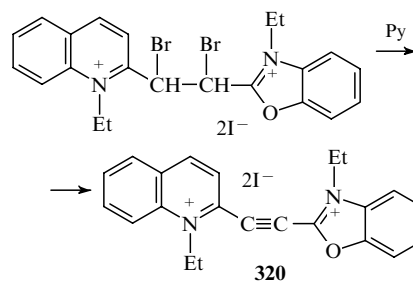
It has been shown by electronic spectroscopy and X-ray diffraction analysis that the alkyne structure **312a** is energetically more favourable than the cumulene structure **312b**. Study of a series of similar conjugated systems containing different heterocycles showed that in this case, an equilibrium of the type **313a** $\rightleftharpoons$ **313b** is established; the isomer in which the positive charge is concentrated on the more basic heterocycle (for example, on a benzimidazole rather than benzothiazole ring) predominates in the mixture. The experimental results and spectroscopic data were confirmed by quantum-chemical calculations.¹⁶⁰



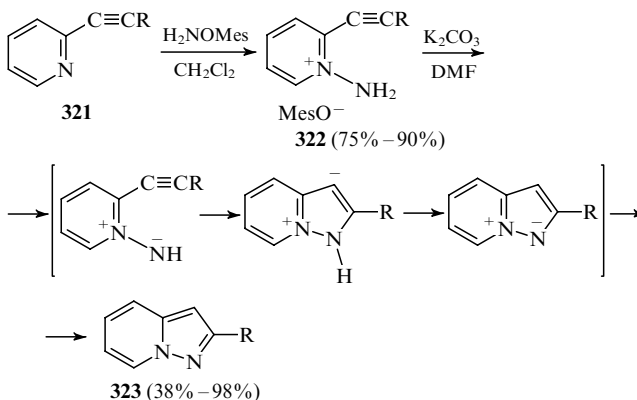
Dyes with similar structures **316** and **319** have been obtained by condensation of the chlorovinylquinolinium salt **314** with betaine **315**¹⁶¹ or by condensation of benzothiazolium salts **317** and **318** with each other.¹⁶²



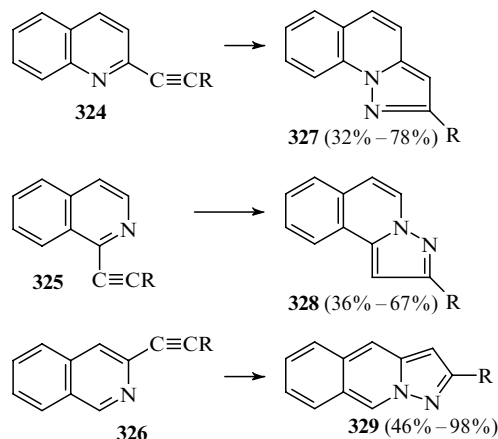
Synthesis, spectral characteristics and chemical properties of dyes including compounds **320** in which an acetylenic fragment connects two heterocyclic cations have been reported.¹⁶³



3-Azaindolizine derivatives **323** are formed upon cyclisation of 2-ethynylpyridine-*N*-imides **322**. The latter, in turn, are obtained by *N*-amination of 2-alkynylpyridines **321** followed by treatment with potassium carbonate in the presence of DMF.^{164, 165} Similar cyclisation of 2-alkynylquinoline **324** and alkynylisoquinolines **325**, **326** yields pyrazolo[2,3-*a*]quinolines **327** and pyrazoloisoquinolines **328**, **329**.¹⁶⁵



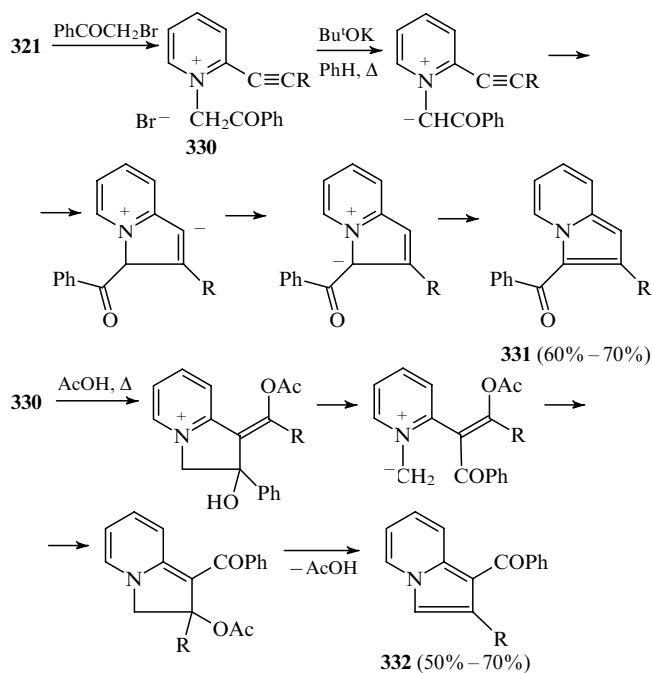
R = H, Me, Bu, CH₂OH, Ph.



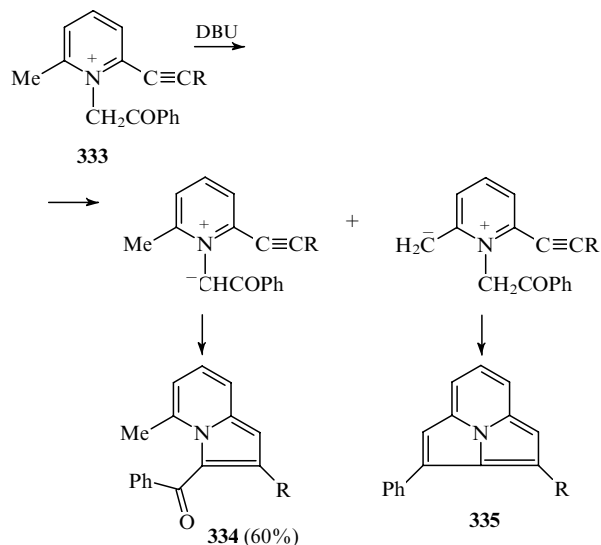
R = Bu, CH₂OH, Ph.

Transformations of 2-alkynyl-*N*-phenacylpyridinium salts **330** follow different pathways depending on their structures and reaction conditions.¹⁶⁶ The monosubstituted 2-alkynylpyridines **321** are converted into the alkynylpyridinium salts **330** on treatment with phenacyl bromide. Refluxing of **330** in benzene in the presence of a base (potassium *tert*-butoxide, 1,5-diazabicy-

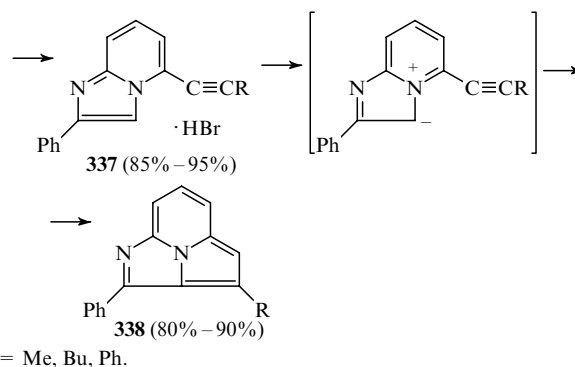
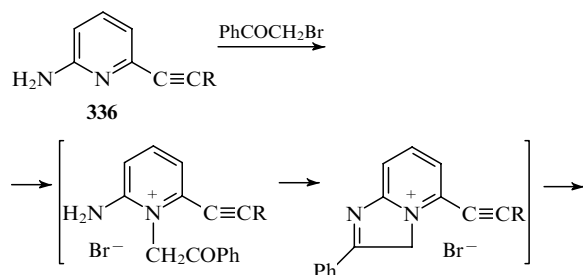
clo[5.4.0]undec-5-ene) affords the corresponding ylides, which cyclise to 3-benzoylindolizines **331**; in boiling acetic acid, the salts **330** are converted into 1-benzoylindolizines **332**.



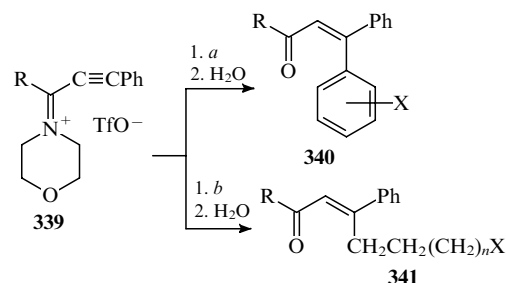
On treatment with bases, 6-methylpyridinium salts **333** give 10%–15% of 2-phenylcyclazines **335** in addition to 3-benzoylindolizines **334**.¹⁶⁶



Unlike the examples described above, 6-amino-2-alkynylpyridines **336** are converted into 1-azaindolizinium salts **337** just upon treatment with phenacyl bromide; treatment of the salts **337** with a solution of sodium carbonate yields 1-azacyclazines **338**.¹⁶⁶

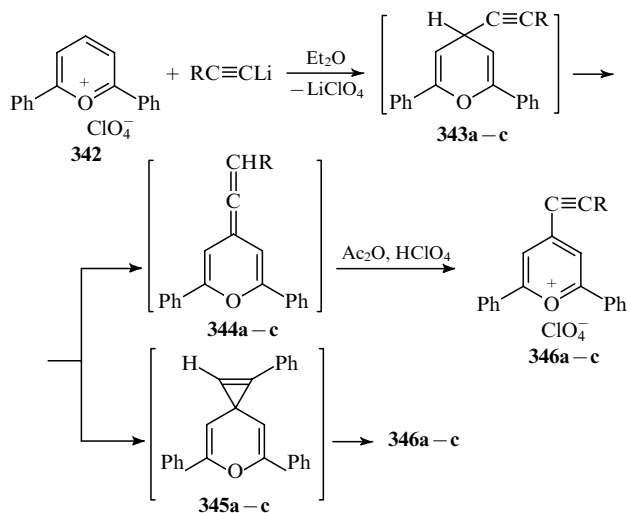


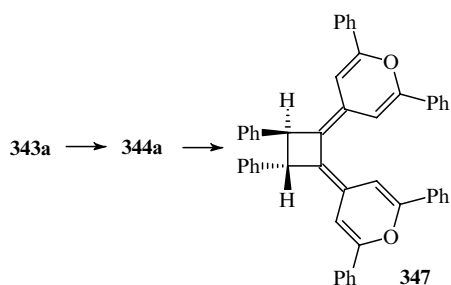
Data on these and other related reactions have been surveyed in a review.¹⁶⁷ Synthesis of a reverse transcriptase inhibitor *via* a 2-alkynylpyridinium intermediate has been described in a recent study.¹⁶⁸ An interesting reaction is the conjugated addition of organozinc-copper reagents to (2-propynylidene)morpholinium triflate **339**. Hydrolysis of the addition products gives α,β -unsaturated ketones **340** and **341**, respectively.¹⁶⁹



(a) $\text{IZnCu}(\text{CN})\text{C}_6\text{H}_4\text{X}$; $\text{X} = 2\text{-CN, 4-CN, 3-COOEt}$;
(b) $\text{IZnCu}(\text{CN})\text{CH}_2\text{CH}_2(\text{CH}_2)_n\text{X}$; $n = 0, 1$; $\text{X} = \text{CN, COOEt}$.

In recent years, extensive studies on cyclic oxonium ions, pyrylium cations containing alkynyl substituents, have been carried out. The first representative of these stable alkynylcarboxonium ions, namely, 2,6-diphenyl-4-phenylethynylpyrylium perchlorate, was prepared by the reaction of 2,6-diphenylpyrylium perchlorate **342** with lithium phenylacetylide and subsequent oxidative dehydration of the pyran intermediate.¹⁷⁰ Later, other lithium acetylide derivatives have also been involved in this reaction.¹⁷¹ Three possible structures, **343**–**345**, have been proposed for the reaction intermediate;¹⁷⁰ based on the data of IR spectroscopy, the allene species **344** was preferred. The IR spectrum of salts **346** contains an absorption band at 2210 cm^{-1} typical of acetylene derivatives.¹⁷⁰

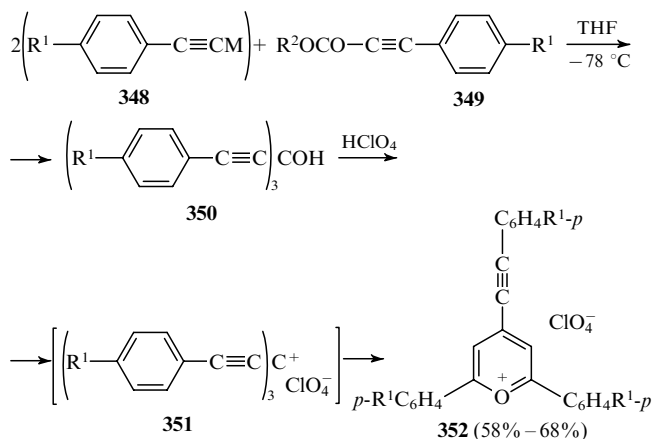




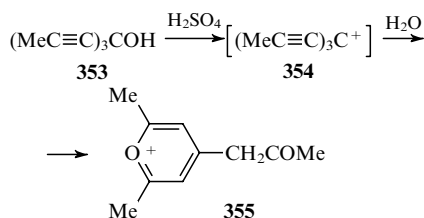
It has been found that the outcome of this reaction depends on the nature of the solvent.¹⁷² When the reaction between the salt **342** and lithium phenylacetylenide was carried out in diethyl ether, only 4-phenylethynylpyran **343a** was formed. The replacement of ether by tetrahydrofuran resulted in the formation of the [2+2]-cycloaddition product **347**. The researcher cited believe¹⁷² that it is formed *via* dimerisation of allenylpyran **344a**.

Later, this difference between the routes of nucleophilic addition to the pyrylium salt **342** was explained¹⁷³ by different conditions of metallation of phenylacetylene. In fact, Doney *et al.*¹⁷² used an equimolar amount of a standard solution of *n*-butyllithium, whereas other investigators^{170,171} employed an excess of butyllithium, which then remained in the reaction mixture and acted as a base during the isomerisation of the compound **343a** to **344a**.¹⁷³

Study of dyes containing carbon–carbon triple bonds have led to the synthesis of acetylenic analogues of triarylmethane dyes, which are able to acquire an alleno-quinoid structure and, hence, they exhibit interesting photochemical properties. Alcohols **350** can be synthesised by the reaction of organometallic derivatives of arylacetylenes **348** with the corresponding esters **349**. The compounds **350** were converted into the corresponding 4-arylethynylpyrylium salts **352** by treatment with 70% HClO₄ in a 2:1 C₆H₆:EtOH mixture.¹⁷⁴

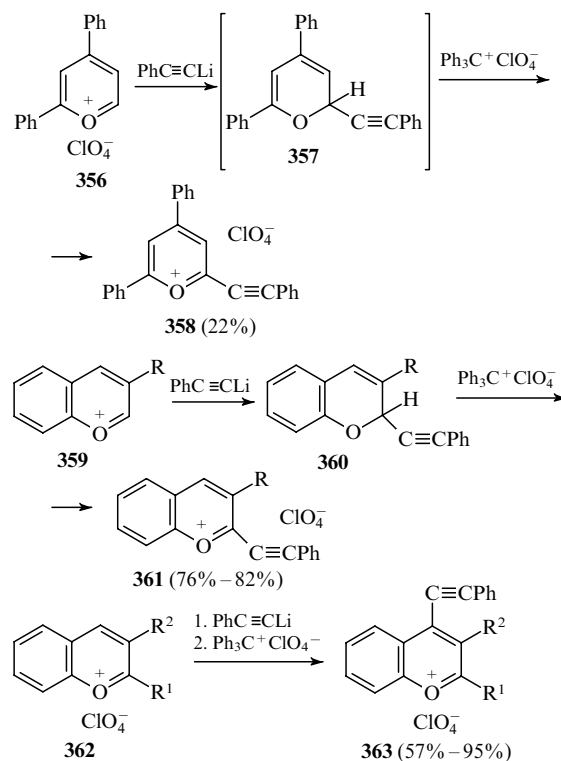


R¹ = H, Me₂N; R² = Me, Et; M = Li, MgBr.



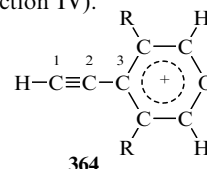
The IR spectra of the salts **352** exhibit absorption bands at about 2170 cm⁻¹. It has been assumed that under the reaction conditions, the trialkynylcarbenium ions **351** undergo the Meyer–Schuster rearrangement to give arylethynyl-substituted pentene-1,5-diones, which then form the pyrylium ring.^{175,176} This was confirmed using simpler systems. Thus treatment of alcohol **353** with an acid gives rise to the 4-acetonilpyrylium cation **355** *via* alkynylcarbenium intermediate **354**.¹⁷⁷

Recently it has been shown that non-symmetrical 2,4-diphenylpyrylium perchlorate **356** adds lithium phenylacetylenide at the free α -position yielding unstable *2H*-pyran intermediate **357**. Oxidative dehydration of the latter affords extremely explosive 2-phenylethynylpyrylium perchlorate **358**.¹⁷⁸ Conversely, *2H*-pyran intermediates **360**, obtained analogously from 2-unsubstituted 1-benzopyrylium salts **359**, are stable and can be isolated. 4-Phenylethynyl-1-benzopyrylium salts **363** were synthesised in the same way from 1-benzopyrylium salts **362** unsubstituted at the 4-position.¹⁷⁸



R¹ = Ph, Bu^t; R² = H, Me, Et.

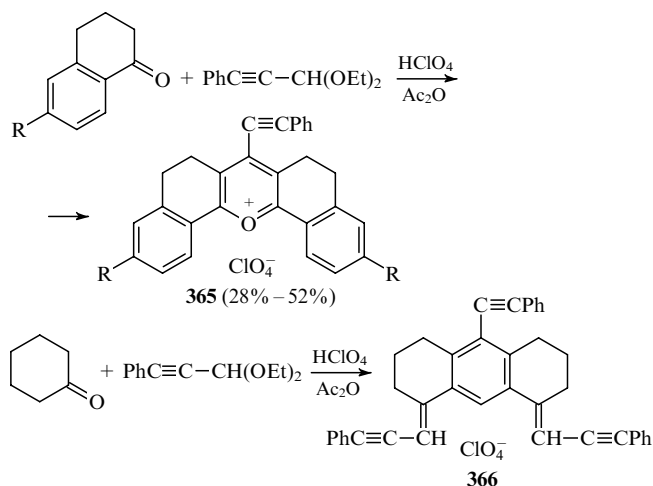
The IR spectra of the salts **358**, **361** and **363** exhibit absorption bands in the region of 2180–2200 cm⁻¹ typical of C≡C triple bond vibrations. This means that in phenylethynylpyrylium salts, this bond is retained, the positive charge being concentrated in the heteroaromatic ring. This conclusion has been confirmed by MINDO/3 quantum-chemical calculations¹⁷⁸ according to which the C(1)–C(2) bond length in species **364** (0.1209–0.1210 nm) is close to the length of a C≡C triple bond, whereas the C(2)–C(3) bond (0.1429–0.1437 nm) is substantially longer than the corresponding bond in an allenyl cation¹⁰⁹ (see Section IV).



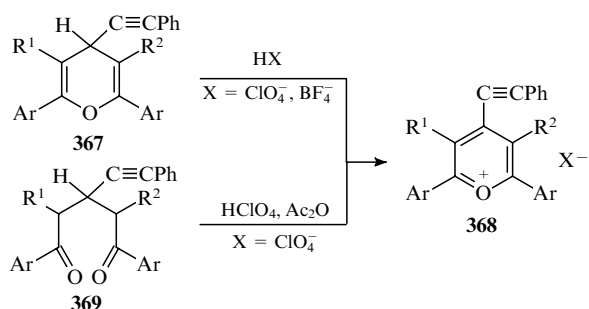
R = H, Me.

The above reactions of the pyrylium salts **342**, **356** and 1-benzopyrylium salts **359**, **362** with lithium phenylacetylenide are, in essence, examples of nucleophilic substitution in the aromatic nucleus, little studied so far. Processes of this type involving heteroaromatic cations as the substrates are known mainly for azinium salts.¹⁷⁹ Study of nucleophilic aromatic substitution with pyrylium salts as substrates is of interest because it does not require substrate activation. In addition, the low nucleofugal activity of hydrogen in the non-charged intermediates (*i.e.*, pyran systems) permits conducting the S_N^H (AE) process¹⁷⁹ in two separate stages.

Besides the nucleophilic substitution of a hydrogen atom in a pyrylium cation by an alkynyl group, alkynylpyrylium salts can also be synthesised by forming a pyrylium ring. Two examples of this type, namely, cyclisation of trialkynyl carbocations **351** and **354**, are shown above.^{174, 177} However, methods for the synthesis of pyrylium salts involving two or three components^{175, 176} are not very suitable for the preparation of alkynyl-substituted derivatives, because of the high probability of involvement of the triple bond in condensation. Only few examples of synthesis of 4-phenylethynylpyrylium salts such as **365** and **366** by the reaction of 3-phenylprop-2-ynal diethyl acetal with cyclic ketones like 1-tetralone or cyclohexanone have been reported.¹⁸⁰



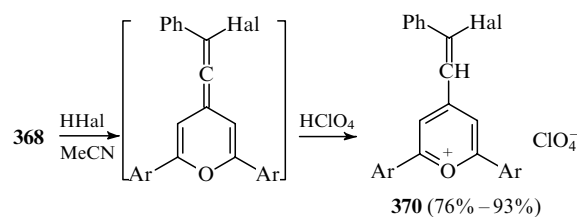
Alkynylpyrylium salts **368** are obtained by oxidative dehydrogenation of the corresponding 4*H*-pyrans **367** on treatment with triphenylmethyl perchlorate (yields 92%–95%), an Ac₂O–HClO₄ mixture (yields 53%–71%) or BF₃·Et₂O (yields 43%–82%),¹⁸¹ or by cyclisation of difficultly accessible 3-alkynylpentane-1,5-diones **369** on treatment with HClO₄ in acetic anhydride, acting as dehydrating and dehydrogenating agent (yields 78%–84%).¹⁸²



R¹, R² = H, Me; Ar = Ph, 4-MeC₆H₄, 4-MeOC₆H₄.

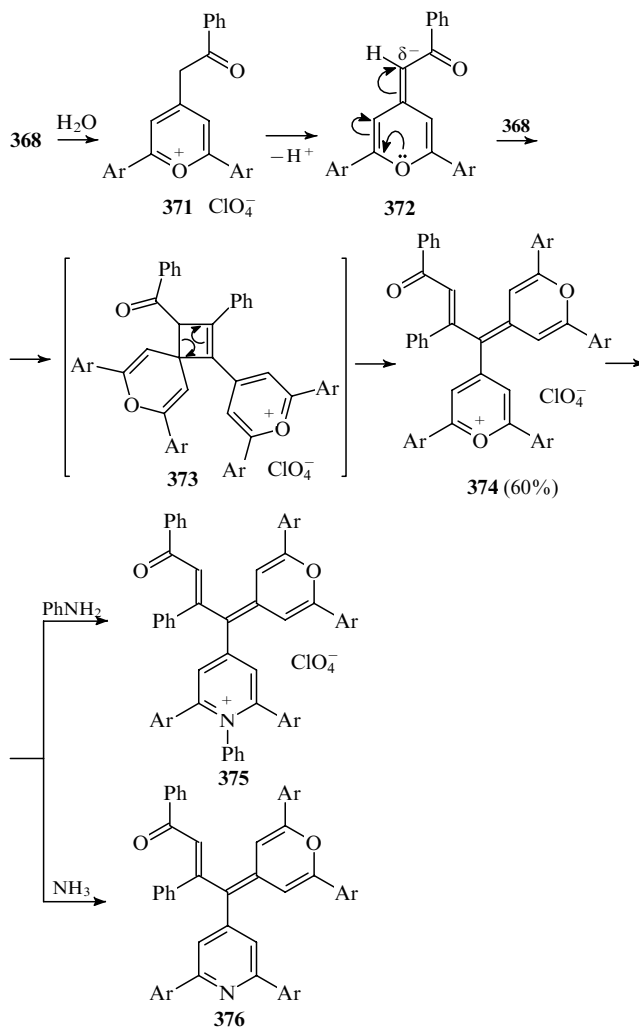
The combination of the highly stable heteroaromatic cation and the alkynyl fragment in the molecules of **368** makes these compounds fairly useful for organic synthesis. Thus the presence of the cationic pyrylium fragment efficiently activates the C≡C bond towards nucleophilic substitution reactions. Nucleophilic reagents, irrespective of their structure, attack the triple bond in the alkynyl substituent at the end that is remote from the heterocycle. It should be emphasised that the reactivity of the pyrylium fragment in the compounds formed in these reactions remains virtually unchanged. Therefore, after the nucleophilic reaction of the alkynyl group, diverse transformations of the oxygen-containing heterocycle can be performed by treatment with the same or other nucleophilic reagents.

For example, 2,6-diaryl-4-phenylethynylpyrylium perchlorates **368** (R¹ = R² = H) easily add hydrogen halides to give halo-derivatives **370**.¹⁸¹



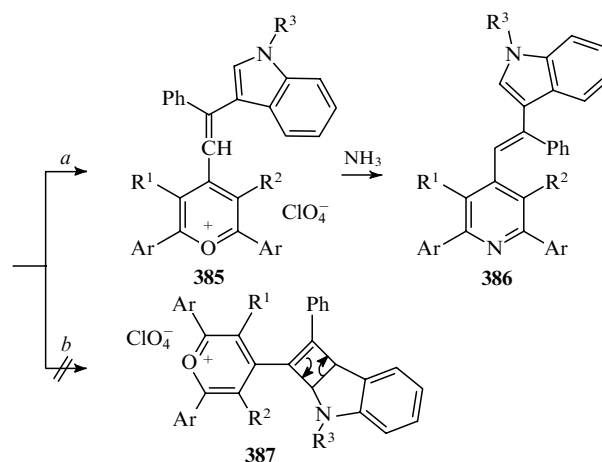
Ar = Ph, 4-MeOC₆H₄; Hal = Cl, Br.

It might be expected that the reactions of **368** with water or alcohols would afford 4-phenacylpyrylium derivatives **371** (or the corresponding alkyl ethers) upon hydration of the triple bond or addition of alcohols. However, refluxing of the salts **368** with water, methanol or ethanol resulted in the isolation of monomethinecyanines **374** the structures of which were confirmed by IR and ¹H NMR spectroscopy and by X-ray diffraction analysis of the pyridinium analogue **376** (Ar = Ph) prepared by the reaction with NH₃.¹⁸³ The pathway to these monomethinecyanines includes hydration of the triple bond in the initial salts **368** yielding benzoylmethylenepyran **372**. However, the reaction does not stop at this stage, and the hydration products **372** react with the 4-phenylethynylpyrylium salts **368** as C-nucleophiles according to the [2+2]-cycloaddition pattern. The final products **374** result from electrocyclic ring opening in the cyclobutene intermediates **373**.

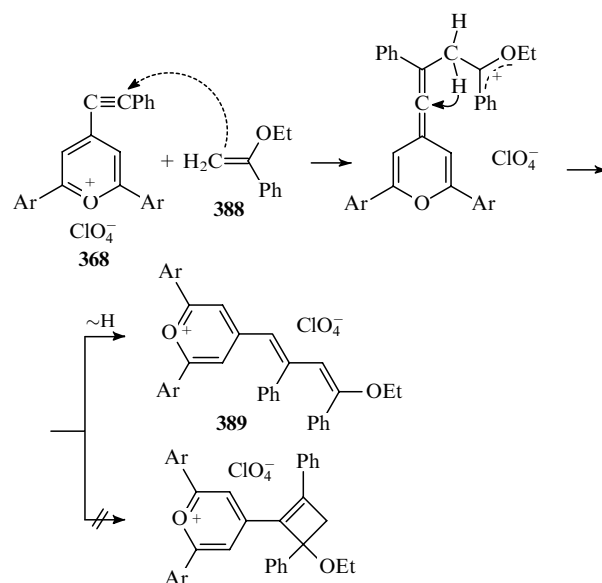


Ar = Ph, 4-MeOC₆H₄.

The 4-phenacylpyrylium salt **378** and benzoylmethylenepyran **379** have been obtained only when the 3,5-dimethyl-substituted 4-phenylethynylpyrylium salt **368** (R¹ = R² = H, Ar = Ph) was treated with alcohols and the resulting vinyl ethers **377** were dealkylated.¹⁸⁴ Apparently, the methyl groups decrease the elec-

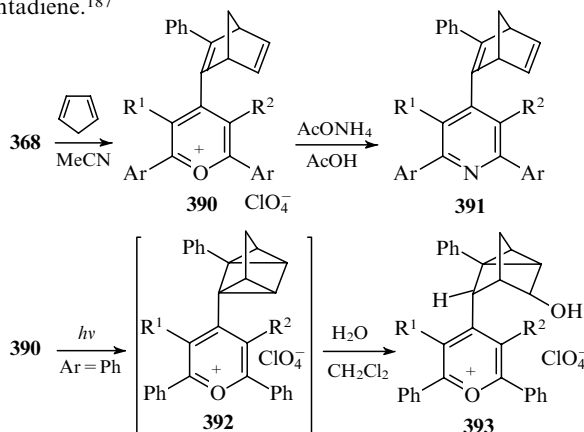


The formation of the cyclobutene intermediate in the reaction of the salts **368** with the benzoylmethylenepyran **372** is apparently due to the fact that the pyran and pyrylium rings can approach each other as a result of π - π donor-acceptor interaction, and this creates favourable conditions for [2 + 2]-cycloaddition. When the salts **368** react with indoles, the reactants do not come close to each other in this way, and, hence, intramolecular proton transfer occurs. This interpretation is quite consistent with the outcome of the reaction of the pyrylium perchlorate **368** ($R^1 = R^2 = H$, $Ar = 4\text{-MeOC}_6\text{H}_4$) with vinyl ether **388** involving a similar proton transfer.¹⁸⁶ The structure of the reaction product **389** was confirmed by the ^1H NMR spectrum.



The 4-phenylethynylpyrylium salts **368** are also able to enter into [2 + 4]-cycloaddition reactions. Thus norbornadiene derivatives **390** containing a positively charged heteroaromatic ring were

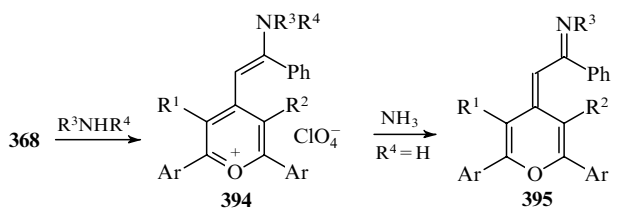
obtained for the first time by the reaction of **368** with cyclopentadiene.¹⁸⁷



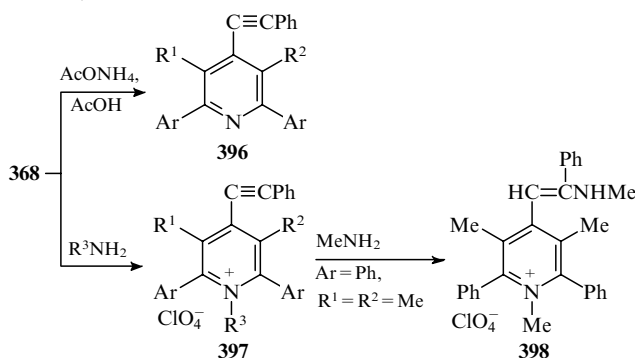
R¹, R² = H, Me; Ar = Ph, 4-MeOC₆H₄.

When solutions of the norbornadiene derivatives **390** are exposed to the light of a mercury lamp ($\lambda_{\text{max}} = 546 \text{ nm}$) or to sunlight, they undergo fast photochemical transformation into quadricyclanes **392**. However, these products are readily hydrated under the reaction conditions, which unfortunately precludes the possibility of thermally induced back reaction.

The pyrylium salts **368** add alcohols and aromatic amines (aniline, *p*-toluidine, *N*-methylaniline) as well as *tert*-butylamine to the *sp*-hybridised carbon atom that is remote from the pyrylium ring; this gives enaminyopyrylium salts **394**.¹⁸⁴ It should be emphasised that in the case of pyrylium salts containing no ethynyl substituent, the reactions with ammonia and amines involve the pyrylium fragment and are used typically to prepare pyridines and pyridinium salts.¹⁷⁶ Unlike normal pyrylium salts, the compounds **394** are deprotonated on treatment with ammonia (at R⁴ = H) to unsaturated imines **395** rather than exchange the oxygen atom in the ring for nitrogen. However, ammonium acetate and methyl-, butyl- and benzyl- amines attack the pyrylium ring in the salts **368**, which gives rise to alkynyl-substituted pyridine derivatives **396** and **397**.¹⁸⁴



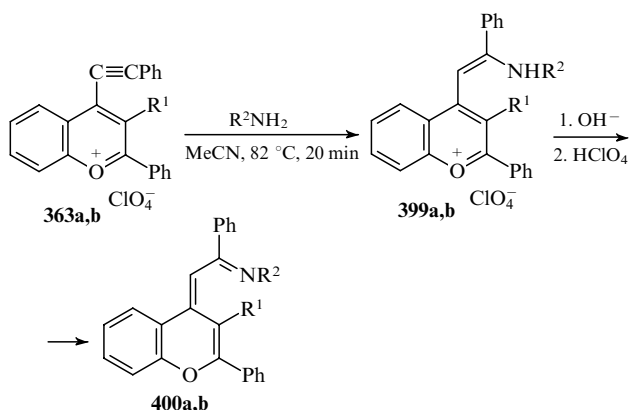
R¹, R² = H, Me; Ar = Ph, 4-MeOC₆H₄; R³ = Bu^t, Ph, 4-MeC₆H₄; R⁴ = H, Me.



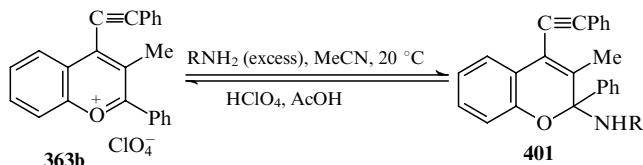
R¹, R² = H, Me; Ar = Ph, 4-MeOC₆H₄; R³ = Me, Bu, PhCH₂.

The acetylenic fragment in the 4-phenylethynylpyridinium salts **397** is still sufficiently activated to add one more amine molecule; this affords aminovinylpyridinium salts **398**.

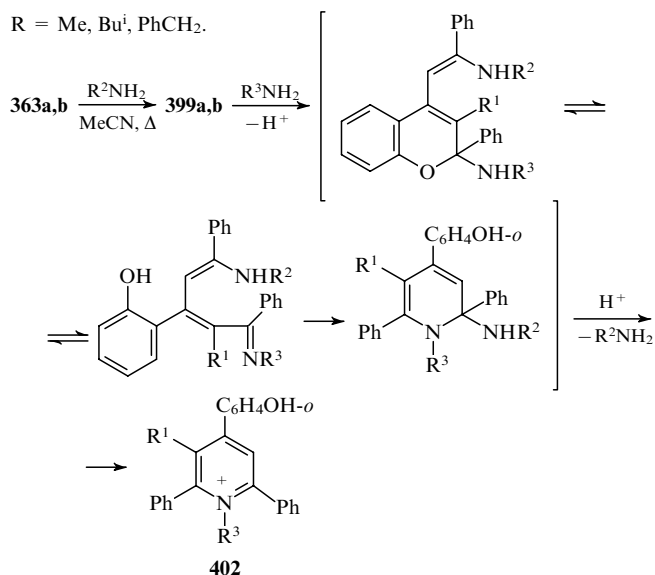
Unlike monocyclic pyrylium salts, 1-benzopyrylium salts do not tend to exchange the ring oxygen atom for nitrogen.¹⁸⁸ Therefore, it comes as no surprise that 4-phenylethynyl-1-benzopyrylium salts **363a,b** are converted into aminovinyl derivatives **400a,b** on refluxing with an equimolar amount of an aliphatic amine or benzylamine followed by treatment with HClO₄.¹⁸⁹ However, when the salt **363b** is mixed with excess amine at room temperature, the products of the amine addition at the 2-position of the ring — 2-alkylaminoflavones **401** — are rapidly formed. On treatment with HClO₄ they easily decompose giving the initial salt **363b**. Thus, this addition is reversible and kinetically controlled. Refluxing of the salts **363a,b** with a two- or three-fold excess of an amine in acetonitrile for 1–5 h affords 4-(2-hydroxyphenyl)pyridinium salts **402**. The same products are formed under similar conditions from the aminovinyl salts **399a,b**, which are evidently formed as intermediates in the transformation of the 4-phenylethynyl-1-benzopyrylium salts **363**.



R¹ = H (**a**), Me (**b**), R² = PhCH₂, Bu^t, Buⁱ.



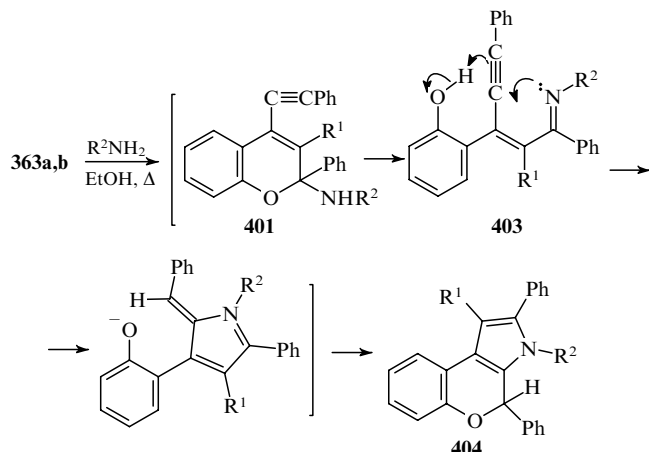
R = Me, Buⁱ, PhCH₂.



R¹ = H (**a**), Me (**b**); R², R³ = Me, Buⁱ, PhCH₂.

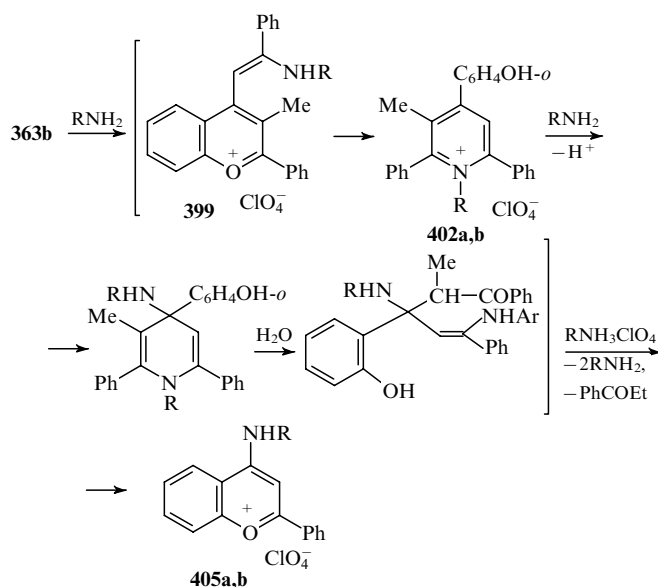
It is obvious that the 2-aminoflavones **401** are not formed as intermediates in this thermodynamically controlled recyclisation. However, the formation of aminoflavones proved to be the key stage in the transformation of the 4-phenylethynyl-1-benzopyrylium salts **363a,b** into 2*H*-chromeno[3,4-*b*]pyrroles **404**.¹⁸⁹ These products are formed in 36%–75% yields upon refluxing of the

salts with excess primary amines in ethanol. Presumably, ethanol acts as a competing nucleophile and suppresses the formation of the 4-alkylaminostyryl salts **399**. The unstable adducts **401** have enough time to undergo ring cleavage yielding phenol intermediates **403**, which again cyclise to chromenopyrroles **404**. The structure of one of the tricyclic products **404** was established by X-ray diffraction analysis.¹⁸⁹



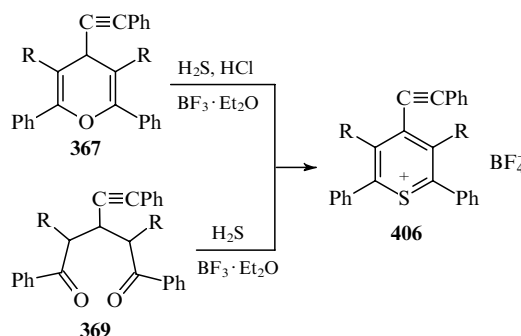
$R^1 = \text{H, Me}; R^2 = \text{Me, Bu}^i, \text{PhCH}_2$.

Recently, unexpected recyclisations of the 3-methyl-2-phenyl-4-phenylethynyl-1-benzopyrylium perchlorate **363b**, which occur on its refluxing with a two- or three-fold excess of aromatic amines, have been reported.¹⁹⁰ Treatment of the salt **363b** with aniline in dichloroethane or acetonitrile gives 4-anilino-2-phenyl-1-benzopyrylium salt **405a**. On treatment with *p*-toluidine under the same conditions, the pyridinium (**402b**) and 4-(*p*-toluidino)-1-benzopyrylium (**405b**) perchlorates are formed. It has been noted above that the compounds **402** result from recyclisation of the 4-aminovinyl-1-benzopyrylium salts **399**. It has been suggested and confirmed experimentally¹⁹⁰ that the compounds **399** can arise as intermediates in the recyclisation of the salts **363b** to the 4-(*R*-amino)-1-benzopyrylium salts **405a,b**.

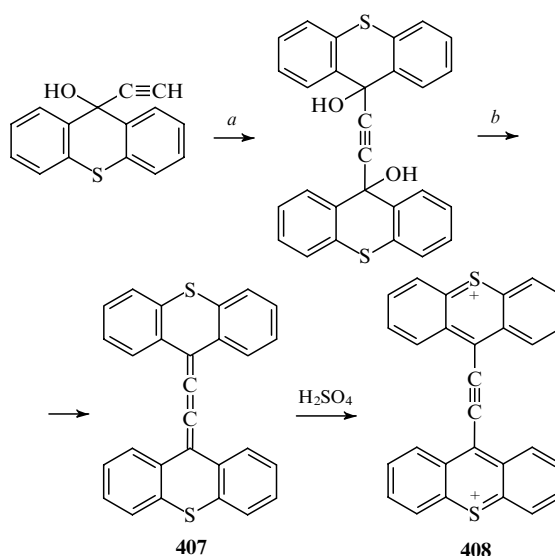


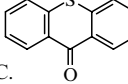
$R = \text{Ph (a), 4-MeC}_6\text{H}_4 \text{ (b)}$.

4-Phenylethynylthiopyrylium salts **406** have been obtained recently from 4-phenylethynyl-4*H*-pyrans **367** (yields 30%–40%) and from 3-phenylethynylpentane-1,5-diones **369** (yields up to 80%) on treatment with hydrogen sulfide in the presence of boron trifluoride etherate.¹⁹¹



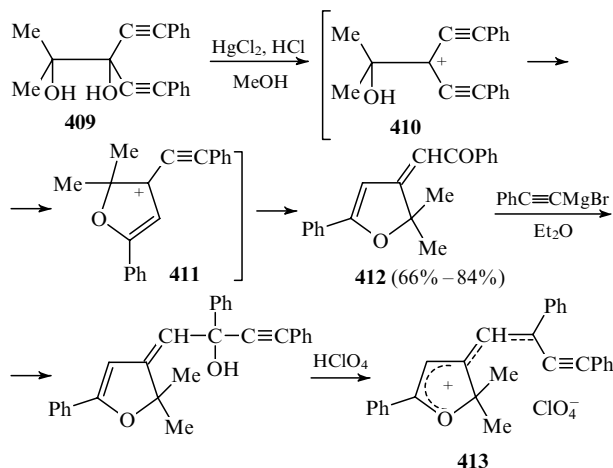
Bis-thioxanthene cumulene **407** has been prepared within the framework of studies aimed at the synthesis of π -electron-donating systems for charge transfer complexes possessing metallic conduction. When this product is treated with concentrated sulfuric acid, it is readily oxidised to acetylenic dication **408**, but does not undergo the expected triple bond protonation.¹⁹²



(a) 1. BuLi, THF, -78°C ; 2. , -40°C

(b) SnCl_2 , HCl, Et_2O , -80°C .

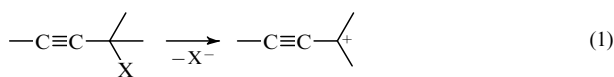
Development of a simple method for the synthesis of 3-acylmethylene-2,3-dihydrofurans from diacetylenic vicinal diols^{193,194} has led to the preparation of the dihydrofurylium salt **413** containing a conjugated enyne fragment. Apparently, the transformation of the diol **409** to the furan **412** occurs via the intermediate formation of dialkynyl carbocation **410** and cyclic alkynyl carbocation **411**, which then undergoes the Meyer–Schuster rearrangement.



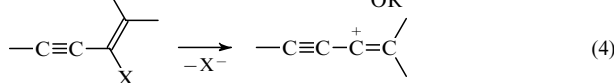
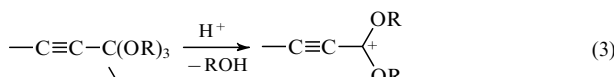
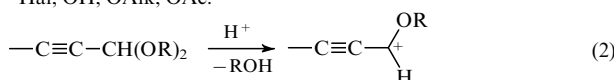
Comparison of the electronic spectra of the cation **413** ($\lambda_{\max} = 509$ nm) with those of some other 4-styryldihydrofurylium salts containing H, Me, Et or Ar instead of the phenylethynyl group has demonstrated that the bathochromic shift caused by the $\text{PhC}\equiv\text{C}$ group is twice as large as that caused by Ph. This is due to the fact that the triple bond efficiently participates in charge delocalisation.¹⁹⁴

To summarise the foregoing, it can be concluded that all the methods that are, in principle, suitable for generation of carbenium ions have been used to generate alkynyl carbocations.²

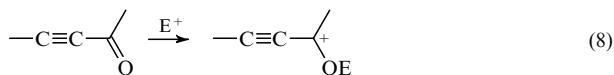
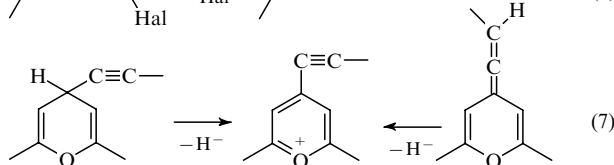
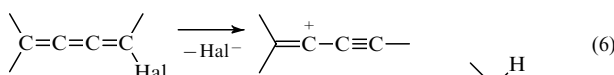
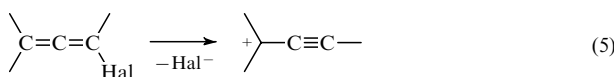
The most widely used procedure is detachment of a nucleofugal species from functional acetylene derivatives of the propargyl type containing one, two or three heteroatomic functions at the sp^3 -hybridised carbon atoms [Eqns (1)–(3)].^{135, 136} Methods based on abstraction of nucleofuges from functionally substituted enynes, allenes and cumulenes [Eqns (4)–(6)] are more difficult for practical implementation and, therefore, are used more rarely.^{113–115, 128, 145, 146} In the two latter cases [Eqns (5), (6)], the appearance of a carbenium centre results as well in the formation of a $\text{C}\equiv\text{C}$ triple bond. The oxidative dehydrogenation of ethynylpyran systems^{171, 181} [Eqn (7)] also belongs to this type of reactions.



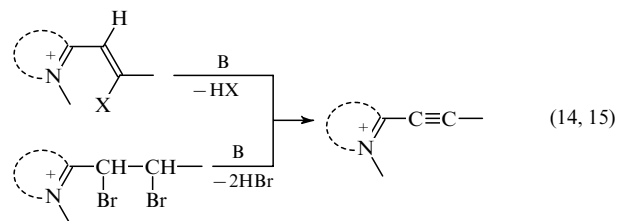
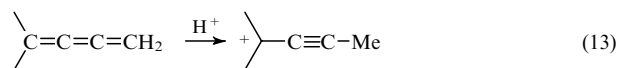
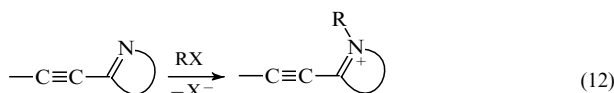
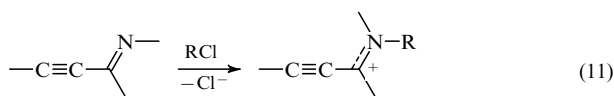
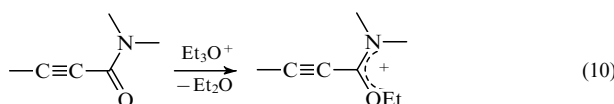
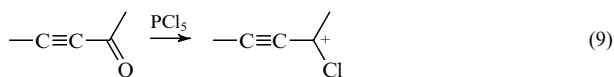
X = Hal, OH, OAlk, OAc.



X = Br, TfO.



E = H, CF_3SO_2 .

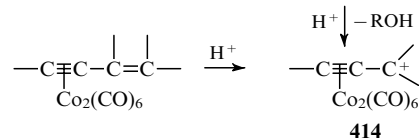
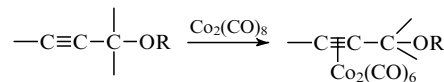


The general approach to the generation of carbocations consisting in the addition of a cationic electrophile to an unsaturated system has also been used for the preparation of alkynylcarbenium ions. Compounds used most often as the precursors are alkynones^{88, 129, 130, 146} [Eqns (8), (9)], amides^{34, 143} [Eqn (10)], linear imines⁸ and nitrogen-containing heterocycles^{156–158, 165–166} [Eqns (11), (12)]. The protonation of terminal cumulenes [Eqn (13)] is represented by only one example.¹²⁷ Electrophilic reactions of enynes deserve a more detailed discussion, which is presented in the last paragraphs of this Section.

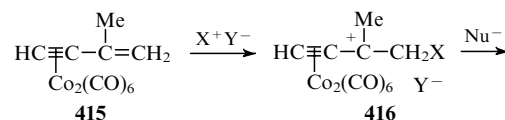
One more fundamental approach to the generation of alkynylcarbenium ions is formation of a carbon–carbon triple bond in cationic structures. Known examples are deprotonation of iminium salts and quaternised nitrogen-containing heterocycles followed by elimination of a nucleofuge (Hal^- , CF_3SO_3^-)^{142, 144, 159–161} [Eqn (14), (15)].

Several studies have been reported in which a carbenium centre near a triple bond was generated *via* 1,2-migration during the pinacol rearrangement;⁷⁹ an example of two-electron oxidation of cumulene to a dication, which is a rarely encountered type of process in the preparative chemistry of carbocations, has also been described.¹⁹²

In the case of conjugated enynes, electrophilic reactions of enynes, which have been mentioned among the methods for generation of alkynyl carbocations, proceed ambiguously.^{4, 195} Therefore, generation of alkynylcarbenium ions from these substrates is problematic. However, it is known that cations of the type **9**, which are not detected even in superacidic media (see Section III), can be readily prepared or even isolated as dicobalt-hexacarbonyl (DCHC) complexes of the type **414**.¹⁹⁶ The DCHC complexes **415** derived from a number of enynes, namely, isopropenylacetylene, 1-ethynylcyclohexene, 1-ethynylcyclopentene, have been used to conduct a large series of Ad_E reactions according to a two-stage pattern. The natures of the electrophile X^+ and the nucleophile Y^- in these reactions can be varied independently, due to the high stability of the alkynylcarbocationic intermediates **416**.^{196–198}

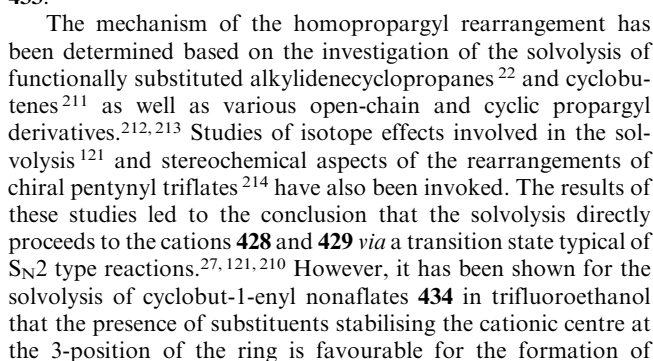
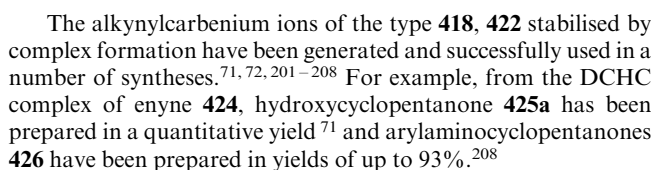


414

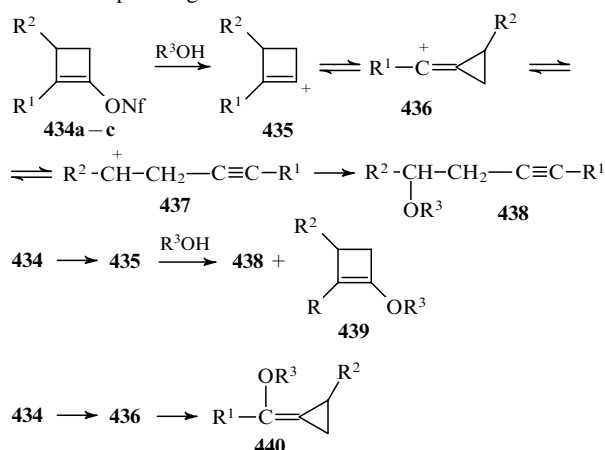


415

416



secondary homopropargyl cations **437**. The latter are converted into the corresponding ethers **438**.^{27, 212, 213, 215}

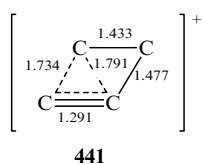


Nf = $C_4F_9SO_2$; $R^3 = CF_3CH_2$.

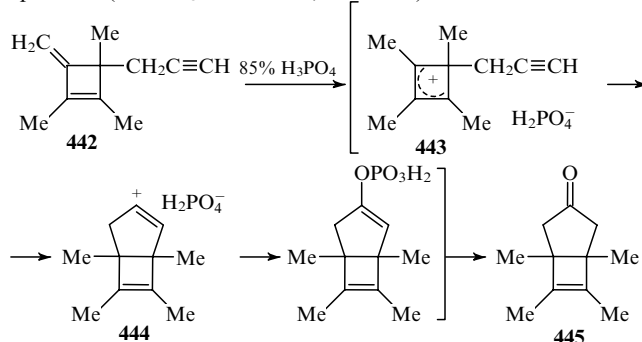
Compound	R^1	R^2	Yield (%)	
			438	439
434a	Me	H	3	95
434b	H	Me	63	34
434c		$(CH_2)_6$	68	32

The homopropargyl rearrangement is important from the synthetic viewpoint as a facile and convenient method for the preparation of cyclobutanones containing diverse substituents including those fused with carbocycles.

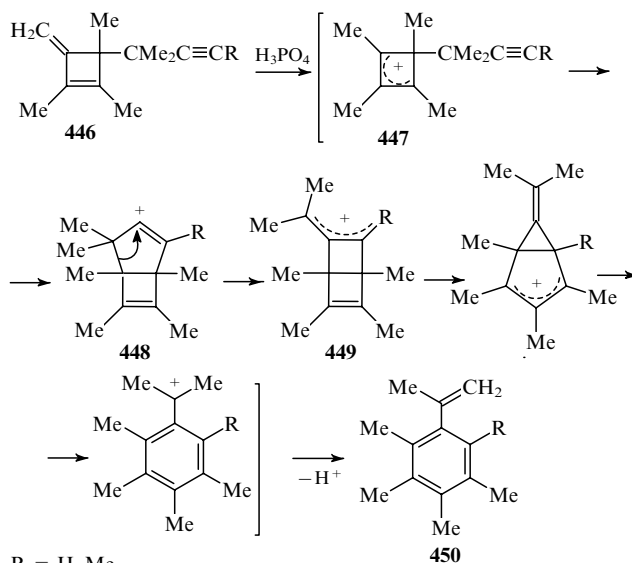
The processes of cyclisation of alkynyl carbocations **197** ($n = 2$) with two methylene units between the triple bond and the carbenium centre are described in detail in Section V.1. It is noteworthy that upon the solvolysis of pent-4-ynyl triflates $R-C\equiv C-(CH_2)_2CH_2OTf$, no cyclic products have been detected.²⁶ This is due to the extremely high strain in the five-membered cyclic vinylic (*i.e.* cyclopent-1-enyl) cations (see structures **K**, Fig. 1, and **202**). Meanwhile, the cyclobut-1-enyl cations **429** and **435** are quite stable owing to delocalisation of the positive charge over three carbon atoms across the ring.^{27, 216} Therefore, the cation **441** is, in essence, a bridged non-classical ion in which the C(3) atom is equidistant from the ends of the double bond.



The cyclopent-1-enyl cations **202** can arise during this process if the cationic intermediates are sufficiently stabilised by appropriate substituents. Thus protonation of 1,2,4-trimethyl-3-methylene-4-(prop-2-ynyl)cyclobut-1-ene **442** affords bicyclic ketone **445**. The reaction scheme includes the formation of cyclobutenyl-allyl cation **443**, which cyclises to bicyclic vinylic cation **444**.²¹⁷ The structure of the cation **443** was confirmed by its ^1H NMR spectrum (in HSO_3F-SO_2FCl , $-120^\circ C$).



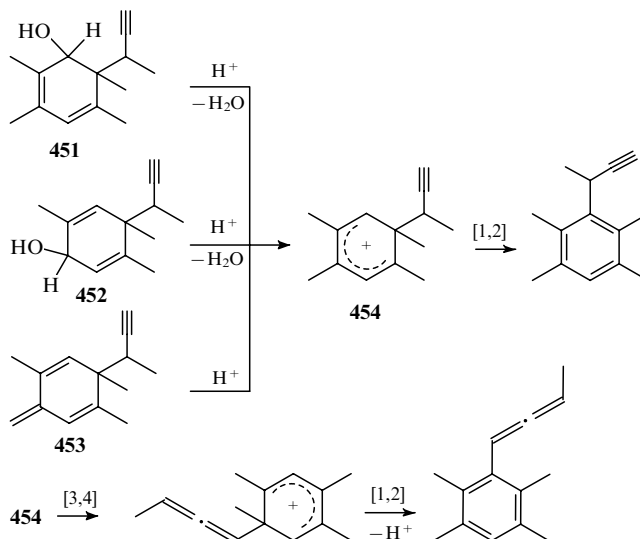
A variation of the degree of substitution in the substrate sharply changes the reaction route. Under the same conditions, cyclobutenes **446** substituted in the side chain afford polymethylated styrenes **450**, presumably according to the following scheme:²¹⁸



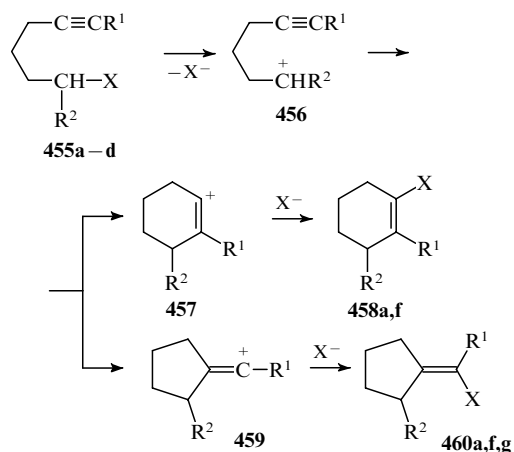
$R = H, Me$.

The spectral characteristics of the cationic intermediates formed in this process have been described in detail.²¹⁹ It is clear that the cations **443** and **447** correspond to structure **B**, the cations **444** and **448**, to structures **L** and **M** and the ion **449**, to allylic cation **Q** (see Fig. 1). Two other theoretically possible cation structures with participation of a $C\equiv C$ triple bond are also formed during this transformation.

Protonation of propynyl-substituted cyclohexadienols **451** and **452** and methylenecyclohexadienes **453** results in the formation of cations **454**. The subsequent [1,2]-migration or two successive migrations of the propynyl fragment give rise to substituted benzenes.²²⁰ Evidently, these rearrangements are energetically favourable because they lead to ring aromatisation.



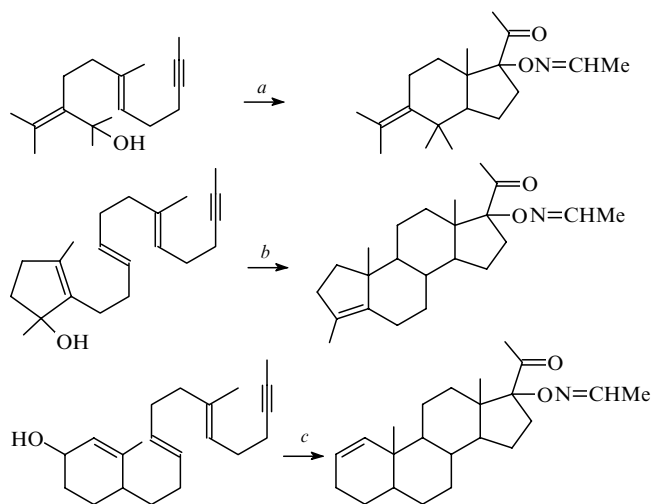
In alkynyl carbocations **456** in which the carbenium centre and the acetylenic fragment are separated by three carbon atoms, due to the close arrangement of groups in space, conditions are created for the formation of cations **457** and **459**. The predominance of one of these ions is determined by their relative stability, which depends on the substituents present in the initial acetylene derivative.



$R^1 = R^2 = H$, $X = \text{OTf}$ (a); $R^1 = \text{Me}$, $R^2 = H$, $X = \text{OTf}$ (b);
 $R^1 = \text{Ph}$, $R^2 = H$, $X = \text{OTs}$ (c); $R^1 = H$, $R^2 = \text{Me}$, $X = \text{OTs}$ (d);
 $R^1 = R^2 = \text{Me}$, $X = \text{OTs}$ (e).

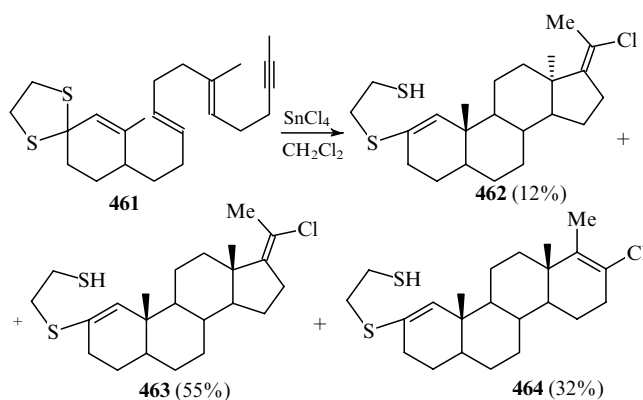
Thus solvolysis of terminal hex-5-ynyl triflate **455a** in trifluoroethanol results in the formation of an open-chain ether ($X = \text{OCH}_2\text{CF}_3$, 58%) and cyclohexene derivatives **458a** (12%) and **458f** ($X = \text{OCH}_2\text{CF}_3$, 24%).²² Conversely, the methyl homologue **455b** is converted by approximately 85% into cyclopentane derivatives **460a** (67%) and **460f** (17%). The introduction of a terminal phenyl group (compound **455c**) stabilises the exocyclic vinylic cation **459** to even a greater extent; therefore, the transformation of **455c** gives almost exclusively methylenecyclopentane derivatives **460g** ($X = \text{OAc}$). The secondary tosylates **455d**, e behave in a similar way.²²

The alkynylcarbenium (**456**) and vinylic (**457**, **459**) cations can arise as intermediates in cascade cyclisations used in elegant syntheses of steroids. Within the framework of a general approach to the preparation of testosterone, biomimetic syntheses of some of its precursors have been reported.^{221–223}



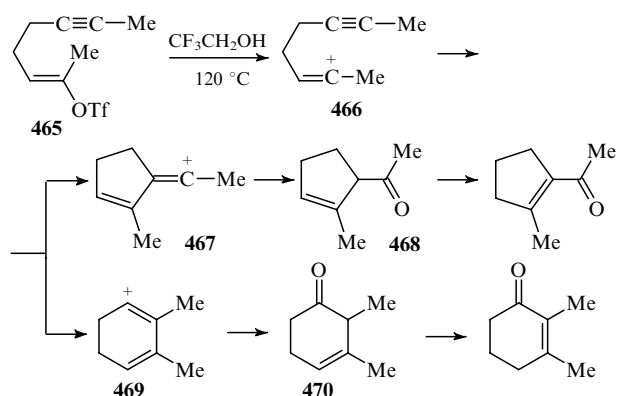
(a) CF_3COOH , EtNO_2 , -78°C , 80%; (b) CF_3COOH , Me_3N , EtNO_2 , -25°C , 30%; (c) Cl_3CCOOH , Me_2CHNO_2 , 0°C , 45%–65%

The treatment of thioketal **461** with SnCl_4 has given a mixture of cyclisation products **462**–**464** in 12%, 55% and 32% yields, respectively.²²⁴



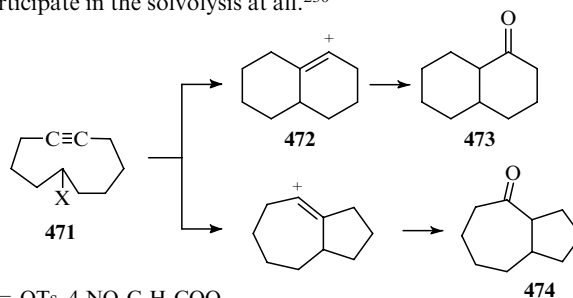
The synthetic potential of an approach to the synthesis of steroids, which, in principle, imitates the transformation of squalene into polycyclic products occurring in living organisms, has been discussed.^{221–225} It was noted that the propynyl group plays a special role, since it makes possible the formation of both five- and six-membered rings *via* two vinyl cationic intermediates. Using this scheme, linear compounds can be converted in one stage into tetracyclic systems with seven chiral centres, this reaction being highly stereoselective (see also relevant reviews^{226, 227}).

Cyclisations of alkynylvinyl cations **466** formed upon solvolysis of vinyl triflates **465** afford vinylic cations **467** and **469**, which are then converted into cyclopentenyl ketones **468** and cyclohexenones **470**, respectively. These ketones are unstable under the solvolysis conditions and rearrange into the corresponding α,β -unsaturated ketones.^{228, 229}

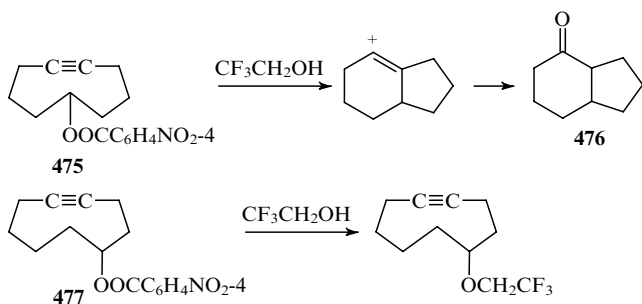


The dependence of the reaction route on the mutual orientation of the carbenium centre and the acetylenic fragment can be clearly followed for the solvolysis of cycloalkynyl esters. Thus cyclodec-5-ynyl derivatives **471** are mostly converted into decalone **473** *via* cation **472**. Only traces of bicyclo[5.3.0]decan-2-one **474** were found in reaction mixtures.^{22, 26, 230, 231}

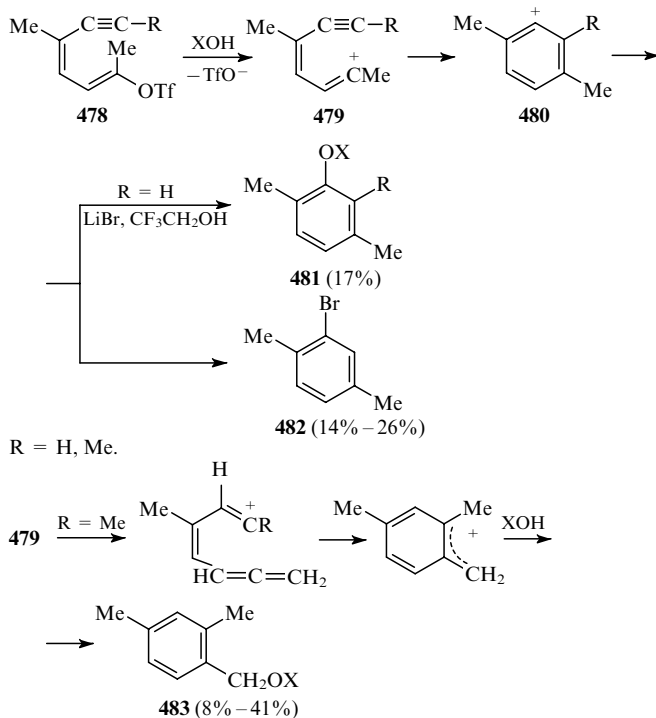
Solvolysis of 4-nitrobenzoate **475** containing a nine-membered ring yields almost quantitatively bicyclic ketone **476**,^{22, 230} whereas in the case of isomeric ester **477**, the triple bond does not participate in the solvolysis at all.²³⁰



$X = \text{OTs}$, 4- $\text{NO}_2\text{C}_6\text{H}_4\text{COO}$.

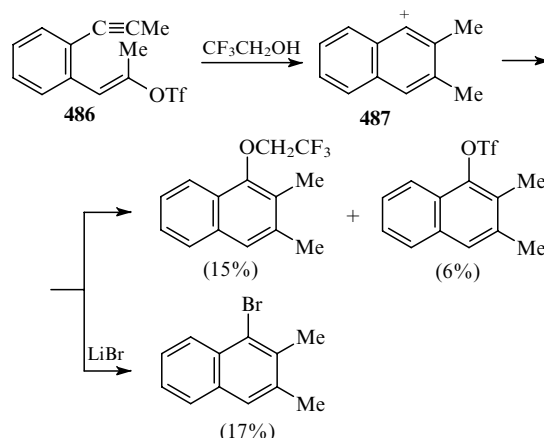
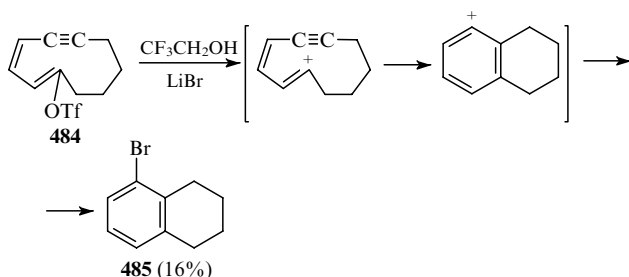


Further progress of the studies described above resulted in the development of a new approach to the generation of fairly unstable phenyl cations of the type **6**.^{27, 229, 232} Suffice it to say that these cations are 20–25 kcal mol⁻¹ less stable than the propen-2-yl cation $\text{H}_2\text{C}=\text{C}^+\text{CH}_3$,²⁹ and it was not until 1985 that they were obtained for the first time by solvolysis.²⁸ The intermediate formation of the phenyl cations **480** was confirmed by the detection of functional derivatives of benzene **481** and **482** among the products of solvolysis of conjugated diene triflates **478**. Benzyl ethers **483** result from transprotonation of the cationic intermediate **479**.



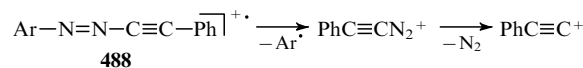
X = H, Et, CF_3CH_2 .

Solvolysis of cyclic diene vinyl triflate **484** in the presence of LiBr gives bromo-substituted tetrahydronaphthalene **485**.²³³ Naphthyl cations **487** have been generated in the same way from enol triflate **486**.^{27, 234}

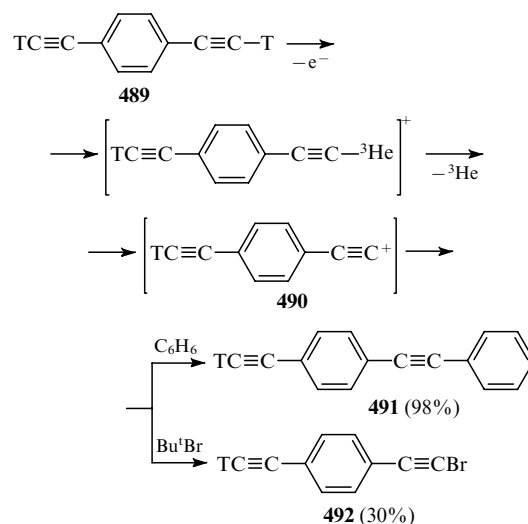


When the carbon–carbon triple bond is further removed from the carbenium centre, the cyclisation becomes virtually impossible.^{22, 26}

Another, barely studied, type of cations with a triple carbon–carbon bond, namely the alkynyl cations $\text{R}-\text{C}\equiv\text{C}^+$, should also be mentioned. These species are extremely unstable; their energy is 130 kcal mol⁻¹ higher than that of primary vinyl cations or phenyl cations described above.²³⁵ Phenylethynyl cations were detected for the first time in the mass spectra of arylazoethynylbenzenes **488**.²³⁶



Alkynyl cations can be generated in solution only by the nuclear-chemical method²³⁵ (see also Ref. 237). Reactions of 1,4-diethynylbenzene **489** containing tritium atoms with benzene and brominated hydrocarbons were studied. The β -decay of tritium yields a helium atom, which is the best leaving group.

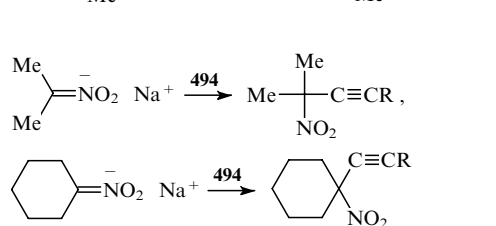
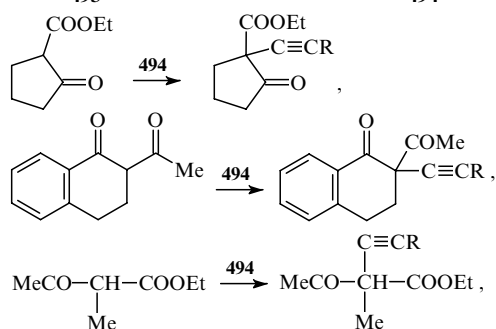
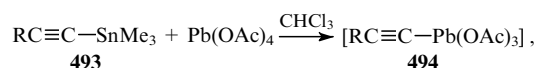


The intermediate formation of alkynyl cation **490** was proved by chromatographic isolation of the products of its reactions **491**, **492**.²³⁵

Recently, in order to find pathways to ethynyl cations, nitrosation of enamines, bis-silylated at the nitrogen atom, has been studied.²³⁸ In the multicomponent reaction mixtures formed upon these reactions, some products that could have arisen with participation of the ions in question were detected.

It has been proposed to use alkynyllead triacetates **494**, which are formed *in situ* on treatment of alkynyltrimethylstannanes **493** with lead tetraacetate, as synthetic equivalents of alkynyl cations; these compounds permit easy introduction of an alkynyl group

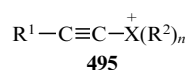
into 1,3-dicarbonyl compounds and nitronates. The reaction products are formed in 47%–87% yields.²³⁹



R = H, Me(CH₂)₅, Ph, Me₃Si.

VII. Hetero-analogues of alkynyl carbocations

The principle of activation of a carbon–carbon triple bond by means of a positively charged substituent can be realised in compounds containing an acetylene fragment and a heteroatomic cation. Unlike alkynylcarbenium ions, onium cations **495** containing an ethynyl group cannot have allenyl structure like **10**.

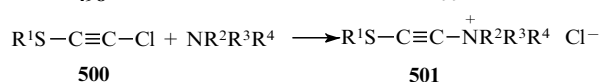
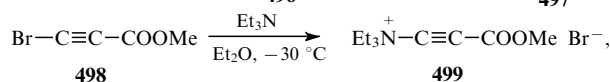
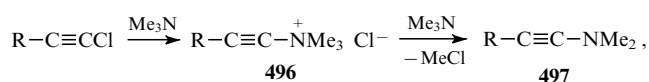


X = N, P, Hal.

An obvious merit of these systems is the possibility of removing the activating heterocationic fragment from the molecule after a transformation of the acetylene group.³⁵

1. Alkynylammonium and alkynyldiazonium ions

Alkynylammonium ions **496** are usually regarded as intermediates in the formation of ynamines **497** from alkynyl halides.³⁶ As a rule, these species are unstable, although in some cases, they have been isolated as salts and characterised. Thus the ethynylammonium salt **499** was prepared from methyl bromopropiolate **498**. The IR spectrum of this salt exhibits an absorption band typical of acetylene derivatives at about 2180 cm⁻¹.²⁴⁰ Organyl chloroethynyl sulfides **500** react with tertiary amines to give quite stable salts **501**, which are soluble in water and alcohols. The acetylene absorption band in the IR spectra of these salts (2205 cm⁻¹) is shifted to shorter wavelengths with respect to this band in the spectra of the initial sulfides (2170 cm⁻¹).²⁴¹

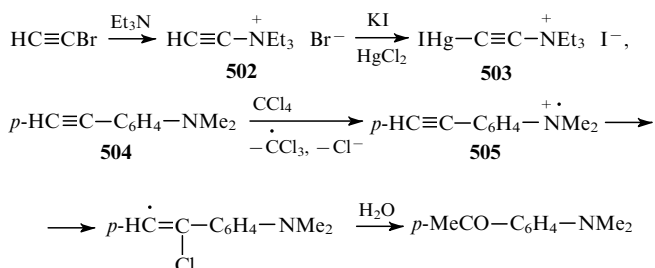


R¹ = Et, Bu; R², R³, R⁴ = Et, (CH₂)₅.

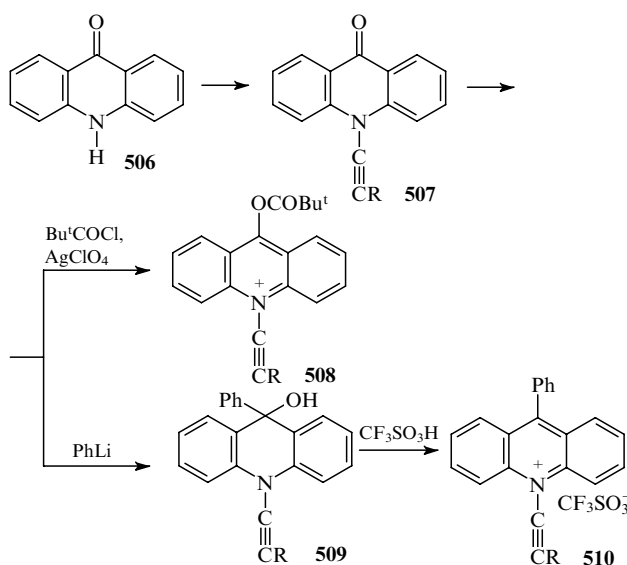
During studies on nucleophilic substitution at an acetylenic carbon atom, fairly unstable ethynyltriethylammonium bromide

502 has been isolated. Upon mixing with an alkaline solution of KI and HgCl₂, this salt was converted into stable mercurioethynylammonium iodide **503**.^{242, 243}

An unusual type of hydration of a C≡C triple bond without a catalyst has been performed²⁴⁴ by irradiation of 4-ethynyl-*N,N*-dimethylaniline **504**. This reaction was assumed²⁴⁴ to occur *via* the formation of radical cation **505**.



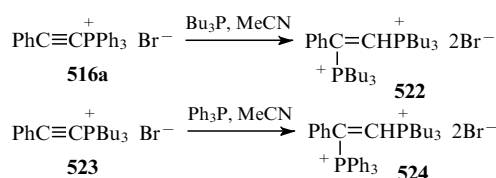
Published data on alkynylammonium cations are scarce. A comprehensive review of the available information can be found in a paper by Katrizky²⁴⁵ devoted to the synthesis and spectroscopic characteristics of heterocyclic ynammonium salts. Since these salts cannot be prepared from highly nucleophilic 4-dimethylaminopyridine, acridone **506** was used as the heterocyclic substrate. This permitted the *N*-alkylation and quaternisation stages to be conducted separately. *N*-Alkynylacridinium salts **508**, **510** were prepared *via* two routes, namely, by *O*-acylation of *N*-alkynylacridones **507** and by dehydroxylation of pseudo-bases **509** with trifluoromethanesulfonic acid.²⁴⁵



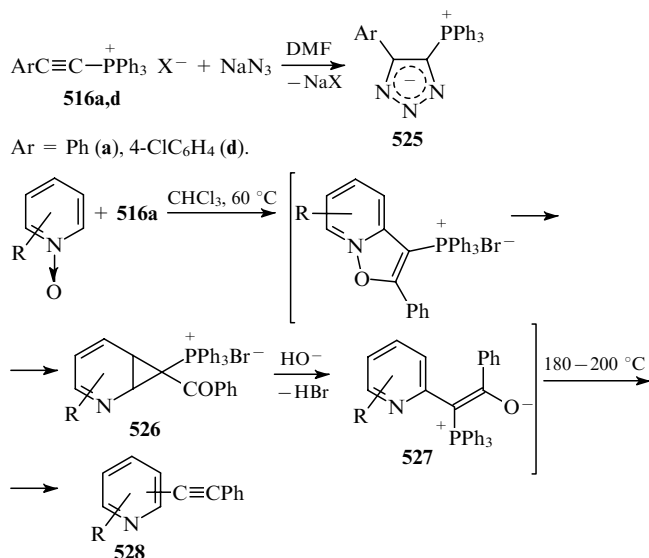
R = Me, Ph, 2,4,6-Me₃C₆H₂.

In the ¹³C NMR spectra of the salts **510**, the signal of the triple-bond carbon atom, more distant from the heterocycle, is shifted downfield (on the average, by 12–14 ppm) in relation to its position in the spectra of the precursors **507**, **509**. On treatment with nucleophiles, the salts **510** are converted into stable ynamines of the type **509**, the attack of the nucleophile being directed at the 9-position of the acridinium ring.²⁴⁵

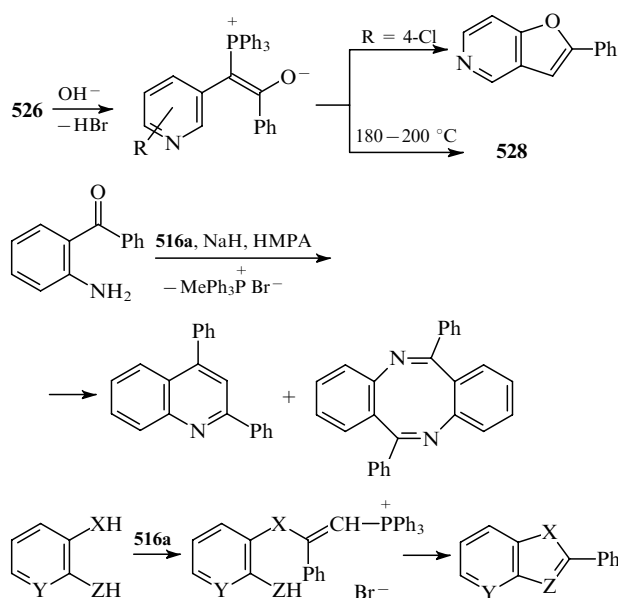
After several unsuccessful attempts to prepare alkynyldiazonium salts, Hanack *et al.*²⁴⁶ described the synthesis of phenylethynyldiazonium salt **512** from α -bromo-1-phenylacetyl chloride **511**. The salt **512** obtained at –30 °C was made to react with nucleophiles without isolation. It was found that nucleophiles first add to the C≡C triple bond. The alkenyldiazonium salts **513** thus formed eliminate a nitrogen molecule. The initial salt **512** itself cannot abstract a nitrogen molecule, because the energy of the alkynyl cation that would result from this process is extremely high (see Section VI).



A method for the synthesis of a new family of heterocyclic ylides **525** based on reactions of alkynylphosphonium salts with sodium azide has been developed.²⁵⁰ Phenylethynylpyridines **528** have been obtained by the reaction of the salt **516a** with pyridine *N*-oxides.²⁵⁵



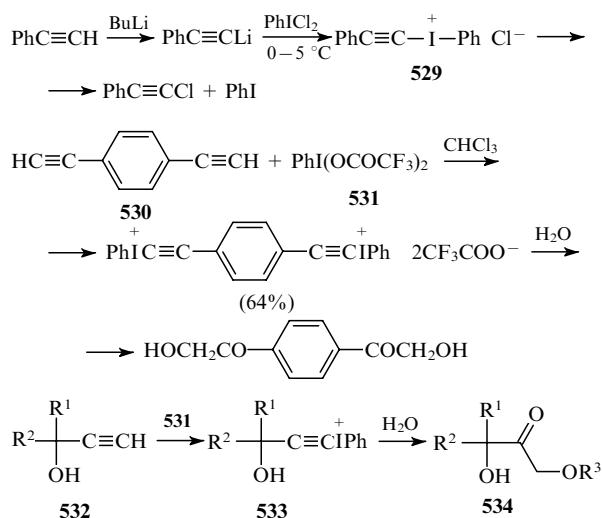
The use of alkynylphosphonium salts in the synthesis of heterocycles comprising the addition of nucleophiles to a triple C≡C bond and subsequent cyclisation with the removal of the activating triphenylphosphine fragment has been demonstrated³⁵ in relation to reactions of the salt **516a**.



Numerous syntheses based on propynylphosphonium salts have been described in a number of studies^{256–258} and have been surveyed in a review.²⁵⁹

3. Alkynyliodonium ions

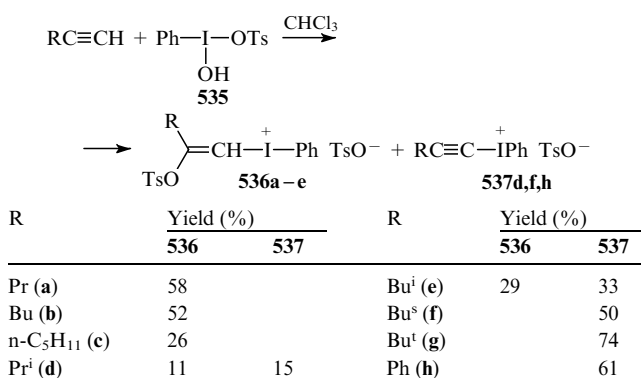
Alkynyl derivatives of tricoordinated iodine have been known since 1965. The interest in the chemistry of tricoordinated iodine, which has sharply increased in recent years,²⁶⁰ has stimulated studies of its ethynyl derivatives. Phenyl(phenylethynyl)iodonium chloride **529** was synthesised in a yield of up to 20% by the reaction of lithium phenylacetylide with λ³-iodanylbenzene dichloride. The IR spectrum of this salt²⁶¹ contains a characteristic absorption band in the region of 2170 cm^{−1}. On storage for several hours at room temperature, the salt **529** spontaneously decomposes to give iodobenzene and chloro(phenyl)acetylene. Phenyliodanyl bis(trifluoroacetate) **531**, capable of oxidising terminal triple bonds in compounds **530**, proved to be a more efficient reagent.²⁶²



R³ = H, CF₃CO.

The reagent **531** was used for efficient transformation of alkynols and arylalkynols **532** into 1,3-dihydroxy 2-carbonyl derivatives **534** via alkynyliodonium intermediates **533**.²⁶³

The first method, really suitable for the preparative-scale synthesis of alkynyliodonium salts, is based on the reaction of alkynes with hydroxy(tosyloxy)iodanylbenzene **535**. Short-term refluxing of the reagents in CHCl₃ gave alkenyl (**536a–e**) and alkynyl (**537d,f–h**) iodonium salts.^{264, 265}



Alkylethynyliodonium salts **538** can be prepared only in those cases where the alkyl group in the alkyne (Prⁱ, Buⁱ) creates steric hindrance hampering nucleophilic attack on the triple bond.²⁶⁶ This strategy was also employed to synthesise 4-alkoxyphenyl-ethynyliodonium salts **539** containing long alkyl chains.²⁶⁷

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The Kabachnik – Fields reaction: synthetic potential and the problem of the mechanism[†]

R A Cherkasov, V I Galkin

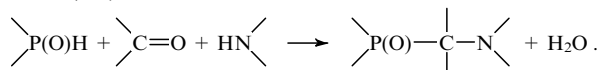
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Abstract. The published data of the last decade concerning the mechanism of the Kabachnik – Fields reaction and its significance for the chemistry of organophosphorus compounds as a method for the synthesis of α -amino phosphonates and their numerous functionally substituted derivatives and analogues, such as phosphinates and phosphine oxides, are generalised and systematised. The review discusses the classical version of the Kabachnik – Fields reaction, its modifications with the use of phosphorus chlorides, neutral esters and inorganic phosphorus acids, as well as chemical processes simulating separate steps of the reaction, *viz.*, hydrophosphorylation of imines and amination of α -hydroxy phosphonates. Data on the practical application of α -amino phosphonates are presented. The bibliography includes 253 references.

I. Introduction

The Kabachnik – Fields reaction corresponds to the classical methods for the synthesis of organophosphorus compounds. It was discovered in 1952 independently by Kabachnik and Medved'¹ and Fields.² The reaction occurs in a three-component system consisting of a hydrophosphoryl compound, a carbonyl compound (aldehyde or ketone), and an amine and results in α -aminoalkylphosphonates commonly named as α -amino phosphonates (AP).



During the subsequent two or three decades, no intense studies in this field were carried out. However, after the discovery in the late 1960's that AP possess practically useful properties, mainly biological activity (see Ref. 3 and references cited therein), and isolation of phosphorus-containing amino acids from natural sources,⁴ the areas of chemistry, biology and medicine related to the synthesis and study of the properties of AP show a real renaissance. As a confirmation it can be noted that more than 5000 studies on this topic had been published by 1993.⁵ By now, this number has increased greatly. The prospects of using AP in

various areas of science and engineering stimulated the development of new ways for the synthesis of AP, including polyfunctional ones. However, in our opinion, none of numerous approaches to the synthesis of AP is as general as the Kabachnik – Fields reaction.

However, no generally accepted viewpoint on the mechanism of this reaction has been developed until recently. The data concerning this matter were isolated and often contradictory. Only in recent years have kinetic and other special studies aimed at a deep study of the Kabachnik – Fields reaction and the establishment of its mechanism been carried out. As a result, the contradictions were resolved to a considerable extent; however, the reviews generalising and analysing these studies are lacking.

On the contrary, the synthetic aspects of the Kabachnik – Fields reaction have been developed rather widely and discussed in monographs^{6–12} and reviews.^{13–19} However, new and important results that deserve thorough consideration have also been obtained in this area during the last five years.

The purpose of the present review is to systematise, analyse and generalise the data published basically in the 1990's and related to the study of the mechanism of the Kabachnik – Fields reaction and its use for the synthesis of AP. Earlier publications will be cited only to the extent required for the understanding of the essence of the problems under discussion. In order to rank the Kabachnik – Fields reaction, estimate its significance among numerous other methods for the synthesis of AP and reveal its synthetic potential, we considered it necessary to present data on the basic methods for the synthesis of AP. Due to the abundance of data in this field, the topic is inevitably covered superficially, and we confine ourselves to the analysis of only the latest publications. Whenever necessary we have to refer the reader to the literature cited in these papers.

Chemical processes that simulate separate steps of this reaction and its versions and involve other derivatives of three-coordinate phosphorus, such as neutral esters, chlorides, inorganic acids and their silyl derivatives instead of hydrophosphoryl compounds, are discussed in more detail. We believe that the reactions of the silyl derivatives with carbonyl compounds and amines or amides in a three-component system may also be rightfully attributed to reactions of the Kabachnik – Fields reaction type. As will be shown below, reactions of P(III) derivatives often produce hydrophosphoryl compounds that react exactly in the same way as those in the 'classical' system.

R A Cherkasov and V I Galkin Kazan State University,
ul. Kremlevskaya 18, 420008 Kazan, Russian Federation.
Fax (7-843) 238 09 94. Tel. (7-843) 231 51 86.
E-mail: rafael.cherkasov@ksu.ru (R A Cherkasov)

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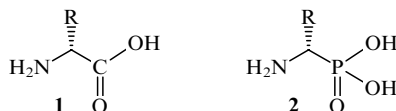
[†] The review is devoted to the memory of Academician M I Kabachnik (1908–1997).

Special attention is given to the hydrophosphorylation of imines. On the one hand, this represents one of the steps of the Kabachnik–Fields reaction and, on the other hand, a version of the Pudovik reaction, which was described in 1952²⁰ almost simultaneously with the pioneer research by Kabachnik and Medved' (and published in the same volume of *Doklady Chemistry*). In addition, we found it necessary to present brief information on the main areas where AP are used.

II. Application areas and principal methods for the synthesis of α -amino phosphonates

1. Application areas of α -amino phosphonates

It is believed³ that aminomethylphosphonic acid was first mentioned in the literature in 1943.²¹ Being structural analogues of α -aminocarboxylic acids **1**, α -aminoalkylphosphonic acids **2** (APA) possess diverse biological activities. For this reason, they attract steady attention of chemists, biologists, pharmacologists, physicians and other specialists who study biologically active compounds.^{3, 11, 16, 18, 22, 23} Organophosphorus analogues of almost all proteinogenic amino acids have been synthesised. APA isostructural to tyrosine have been isolated from natural sources (see Ref. 24 and references cited therein).



APA resulting from replacement of the carboxy groups in 'normal' amino acids by the phosphonate groups inhibit the enzymes or receptors to which natural amino acids normally bind. Therefore, APA are their antagonists (see Refs 3, 25 and references cited therein). The inhibitory action of APA predetermines their physiological activity as antibacterials, neuroactive agents, antibiotics, carcinostatic, cytotoxic and other compounds of pharmacological importance.³

Much attention is given to the use of AP (the acids themselves, *i.e.*, APA, their mono- and diesters and some other derivatives) in peptide synthesis.^{3, 26–31} Phosphonopeptides represent models of the tetrahedral transition states (activated complexes) in the hydrolysis of natural peptides.^{32–34} In addition, they exhibit diverse and rather high physiological activities, such as pesticide,³⁵ fungicide³⁶ and growth-controlling³⁷ ones. Phosphonopeptides are inhibitors of thrombin³⁸ and pepsin³⁹ and are used as haptens of antigens affecting the production of antibodies.⁴⁰ They also manifest other kinds of physiological activities.³

Numerous studies have been devoted to the synthesis and study of APA possessing herbicidal properties. Of these, *N*-(phosphonomethyl)glycine, $^{-}\text{HO}_3\text{PCH}_2\text{N}^+\text{H}_2\text{CH}_2\text{COOH}$ is known under the trade name glyphosate and used most widely (see Ref. 41 and references cited therein). Its numerous analogues have also been obtained.⁴²

A series of studies^{43–45} have dealt with the development of methods for the synthesis of α -aminofluorenylphosphonates, -phosphinates and -phosphine oxides. As structural analogues of a synthetic phytohormone morfactin, they represent an interesting class of plant growth regulators and herbicides. Wide prospects of practical application of this type of AP stimulated in-depth spectroscopic studies of their structures.⁴⁵ Attempts at establishment of quantitative structure–biological activity relationships were also made.⁴⁶ It should be noted that the relation between the structure of a number of neutral AP and their antimicrobial⁴⁷ and fungicide⁴⁸ activities is well described by correlation equations.

Although the biological activity is certainly a very valuable and the most attractive property of AP, this by no means confines the prospects of their practical use. APA themselves, as well as their derivatives and analogues, correspond to polyfunctional organophosphorus compounds. They can form complexes, in which they act as mono-, bi- and polydentate ligands.⁴⁹ The

electron-donating atoms of nitrogen and phosphoryl oxygen serve as coordination centres, the acid groups of APA form the corresponding salts, and the suitable functional groups specially introduced to nitrogen and phosphorus atoms and α -carbon atoms can provide additional bonding to metal ions. The same properties are used as a stereocontrolling factor in enantioselective synthesis of AP (see below).

Kabachnik was one of the first to study the complexing properties of AP,^{50–52} using linear and cyclic (cyclopentand) AP as the complexones. Recently, the first X-ray characteristics of an AP metalcomplex, *viz.*, a coordination compound of Cu(II) with *O*-ethyl hydrogen α -(2-pyridyl)-*N*-isopropylaminomethylphosphonate, have been obtained.⁵³ Complexes of chromium with fluorenylphosphonates have been synthesised.⁵⁴ In recent years, complexes of AP with lanthanides and actinides have been proposed for diagnostics with the use of the NMR technique.^{55, 56}

Extraction processes involving AP have been studied. It was shown that APA can be used in hydrometallurgy.⁵⁷ Processes for gold extraction with neutral AP and efficient separation of Au(III) from the commonly accompanying ions, Fe(III) and Cu(II),⁵⁸ as well as extraction of Pd(II) in strongly acidic media have been reported.⁵⁹ The acid–base properties of *O*,*O*-dialkyl *N*,*N*-dialkyl- α -aminoalkylphosphonates have been studied. As expected, they appeared to be weaker bases than amino acids. The $\text{p}K_{\text{BH}}$ values (in aqueous propan-2-ol) are 9.2–9.7, whereas $\text{p}K_{\text{BH}}$ of histamine is ~ 5 . Substituents at the α -carbon atom and nitrogen do not affect essentially the AP basicity.

Due to the ability of AP to complexation, they can serve as carriers for α -hydroxy and α -amino acids through lipophilic liquid membranes,⁶⁰ which is a new promising direction for their utilisation. *N*-Bornyl-AP,⁶¹ (*d*)-*N*- α -methylbenzyl-AP and other linear and cyclic AP,^{62, 63} as well as calix[4]arenes with α -amino phosphonate fragments in the bottom and top rings were chosen for molecular recognition of substrates.⁶⁴ Generally, the latter derivatives appeared to be more efficient transport agents than their acyclic analogues. The flux of α -hydroxy acids is most strongly affected by the nature of substituents at the α -carbon atom in AP. It is remarkable that the AP studied can also be used for the separation of D- and L-forms of α -hydroxy and α -amino acids.⁶⁰

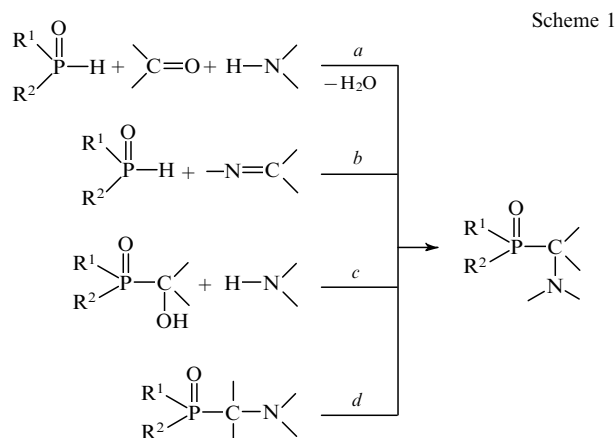
The results of these studies are in good agreement with the data obtained in a study of the thermochemistry of AP.^{65–67} Specific features of dissolution of neutral AP in solvents of various nature (hexane, CCl_4 , CHCl_3) characterise these compounds as distinct proton acceptors. However, with respect to sufficiently strong bases, for example, pyridine, AP behave as proton donors. Calculations of the enthalpy of solvation showed the predominant effect of steric factors of the substituents on the liability to biphilic reactions of this kind.⁶⁸

Finally, it is worthy of mentioning that analytical methods for the determination of enzyme inhibitors, including APA esters, have been developed.⁶⁹

2. Principal methods for the synthesis of α -amino phosphonates

No simple and versatile methods for the synthesis of AP existed before the discovery of the Kabachnik–Fields reaction. Single attempts at the preparation of AP mentioned in the early studies^{1–3, 70, 71} did not satisfy the researchers because of multi-step syntheses and low efficiency. The credit for the intense progress in studies on the chemistry and biology of AP in the last decade should be given to the development of a series of highly efficient one-pot or two- or three-step methods for the synthesis of AP. The Kabachnik–Fields reaction occupies the leading position among these methods. It is now believed that the Kabachnik–Fields reaction and its constituting separate steps are the most convenient methods for the synthesis of AP, including homochiral ones (see Section IV).

The basic problem in the synthesis of AP is the formation of the aminoalkylphosphonate fragment, $\text{P}(\text{O})\text{—C—N}$. Therefore,

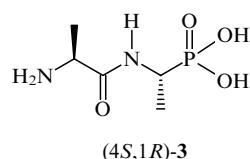


$R^1, R^2 = \text{Alk, Ar, AlkO, ArO, H, OH, OSiR}_3$;

(a–d) — see the text.

the synthetic routes shown in Scheme 1 are of prime interest. However, prior to the discussion of the synthetic versions presented in the scheme, it should be mentioned that the stereochemical aspects of these reactions are very important.

As in case of α -amino acids, the biological activity of AP is largely determined by the absolute configuration of the stereogenic α -carbon atom. Of the four possible diastereomers of the antibiotic alaphospholine **3**, the (*S,R*)-diastereomer manifests the greatest activity against pathogenic microorganisms. The three other stereoisomers are much inferior to this compound in activity (see Ref. 72 and references cited therein).



The first synthesis of an optically active APA was carried out in 1972.⁷³ The most comprehensive information on the methods for the stereoselective synthesis of AP is presented in the review by Kukhar' *et al.*¹⁸ containing the data published before the middle of 1992. Since then, a large number of publications describing new ways for the enantioselective synthesis of AP have appeared; the main attention in the present review is given to these methods.

The strategy for the synthesis of AP that envisages the formation of the amino phosphonate framework, $\text{P(O)}-\text{C}-\text{N}$, is based mainly on the use of the Kabachnik–Fields reaction in a three-component system 'phosphite–carbonyl compound–amine' and its various versions [Scheme 1, pathway (a)]. As will be shown below, the Pudovik reaction, *i.e.*, catalysed or non-catalysed addition of hydrophosphoryl compounds to imines [pathway (b)], as well as nucleophilic amination of hydroxy phosphonates [pathway (c)], represent separate steps of the two- (or more)-step Kabachnik–Fields reaction. We shall consider these three most important methods for the synthesis of AP separately in Section III.

In the present section, we pay the main attention to the strategy designated as pathway (d) in Scheme 1 (C-, N-, P-

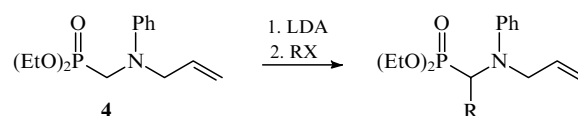
modification). Numerous methods for the synthesis of AP based on this approach assume that a preliminarily created combination of phosphoryl, α -carbon and amine fragments is used as the key synthon. The synthesis of the target AP, including peptides, homochiral APA, *etc.* is carried out by introduction of the desired functional groups to the α -carbon atom (C-modification), to the nitrogen atom (N-modification) and to the phosphorus atom (P-modification). It should be noted that this strategy is being developed intensely in recent years. Special attention has been paid to the stereocontrolled functionalisation of AP at all the reaction centres specified above. Data published before the middle of 1992 have been systematised in a review (Ref. 18). Here we present only the studies that have not been mentioned there and in subsequent publications.

a. C-Modification

It is known that the carbon atom bonded with the phosphoryl group, which has considerable electron-withdrawing properties, possesses a pronounced anionoid character. This circumstance is widely used in organic and organometallic synthesis, for example, for functionalisation of the α -carbon centre or for olefination of carbonyl substrates by the Horner–Wittig–Emmons reaction.⁷⁴ Generation of carbanions from AP and their subsequent C-functionalisation is a popular approach for the synthesis of diverse polyfunctional AP by reactions of α -phosphoryl amino carbanions with appropriate electrophilic reagents. In these processes, the following starting compounds are used: APA or their esters containing the P(O)CH(R)N moiety with a terminal primary, secondary or tertiary amino group or imines incorporating the $\text{C}=\text{N}-\text{CH(R)P(O)}$ fragment. The latter are usually obtained by the reaction of AP having a primary amino group with aldehydes or ketones.⁷⁵ Other procedures, *e.g.*, the reaction of α -oxo phosphonates with primary amines⁷⁶ or the reaction of dialkyl phosphites with hexahydrotriazine, have also been reported.⁷⁷

C-Alkylation of acyclic AP [Scheme 2, pathway (a)] is used rather seldom, probably because of their rather low CH-acidity. The α -phosphoryl carbanion is probably insufficiently stable due to the presence of an electron-withdrawing phosphoryl group and an electron-donating amino group.

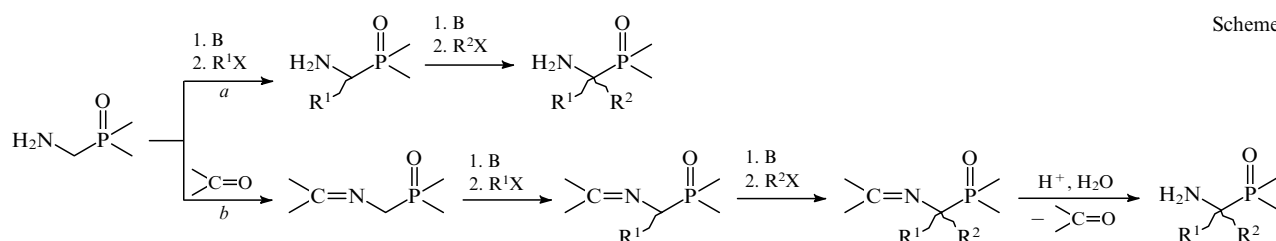
Nevertheless, easy introduction of a methyl, phenylthio, and other heteroatomic groups to the α -carbon atom of AP **4** (THF, -70°C) by treating phosphoryl carbanions with appropriate halogen-containing reagents of the RX type has been described recently.⁷⁸



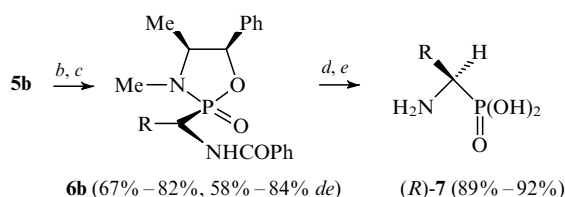
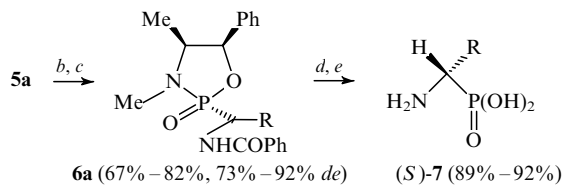
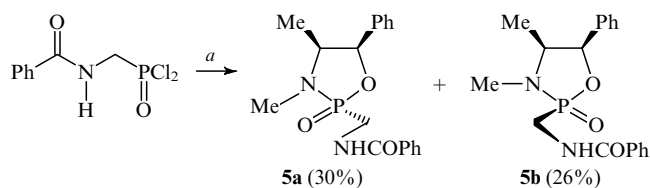
$\text{LDA} = \text{LiNPr}_2$;

$\text{R} = \text{SiMe}_3$ (79%), SnBu_3 (52%), SPh (60%), Me (70%).

However, in the series of heterophosphacyclanes containing endo- and exocyclic nitrogen atoms, the method for the synthesis of AP discussed above [Scheme 2, pathway (a)] is much more popular. A scheme for the synthesis of APA by alkylation of a five-membered cyclic ephedrine derivative **5** can be given as an example.⁷⁹

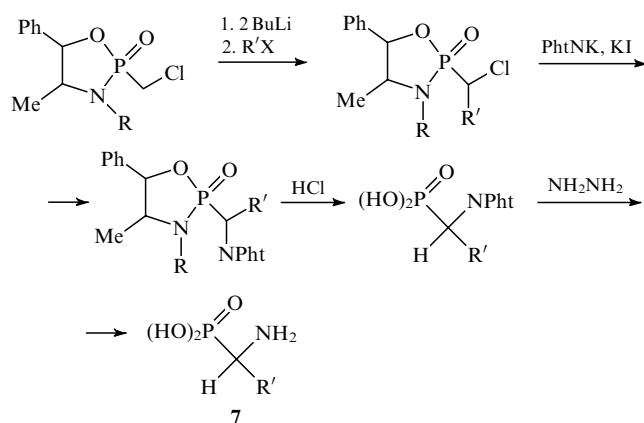


Scheme 2



(a) Ephedrine, NEt_3 , THF; (b) BuLi , THF, -70°C ; (c) RX , -70°C ;
(d) conc. HCl , 110°C , 20 h; (e) Me –; *de* is diastereomeric excess.

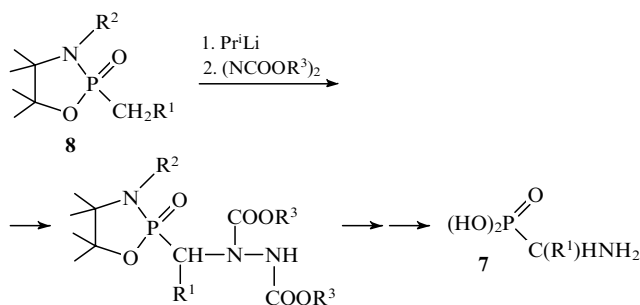
Homochiral 2-benzoylaminoethyl-3,4-dimethyl-2-oxo-5-phenyl-1,3,2-oxazaphosphorinanes **5a** and **5b** ('chiral phosphorus'), epimeric at position 2, were separated by column chromatography and subjected to C-alkylation under mild conditions to give enantiomers **6a** and **6b**. Subsequent hydrolysis of compounds **6a** and **6b** resulted in the APA (*S*)-7 and (*R*)-7, respectively. Later,⁸⁰ this strategy was used for the synthesis of APA 7 from enantiomeric oxazaphosphorinanes with the exocyclic chloromethyl group.



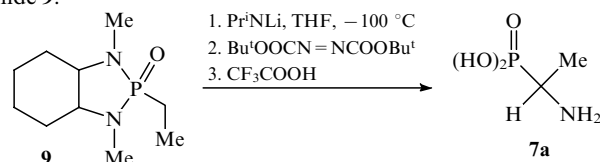
Pht is phthaloyl.

In recent years, functionalisation of methylphosphonates has been carried out according to the electrophilic amination scheme (see Ref. 72 and references cited therein). Strictly speaking, these processes do not conform to the strategy of C-alkylation of AP [Scheme 2, pathway (a)], as the amino group is not 'yet' present at the α -carbon atom of the starting phosphonates. However, since we are speaking of reactions of α -phosphoryl carbanions, we considered it appropriate to mention here this method for the synthesis of AP.

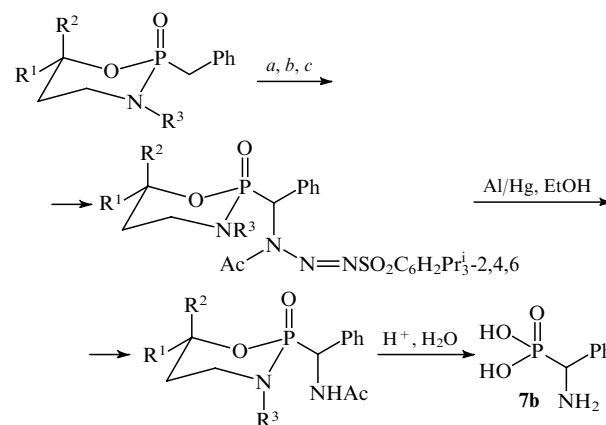
The reaction of oxazaphosphorinanes **8** with Pr^iLi and then with azodicarboxylate results in products of the addition to the $\text{N}=\text{N}$ bond. Their subsequent hydrolysis gives the APA 7.⁸¹



The same reaction was carried out with bicyclic phosphonamide **9**.⁸²



In the reaction with oxazaphosphorinane, aryl azide serves as the aminating reagent.⁸³



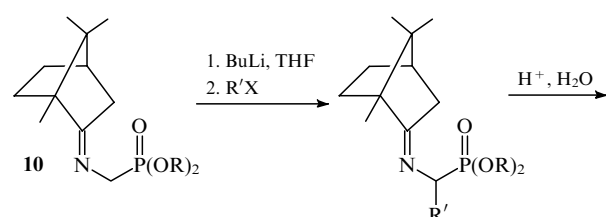
(a) BuLi ; (b) 2,4,6- $\text{Pr}_i^3\text{C}_6\text{H}_2\text{SO}_2\text{N}_3$; (c) Ac_2O .

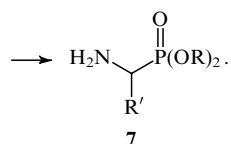
In all cases, high diastereoselectivity of amination and high chemical yield of APA 7 were achieved (see also Ref. 18).

Successful use of carbanions stabilised by 1,3,2-diheterophosphacyclic substituents in the C-modification is, probably, largely caused by the rather high CH-acidity and, accordingly, high stability of these systems. It is known that incorporation of a four-coordinate phosphorus atom in a ring increases its electron-withdrawing properties.⁷⁴ This is particularly pronounced in the chemical behaviour of 1,3,2-diheterophosphorinanes.⁸⁴

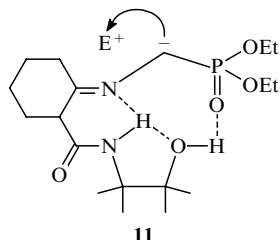
A similar effect is achieved in the case of iminomethylphosphonates [Scheme 2, pathway (b)]. Charge delocalisation by two acceptor substituents, *viz.*, the imino and phosphoryl groups, lowers the energy of a carbanion.

Enantioselective syntheses of AP by C-modification, *i.e.*, alkylation of an α -imino carbanion with alkyl halides, carbonyl compounds and unsaturated electrophilic reagents, have been performed successfully with camphor derivatives **10** and a number of similar structures.

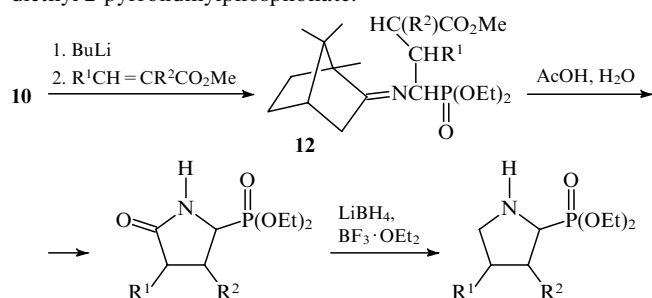




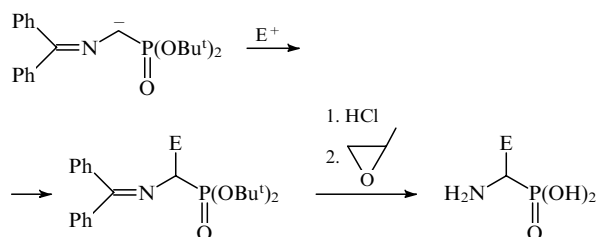
It was shown recently that high diastereomeric excess (*de*) in C-modification can be achieved due to the chelation effect⁸⁵ provided by the introduction of suitable functional groups capable of forming intramolecular hydrogen bonds, as, *e.g.*, in structure **11**.



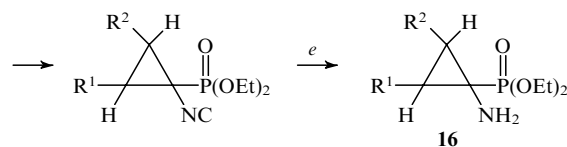
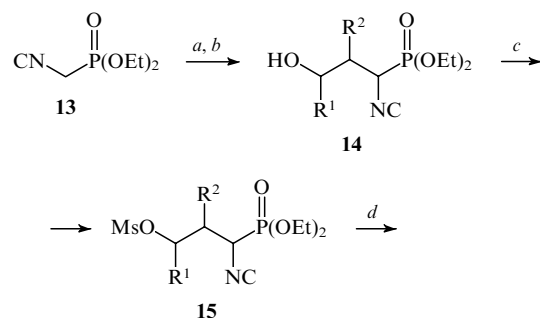
The carbanions generated from phosphorus-containing Schiff's bases **10** ($\text{R} = \text{Et}$) enter into the Michael reaction.⁸⁶ Adducts **12** undergo cyclisation in acidic medium to 5-oxo-2-pyrrolidinylphosphonate subsequent reduction of which results in diethyl 2-pyrrolidinylphosphonate.



Secondary processes occurring after the electrophilic step of C-modification of AP expand the synthetic potential of phosphorylated imines. More often, however, the alkylation product is subjected to acid hydrolysis in order to obtain APA.⁸⁷



It has to be noted that the carbonyl compounds from which imine synthons are obtained can be regenerated by acid hydrolysis of phosphorylimines.¹⁸ This strategy for the synthesis of AP has been expanded⁸⁸ for isocyanomethylphosphonate **13**.



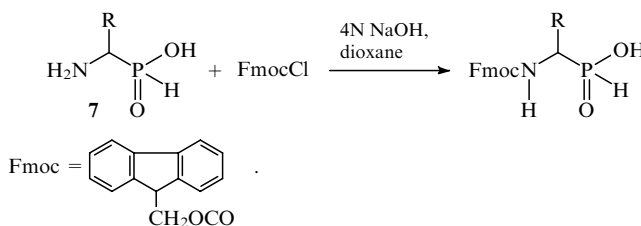
- (a) BuLi or Bu^tCH₂OK; (b) R¹—, BF₃·OEt₂; (c) MsCl, Et₃N; (d) Bu^tCH₂OK; (e) HCl, MeOH.

(1-Aminocyclopropyl)phosphonates **16** were obtained by alkylation of the phosphonate **13**-derived carbanion with epoxides to give the hydroxy phosphonate **14**. The mesylate of **14** obtained from the latter undergoes cyclisation in the presence of bases to give a cyclopropane intermediate subsequent methanolysis of which in acidic medium results in the target product **16**. Other examples of similar reactions are described in Ref. 18.

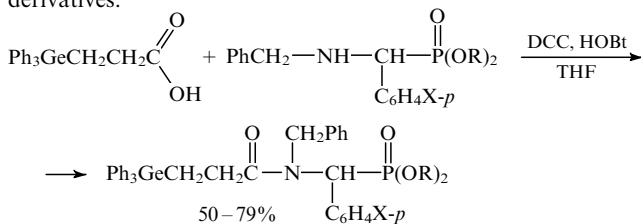
b. N-Modification

This type of AP reactions is responsible for their inhibitory effect with respect to enzymes and enables the involvement of APA and their esters in peptide synthesis. These processes were analysed in the reviews cited above,^{3, 16, 34, 38, 39} and their examination is beyond the scope of our review; we shall describe only some of the results obtained in this field lately.

Fluorenylmethyl chloroformate was used as an acylating agent in the synthesis of α-(9-fluorenylmethoxycarbonyl-amino)alkylphosphinates.⁸⁹



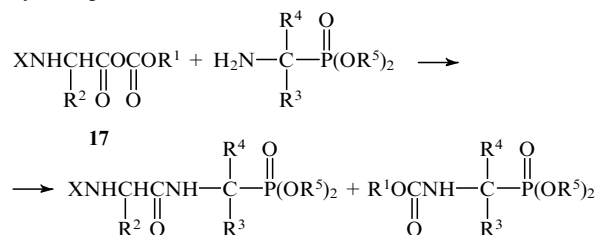
α-Aryl-(N-benzyl)aminomethylphosphonates react with β-tri-phenylgermylpropionic acid to afford germylated AP derivatives.⁹⁰



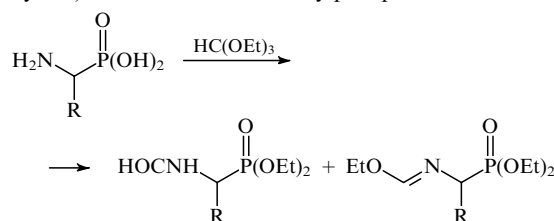
DCC is dicyclohexylcarbodiimide; HOBT =

Germylated AP manifest high antitumour activity that surpasses the efficiency of nongermylated AP derivatives in assays with sarcoma-180.⁹⁰

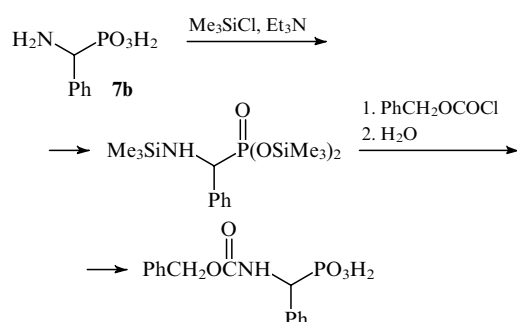
Acylation of AP containing a primary amino group with asymmetrical anhydride **17** results in a mixture of both possible N-acylated products.⁹¹



The readily occurring reaction of APA with ethyl orthoformate⁹² results in a mixture of (*N*-formyl)amino- and (*N*-ethoxymethylene)imino derivatives of alkylphosphonates.

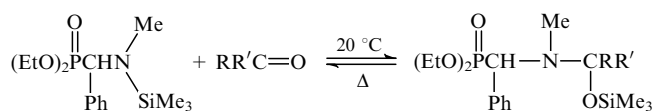


The well-known method to increase the nucleophilicity of the nitrogen atom by introduction of a trialkylsilyl group ('silyl activation') was successfully used in peptide synthesis in the *N*-acylation of APA **7b** with benzyl chloroformate.⁹³



It should be noted that this synthetic technique has also been used in the synthesis of phosphorus analogues of glycine containing the dimethylphosphine oxide group.⁹⁴

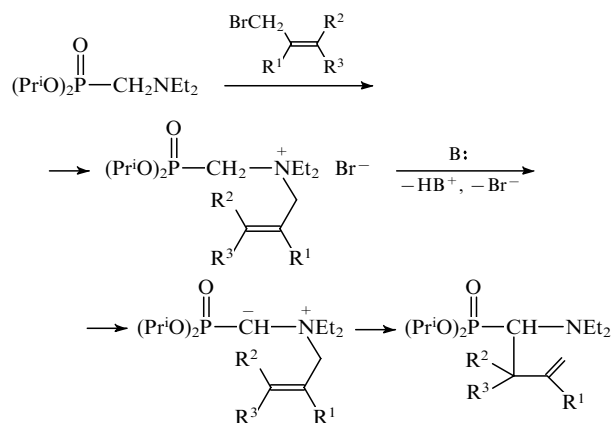
N-Silylated AP add to acetone, benzaldehyde and *p*-bromobenzaldehyde at room temperature.⁹⁵



Distillation of (*N*-methyl-*N*-silyloxyalkyl)phenylmethylphosphonates results in their dissociation to the original AP and carbonyl compounds.

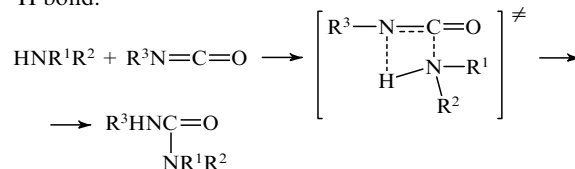
Nucleophilic reactions involving the nitrogen atom of AP are not limited to the substitution processes. Other reactions characteristic of primary, secondary and tertiary amines are also typical of AP. Among these, reactions of quaternisation and especially reactions of addition to unsaturated compounds are well studied.

An unusual sigmatropic [2,3]-rearrangement of *N*-allyl-ammoniomethyl phosphonates occurs in the presence of bases.⁷⁸



In this case, quaternisation of the tertiary amine centre is followed by the Cope rearrangement into the corresponding C-substituted AP, *viz.*, 1-aminobut-3-enylphosphonate.

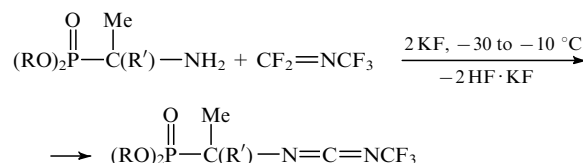
Of addition reactions, those of AP with aryl isocyanates have been studied in detail.^{96–100} Comparative study of the kinetics of addition of amines and their α -phosphorylated analogues, *i.e.*, AP, to phenyl isocyanate revealed similarity of the addition mechanisms. In both cases, a concerted mechanism of addition is postulated with a four-centred transition state in which the C–N bond is formed in the activated complex somewhat earlier than the N–H bond.^{96–98}



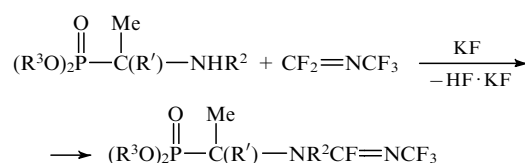
$\text{R}^1 = \text{Alk}, \text{Ar}; \text{R}^2 = \text{H}, \text{Alk}, \text{Ar}, \text{CH}_2\text{P}(\text{O})(\text{OR})_2; \text{R}^3 = \text{Ar}.$

The small activation enthalpies and the high negative activation entropies are in good agreement with this conclusion. As was to be expected, AP are appreciably less active in this reaction than their aliphatic analogues, *i.e.*, dialkylamines. This is due to a decrease in the nucleophilicity of the amino group in the AP molecule due to the electron-withdrawing effect of the phosphoryl group. In a series of phosphorylated nucleophiles, good agreement between their reactivities and steric effects of the substituents at the phosphorus atom is observed, as follows from high correlation factors of the corresponding equations.⁹⁶

Reactions of AP with perfluoro-*N*-methylformimine probably occur according to the addition–elimination scheme.¹⁰¹ The synthetic result of this reaction, which occurs under very mild conditions, depends on the degree of substitution at the α -amino group. Primary α -phosphorylalkylamines are transformed to the corresponding α -(*N*'-trifluoromethylcarbodiimido)alkylphosphonates.



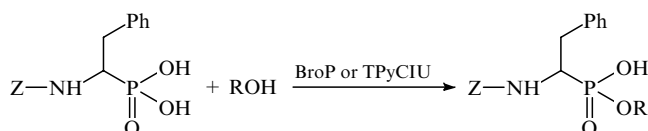
Secondary amines react with the elimination of one molecule of hydrogen fluoride and form α -(perfluoro-*N*-methylformamidino)alkylphosphonates under the same conditions.



c. P-Modification

In the chemistry of AP, this type of reactions is normally represented by saponification and esterification of phosphorus acid derivatives. Though these reactions play an important role in the synthesis of APA and their esters, they are of no special interest in the context of this review. Of recent studies, we shall mention only Ref. 102.

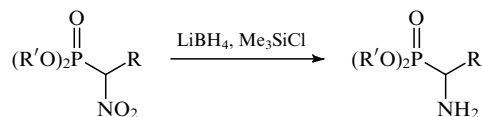
Selective mono-esterification of APA occurs with sterically hindered alcohols in the presence of bromo[tris(dimethyl-amino)]-phosphonium hexafluorophosphate (BroP) or *N,N,N',N'*-bis(tetramethylene)chloronium tetrafluoroborate (TPyCIU).



d. Other methods

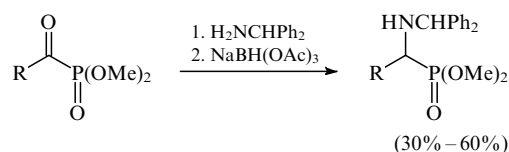
The simplest and rather common method for the synthesis of AP is reduction of nitrogen-containing organophosphorus compounds that already have a phosphonate framework with the α -nitrogen atom under the action of various hydrogenating agents.

For example, α -nitro phosphonates can easily be transformed to AP even at room temperature in almost quantitative yields.¹⁰³



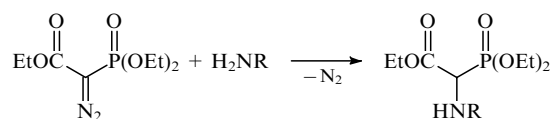
Reduction of hydroxyiminophosphonate with sodium borohydride occurs in the presence of MoO_3 or $NiCl_2$ (see Ref. 104).

Reductive amination of α -oxo phosphonates in the presence of triacetoxyborohydride gives the corresponding AP in moderate yields.⁷⁶



This reaction occurs in two steps: Schiff's bases are formed in the first step and reduced in the second step.

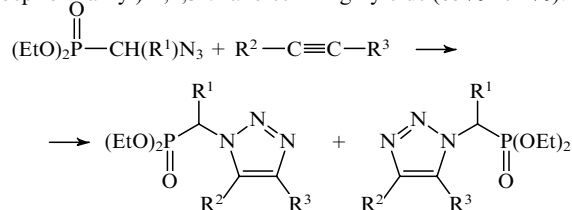
Other reactions of unsaturated organophosphorus compounds containing, or devoid of, a potential amino group were used in the synthesis of AP. Ethyl (diethoxyphosphoryl)diazooacetate is obviously inserted as a carbene into the N–H bond of amines and amides.¹⁰⁵



R = Alk, Ar, Ac, COOBu^t etc.

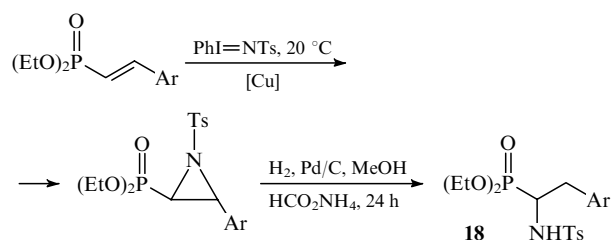
The reaction takes place under drastic conditions, viz., refluxing in toluene in the presence of palladium salts.

Diethyl azidoalkylphosphonate undergoes 1,3-dipolar cycloaddition with alkynes to give 4,5-disubstituted 1-(1-diethoxyphosphorylalkyl)-1,2,3-triazoles in high yields (85%–92%).¹⁰⁶



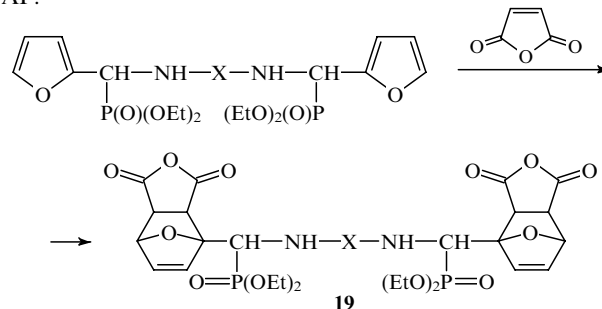
Reactions of unsaturated organophosphorus compounds with nitrogen-containing 1,3-dipoles are well studied and are discussed in a review.¹⁰⁷

Vinylphosphonates are attractive synthons when choosing a strategy for the synthesis of AP. Recently,¹⁰⁸ a convenient method to involve them in the reaction with *N*-tosyliminophenyl- λ^3 -iodane in the presence of Cu(II) or Cu(I) triflate has been described.



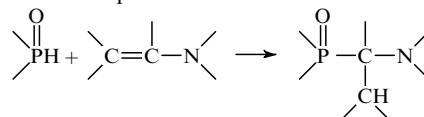
Catalytic hydrogenation of the aziridine intermediate occurs regioselectively to give the AP **18**. The solvent used in this reaction affects essentially the rate of the process. For example, a 70%–80% yield of compound **18** is reached in 10 min in acetonitrile, in 1–3 h in CH_2Cl_2 , and in 76–90 h in benzene. Enantioselective synthesis of AP from vinyl-phosphonates and -phosphinates was also carried out with the use of nickel complexes of natural amino acids. As a result, the latter undergo condensation at the terminal carbon atom of the phosphorus reagent.^{18, 109}

Polyfunctional AP can be obtained by functionalisation involving other unsaturated fragments as well. For example, bisphosphonates **19** were synthesised¹¹⁰ which represent the Diels–Alder adducts of maleic anhydride with furan derivatives of AP.

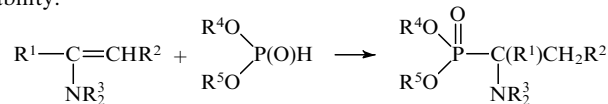


Yet another promising strategy for the synthesis of AP has found quite a limited use so far. This is phosphorylation of unsaturated compounds containing the nitrogen atom at the α -position to the double bond, for example, enamines and similar compounds.

The so-called electrophilic version of the Pudovik reaction makes an exception.



It is known¹⁰ that hydrophosphorylation of enamines under classical conditions of the Pudovik reaction, which is base-catalysed addition, could not be carried out until the late 1980's. A simple one-step method for the synthesis of AP was created only after the discovery of the electrophilic version of the Pudovik reaction, which occurs with vinyl ethers, enamines and other electron-excess alkenes and five-membered cyclic alkylene-phosphorous acids characterised by an increased proton-donor ability.^{111–115}



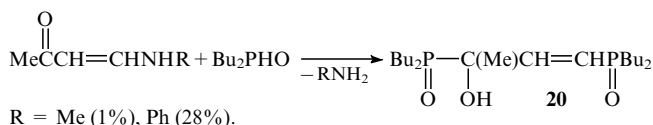
R¹ = Alk, Ar; R² = H, COOEt, COMe etc.;

R³ = (CH₂)₅, CH₂CH₂OCH₂CH₂, Me₂;

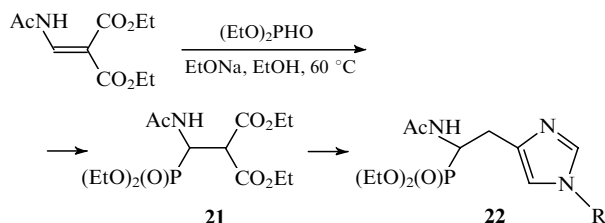
R⁴, R⁵ = CH(Me)CH(Me), CH(Me)CH₂, CMe₂CMe₂, CH₂CMe₂CH₂, *o*-C₆H₄; R⁴ = R⁵ = CHF₂CF₂CH₂, ClCH₂CH₂.

Synthetic, kinetic and thermochemical studies^{8, 111–115} of this reaction together made it possible to establish its mechanism. It consists of pre-equilibrium transfer of a proton from the phosphorous acid to the enamine and addition of the cyclophosphite anion to the α -carbon atom. As is frequently observed in electrophilic addition of proton-containing reagents, the addition occurs according to the Markovnikov rule. However, this method was found to be unsuitable for the hydrophosphorylation of amino-butenones.¹¹⁶ Enamino ketones with *N*-methyl and *N*-phenyl groups react without participation of the carbon–carbon double bond. Dibutylphosphine oxide adds to the ketone carbonyl group,

and the second phosphine oxide molecule replaces the amino group to give the diphosphorylated unsaturated alcohol **20**.

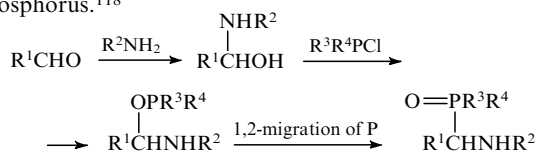


It is rarely possible to employ the classical nucleophilic Pudovik reaction for the synthesis of AP.¹¹⁷ For example, the addition of diethyl phosphite to *N*-acetylaminomethylidenemalononic ester gave the AP **21**, which served as the starting reagent in the synthesis of phosphonohistidine **22**.



This reaction was successful due to the presence of three strongly electron-withdrawing substituents in the unsaturated electrophilic reagent, *viz.*, two ethoxycarbonyl groups and an acylamino group.

Finally, we shall note the unusual synthesis of AP through 1,2-phosphorylotropic migration in a series of *N*-acylated derivatives of α -aminoalkyl compounds of three-coordinate phosphorus.¹¹⁸



R¹ = CCl₃, H(CF₂)₄, H(CF₂)₆; R² = PhCO, P(O)(OEt)₂, P(O)Ph₂;

R³ = R⁴ = AlkO, Alk₂N, Ar.

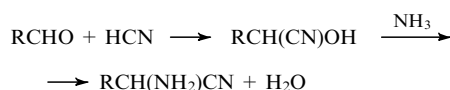
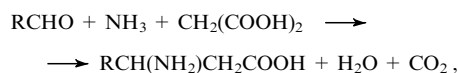
The α -amino alcohol formed in the first step of the reaction esterifies the P(III) halide to give the P(III) alkoxy derivative, which then undergoes isomerisation to the corresponding AP.

The material presented in this section shows that essential progress in the creation of new types of AP has been achieved during the search for practically useful compounds. The ever-increasing complication of the AP structures demands a wider use of diverse approaches for the functionalisation of the starting substances. However, the analysis of the results obtained shows that the main problem in AP chemistry, *viz.*, the formation of the α -alkylaminophosphinyl fragment P(O)–CR₂–N, can be best solved using the Kabachnik–Fields reaction. This explains, first of all, the keen interest of researchers in the studies of various aspects of the Kabachnik–Fields reaction in the last decade. This primarily corresponds to the investigations into the reaction mechanism, as the desired synthetic result can only be achieved on the basis of in-depth understanding of the factors governing this complex process.

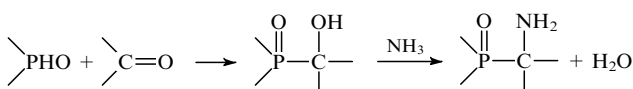
III. The mechanism of the Kabachnik–Fields reaction

As noted above, the Kabachnik–Fields reaction, *i.e.*, a three-component reaction of hydrophosphoryl compounds with ammonia, amines or other NH-compounds and aldehydes or ketones, is a unique method for the formation of the AP framework [N–C–P(O)]. However, a common viewpoint on the mechanism of this reaction has not been worked out until recently, as the conclusions were based mainly on synthetic studies. Spectral and kinetic data were obtained later.

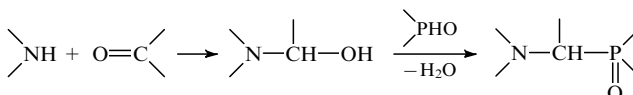
The main problem in the understanding of the mechanism of the Kabachnik–Fields reaction is the determination of the sequence of separate steps of this process. In their early studies, Kabachnik and Medved' believed that it was similar to the Rodionov reaction employed for the synthesis of β -amino acids or the Zelinsky reaction, *i.e.*, the formation of amino nitriles upon treatment of aldehydes with ammonium cyanide (see Refs 1, 119–121 and references cited therein).



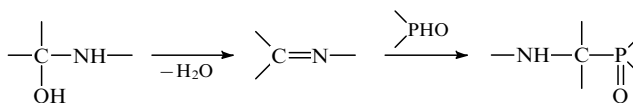
Studies of the reaction of hydrophosphoryl compounds with aldehydes¹ and ketones¹¹⁹ made it possible to suggest a scheme of aminoalkylation of hydrogen phosphites and phosphonites,^{120, 121} which involves the addition of a hydrophosphoryl compound to the C=O bond with subsequent replacement of the hydroxy group of the α -hydroxy phosphonate by the amino group.



Fields² used primary and secondary amines instead of ammonia in a three-component mixture containing dialkyl phosphites and carbonyl compounds. For example, exothermic reaction of diethyl phosphite with diethylamine and formaldehyde gives *N,N*-diethylaminomethylphosphonate in 94% yield. Fields² believed that the reaction occurred as the Mannich reaction, *viz.*, the reaction of an amine with an aldehyde first produces an α -amino alcohol, which reacts with a hydrophosphoryl compound to give finally an AP.

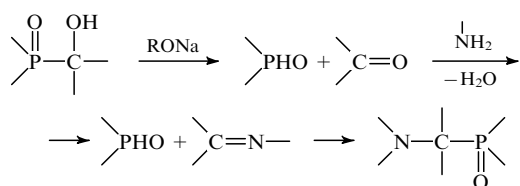


In the opinion of Fields,² the reaction with primary amines might also occur through intermediate imines. An imine formed in the first step, *i.e.*, the product of dehydration of an α -amino alcohol, readily added a hydrophosphoryl compound.



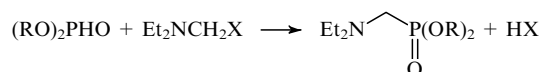
Thus, in the studies of the Kabachnik–Fields reaction,² the important assumption has been made that aminoalkylation of hydrophosphoryl compounds could occur through a step of formation of an imine and its subsequent involvement in the Pudovik reaction.

The experimental fact that the methoxy group in methoxymethylphosphonate is not exchanged for the amino group on heating with ammonia provides evidence in support of the 'imine' pathway of the Kabachnik–Fields reaction.¹²² In addition, hydroxy phosphonates, *i.e.*, addition products of dialkyl phosphites to carbonyl compounds, do not react with ammonia under the mild reaction conditions used by Fields.² The hydroxy group can be replaced by the amino group only in the presence of sodium alkoxide. It is believed to cause the decomposition of a hydroxy phosphonate into the original compounds, *viz.*, hydrogen phosphite and a carbonyl compound.¹²² The process subsequently goes through a step of formation of an imine, which adds a hydrophosphoryl compound according to the Pudovik reaction scheme.



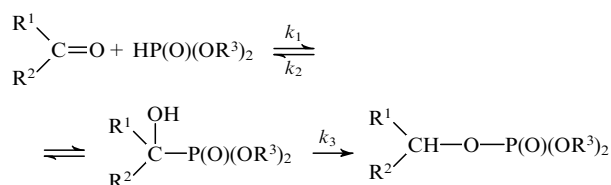
The reversibility of the formation of hydroxy phosphonates received a convincing experimental confirmation in the studies by Gancarz *et al.*^{5, 123–125} It was found that hydroxy phosphonates obtained from aliphatic and aromatic aldehydes and ketones decompose into the original hydrophosphoryl and carbonyl compounds under certain conditions in the presence of primary or tertiary amines (butylamine, triethylamine), as well as amines in the presence or in the absence of proton donors (ethanol). Hence, the formation of hydroxy phosphonates under conditions of the Kabachnik–Fields reaction does not necessarily imply that the formation of the ultimate AP should definitely occur according to the ‘hydroxy phosphonate’ pathway. As shown above, the phosphite and carbonyl compound formed upon decomposition of hydroxy phosphonates can give the final AP according to the ‘imine’ pathway, *viz.*, through condensation of a carbonyl compound and an amine into an imine and its subsequent hydrophosphorylation.

At first glance, this viewpoint does not explain the participation of secondary amines in the Kabachnik–Fields reaction. However, according to the data obtained by Petrov *et al.*,¹²² in this case either the addition of hydrophosphoryl compounds to iminium salts or the Mannich reaction occur. The possibility of the latter pathway is confirmed by the formation of AP in the reaction of dialkyl phosphites with *N,N,N',N'*-tetraethylmethylenediamine or with ethoxymethyldiethylamine.



X = NEt₂, OEt.

On the other hand, it was found^{123–125} that hydroxy phosphonates are not only formed reversibly from aromatic ketones under conditions of the Kabachnik–Fields reaction but also are irreversibly converted to phosphates according to the well-known phosphonate–phosphate rearrangement scheme.



R¹, R² = Ar;

Relative reaction rate constants: $k_1 = 100$, $k_2 = 1$, $k_3 = 6$.

The fastest step of the reaction is the formation of a hydroxy phosphonate. Its rearrangement to a phosphate occurs six times faster than the decomposition to the original compounds.

It is necessary to emphasise that both Kabachnik with Medved' and Fields have made their conclusions on the sequence of the reaction steps without carrying out special mechanistic studies. Therefore, they did not contrast the two possible routes of the aminoalkylation of hydrophosphoryl compounds, *viz.*, the ‘hydroxy phosphonate’ and ‘imine’ pathways. The experimental data reported in their and other studies cited above^{2, 119–121} as well as in some later publications^{122, 126, 127} allow one to assume that, depending on the nature of the reactants (hydrophosphoryl and carbonyl compounds and amines), the reaction mechanism and the sequence of steps can vary.

An assumption was made^{128–130} that the formation of AP *via* hydroxy phosphonates occurs with amines whose basicity is

sufficiently high ($\text{p}K_{\text{a}} > 6$). Otherwise ($\text{p}K_{\text{a}} < 6$), the ‘imine’ mechanism operates. This conclusion is based on the shift of signals in the ³¹P NMR spectrum of diethyl phosphite in its mixtures with amines. The δ ³¹P value is the higher the more basic the amine. Furthermore, it was considered^{129, 130} that the increase in the yield of AP in the Kabachnik–Fields reaction with weakly basic amines upon addition of crown ethers confirmed the scheme discussed above.

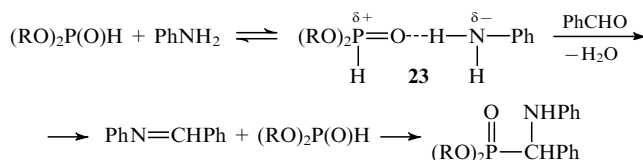
The idea that the mechanism of the Kabachnik–Fields reaction displays certain dualism seems quite reasonable. However, not all of the statements given in Ref. 129 appear to be convincing, and some of the postulates seem unlikely. Thus the suggestion that weakly basic amines can protonate the phosphoryl oxygen atom of a phosphite and the amide anion thus formed adds to a carbonyl compound to form methylolamine and/or imine¹²⁹ is wrong, in our opinion, as the amines are too weak acids to protonate the weakly basic oxygen atom of the P=O group.

A confirmation that the Kabachnik–Fields reaction can follow both of the pathways discussed here, *viz.*, ‘hydroxy phosphonate’ and ‘imine’, was obtained^{131–139} by the authors of the present review in a complex study including kinetic, spectroscopic and preparative methods.

We studied three-component systems containing a hydrophosphoryl compound, a carbonyl compound, and an amine, in which the nature of each reagent and the reaction conditions (solvent, additives of various types) were varied widely. We also studied the possibilities of bimolecular processes in the following pairs: hydrophosphoryl compound–carbonyl compound, hydrophosphoryl compound–amine, hydroxy phosphonate–amine, and hydrophosphoryl compound–imine. It was found that each of the reaction partners affects somewhat the reaction efficiency and its pathway.

A kinetic study of the reaction in the system dialkyl(methyl or pentyl) phosphite–benzaldehyde–aniline and reactions in the pairs PhNH₂ + PhCHO, dipentyl phosphite + PhCHO, and dipentyl phosphite + PhN=CHPh has made it possible to establish that the ‘imine’ mechanism operates in this case.¹³¹ UV spectroscopic study of the reaction kinetics permitted detection of an increase in the optical density of the mixture due to the formation of an imine chromophore in the beginning of the process. The formation of an imine is the fastest reaction of all reactions possible in this system. It is catalysed by a dialkyl phosphite. The reaction of phosphites with benzaldehyde in the absence of acidic additives (formic acid or aniline hydrochloride) does not occur at all. Pyridine, whose basicity is equal to that of aniline, but which cannot serve as a proton donor and does not participate in the reaction, does not catalyse it. Hence, the basicity of aniline is insufficient to catalyse the addition of dialkyl phosphites to benzaldehyde. This rules out the intermediate formation of hydroxy phosphonates.

Thus, due to low basicity, aniline manifests proton-donor properties and forms a pre-reaction complex of the type **23** with the phosphite. The reaction of the complex **23** with benzaldehyde results in an imine hydrophosphorylation of which gives the target AP.

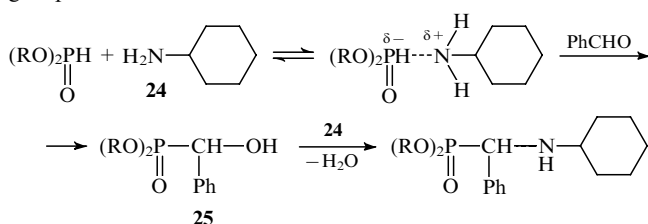


A study of this system in solvents of different nature, *viz.*, in benzene (neutral medium) or propan-2-ol (a potential proton donor), in the presence and in the absence of acidic admixtures made it possible to reveal the effect of acid catalysis on the rate of each step of this reaction. The use of a strong proton donor, such as HCOOH, always accelerates the reaction by the general acid catalysis mechanism. This effect is most pronounced in a polar solvent, *viz.*, propan-2-ol. Propan-2-ol itself is inefficient as a

proton donor. It manifests only solvation effects, slowing down the reaction in some cases due to the formation of H-complexes with basic reagents.

Different kinetics were observed if the relatively weak base, aniline, was replaced by the appreciably more basic cyclohexylamine **24**.¹³⁶ It was found that the reaction of amine **24** with benzaldehyde is very slow and results in benzylidenecyclohexylamine, which is practically insoluble both in the selected media and in the majority of organic solvents. Attempts of addition of dialkyl phosphites to *N*-cyclohexylbenzylideneamine even in the presence of strong acids and bases failed.

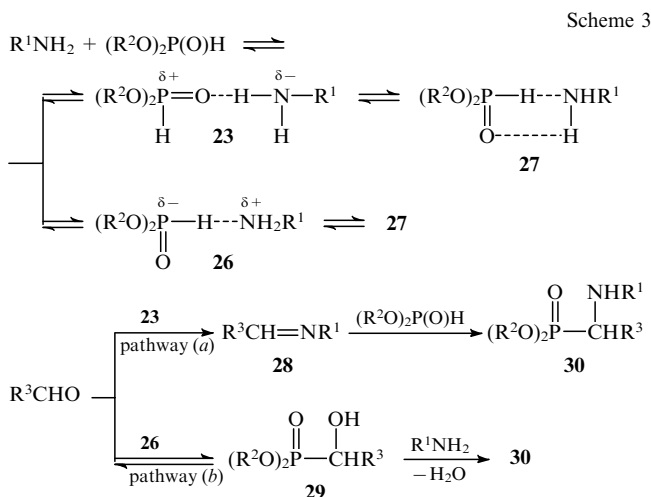
These data indicate that in the system 'hydrophosphoryl compound–amine **24**–benzaldehyde', the 'hydroxy phosphonate' mechanism operates. According to this pathway, the reaction starts with the addition of a phosphite to benzaldehyde catalysed by the amine **24** (the Abramov reaction), followed by the replacement of the hydroxy group by the cyclohexylamino group.



A special ³¹P NMR study made it possible to detect the formation of the hydroxy phosphonate **25** in all cases. If a catalytic amount of the amine **24** is used, the phosphonate **25** is the sole reaction product. As the amine concentration increases, the signal intensity for the final product (AP) increases, while that for the phosphonate **25** decreases. In the system with aniline discussed above, the formation of the hydroxy phosphonate was never detected.

The results of these studies lead to the conclusion on the decisive role of the amine basicity. Variation of the nature of the amine enables 'switching' of the reaction from one pathway to the other.

To estimate the effect of the carbonyl component on the reaction pathway, the same complex of studies was carried out in the system 'dialkyl phosphite–aniline–substituted benzaldehyde'. Electron-donating *p*-methoxy and *p*-dimethylamino groups and electron-withdrawing *p*-bromo and *m*-nitro groups were used as the substituents. It was found that in all cases the 'imine' reaction pathway (Scheme 3) was realised and its general laws were obeyed. However, on switching from electron-donating substituents to electron-withdrawing ones, the rate of imine formation increases both in the carbonyl compound–amine pair and in the three-component system.



On the other hand, unlike benzaldehyde, its derivatives with both electron-donating and electron-withdrawing substituents undergo the Abramov reaction with phosphites to produce the corresponding hydroxy phosphonates. Moreover, simultaneous formation of both an imine and a hydroxy phosphonate was reported. The rate of the Abramov reaction for the aldehydes with electron-donating substituents exceeds the rate of imine formation by almost an order of magnitude. However, this does not suggest that the 'hydroxy phosphonate' mechanism is preferable kinetically, since, first, the Abramov reaction is reversible, and, second, the ability of transformation of hydroxy phosphonates to AP depends on the basicity of the amine. Weakly basic amines cannot replace the hydroxy group in a hydroxy phosphonate molecule. Thus, even if the formation of the latter is preferable kinetically, thermodynamic control directs the reaction with weakly basic amines to the 'imine' pathway.

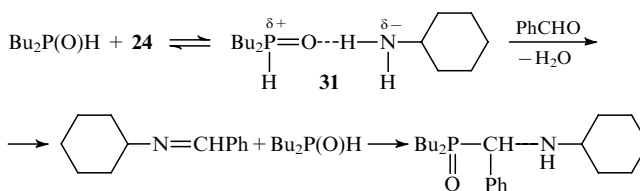
In some cases, *e.g.*, for anisaldehyde, the ratio of rates of all pairwise reactions possible under the Kabachnik–Fields reaction conditions allows both reaction pathways. However, even in this case, the reaction follows mainly the 'imine' pathway, while the 'hydroxy phosphonate' pathway is minor if aniline is used as the amino component.¹³⁷

In the general case, the basicity of the amine is the crucial factor that determines the reaction pathway, in particular, the possibility of formation of pre-reaction complexes **23** or **26** (Scheme 3). Weakly basic amines, which can act with hydrophosphoryl compounds as H-donors, direct the reaction to the 'imine' pathway [pathway (a)].

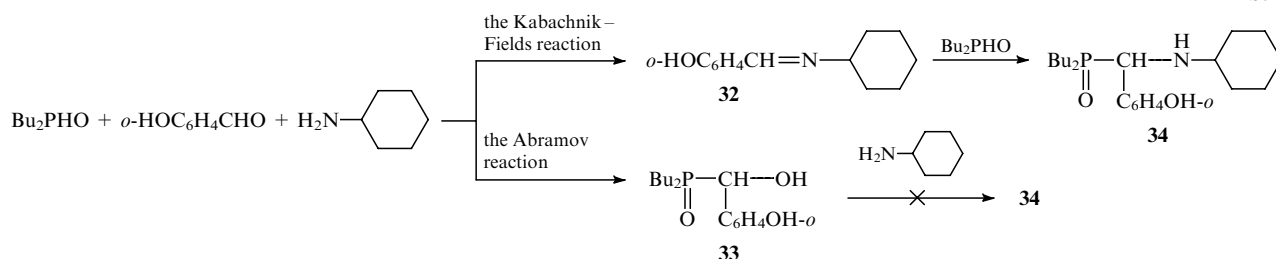
Strong bases enable nucleophilic interaction of the pre-reaction complex **26** with carbonyl compounds and thus favour the 'hydroxy phosphonate' direction. An important role belongs to the reactivity of reactants, which affects the ratio of rates of decomposition of the hydroxy phosphonate and replacement of the hydroxy group in it by the amino group according to the pathway **29** → **30**. An intermediate case is possible as well: a biphilic reaction of a hydrophosphoryl compound with an amine with the formation of the complex **27**. This version assumes the probability of parallel reactions through both pathways.

The importance of consideration of all factors in the determination of the reaction pathway is clearly seen where salicylaldehyde is used in the reaction.¹³⁸ Irrespective of the amine basicity, the reaction with salicylaldehyde occurs exclusively according to the 'imine' pathway. The reason for this is the thermodynamic instability of the hydroxy phosphonate obtained from this aldehyde in the Abramov reaction.

The nature of the hydrophosphoryl compound is also of significant importance.¹³⁹ As will be shown below (Section IV) and as follows from Scheme 3, the acid–base interaction of a hydrophosphoryl compound with an amine is the crucial factor that determines the direction of the reaction. Replacement of the alkoxy groups by alkyls in a hydrophosphoryl compound, *i.e.*, going from dialkyl phosphites to dialkyl phosphinites and especially to phosphinous acids, alters the ability of a hydrophosphoryl compound to form a pre-reaction complex with an amine. High basicity of the phosphoryl oxygen atom in dibutylphosphinous acid and the decrease in PH-acidity of the hydrophosphoryl compound due to the replacement of electron-withdrawing alkoxy substituents at the phosphorus atom by electron-donating alkyl groups is the reason for the 'switch' of the reaction pathway from the 'hydroxy phosphonate' pathway, which is typical of dialkyl phosphites, to the 'imine' one if cyclohexylamine **24** is used as the amine component.



Scheme 4



Although phosphinous acids undergo smooth addition to carbonyl compounds, even in the absence of catalysts, the effect of the pre-equilibrium step, which involves the formation of the complex **31** and the addition of cyclohexylamine **24** to benzaldehyde catalysed by dibutylphosphinous acid, is more essential. An alternative mechanism involving nucleophilic attack of the dibutylphosphinite anion on the carbonyl carbon atom is noncompetitive in this case.

In a three-component system ‘dibutylphosphinous acid–salicylaldehyde–cyclohexylamine’, the hydrophosphoryl compound can enter into nucleophilic reactions both with an amine, which determines the ‘imine’ mechanism of the Kabachnik–Fields reaction, and with salicylaldehyde. However, in the latter case, the product of the Abramov reaction, *viz.*, compound **33**, does not react with cyclohexylamine, and the product of the Kabachnik–Fields reaction, *viz.*, aminomethylphosphine oxide **34**, is not formed (Scheme 4).

High stability of the hydroxy phosphonate **33** precludes its decomposition into the original components. Both addition processes resulting in the imine **32** and hydroxy phosphonate **33** are competitive, and compound **33** is the side reaction product. This result confirms once again the general scheme of the Kabachnik–Fields reaction (Scheme 3) and explains numerous experimental observations that the purity and yield of the reaction product increase if the reaction is carried out not in a three-component system but rather in a stepwise manner, for example, with isolation of the imine.^{140, 141} It is difficult to interpret unequivocally the competitive reactions of two nucleophiles in a system ‘hydrophosphoryl compound–carbonyl compound–amine’, *viz.*, the phosphite (the Abramov reaction, the ‘hydroxy phosphonate’ pathway) and the amine (the ‘imine’ pathway), in terms of electrophilicity of the carbonyl carbon atom.^{142, 143} It was not possible to reveal the relationship between the preference of attack by a particular nucleophile (amine or phosphite) and the steric requirements for the formation of adducts.¹⁴² It is believed^{142, 143} that the experimental results obtained from kinetic data and density functional¹⁴³ calculations are best explained from the HSAB standpoint. According to this concept, hard acids (aliphatic aldehydes and ketones) react faster with the hard bases (amines). Soft bases, *i.e.*, phosphites, preferably react with soft acids, such as aromatic carbonyl compounds. Similar opinions have also been expressed earlier.¹⁴⁴ We believe that these observations are only estimates that cannot rationalise the diversity of factors that determine the reaction pathway (for example, its changes on varying the substituents at the phosphorus atom in a hydrophosphoryl compound¹³⁹).

The general mechanism of the Kabachnik–Fields reaction presented in this section (Scheme 3) has much larger interpretative and predictive power.

IV. Synthetic potential of the Kabachnik–Fields reaction

The ample synthetic potential of the Kabachnik–Fields reaction has allowed it to occupy a deserved position in the arsenal of preparative chemistry of organophosphorus compounds. The

possibility of variation of the functional groups in the carbonyl and amine components, the involvement of various types of derivatives of trivalent (three-coordinate) phosphorus in the reaction, the rather mild reaction conditions and the possibility of further one-pot modification of the resulting AP, all these attractive aspects of the three-component method for the synthesis of AP by the Kabachnik–Fields reaction stimulated the search of newer substrates for this reaction. Here we make an attempt to classify the versions of the Kabachnik–Fields reaction according to the starting P(III) compound.

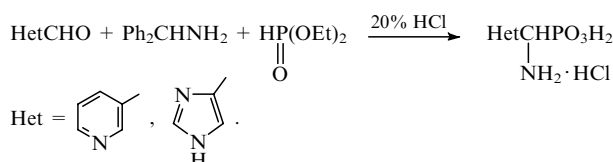
1. The classical version

a. Reactions of hydrophosphoryl compounds

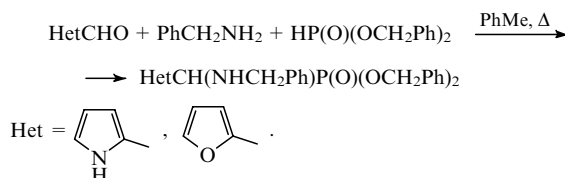
The scope of the Kabachnik–Fields reaction and its applicability to various types of hydrophosphoryl compounds, aldehydes and ketones, and secondary amines and ammonia outlined in the early studies satisfied to a certain extent the needs for the synthesis of AP with rather simple structures. The results of these studies are covered in reviews.^{6, 12} The scope of compounds that are being used in this reaction has now expanded appreciably.

First, this refers to the synthesis of AP containing heterocyclic substituents at the C- and N-centres.

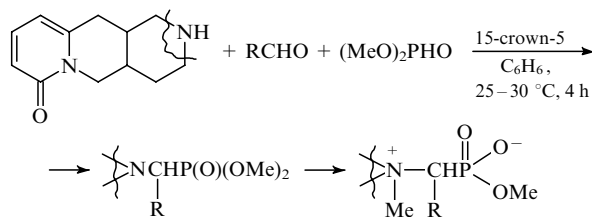
Pyridine, pyrrole and imidazole derivatives were synthesised by a one-pot procedure using diethyl phosphite and benzhydrylamine.¹⁴⁰ In the presence of hydrochloric acid, the benzhydryl protective group is removed and the process goes through condensation and hydrolysis to give the corresponding α -amino-hetarylmethylphosphonic acids.



The reaction of heterocyclic aldehydes with benzylamine and dibenzyl phosphite occurs at elevated temperature and results in *O,O,N*-tribenzyl phosphonates. Consecutive addition of the amine and the phosphite to the aromatic aldehyde assumes the initial formation of a Schiff's base.¹⁴⁰



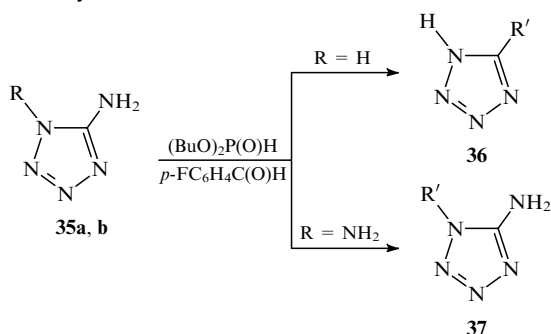
The alkaloid cytosine reacts with aliphatic and aromatic aldehydes and dimethyl phosphite under mild conditions in the presence of catalytic amounts of crown ethers to give the corresponding AP.¹⁴⁵ On refluxing in benzene, amino phosphonate derivatives of cytosine form internal salts.



R	Pr ⁱ	Ph	4-MeOC ₆ H ₄
Yield (%)	78	80	90

It should be noted that dealkylation involving the dimethoxyphosphoryl group can complicate the Kabachnik–Fields reaction, especially if weakly reactive aromatic aldehydes, that are most susceptible to this process, are used.¹⁴⁶

Phosphorylmethyl derivatives of aminotetrazoles are readily formed in the reaction with dibutyl phosphite and *p*-fluorobenzaldehyde.



R = H (**a**), NH₂ (**b**); R' = (BuO)₂P(O)CH(C₆H₄F-*p*)NH.

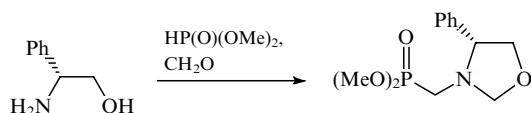
5-Aminotetrazole (**35a**) reacts with dibutyl phosphite on the amino group at position 5 to give compound **36**, whereas in 1,5-diaminotetrazole (**35b**) it is the amino group at the nitrogen atom that undergoes phosphorylation. Taking into account the tendency of 1,5-diaminotetrazole (**35b**) to form Schiff's bases, the 'imine' pathway of the reaction resulting in the AP **37** seems to be preferential.¹⁴⁷

In a search for biologically active AP, aminomethyl-diphenylphosphine oxides¹⁴⁸ as well as bisphosphonate derivatives of tetrahydropyran, its thio and seleno analogues¹⁴⁹ have been synthesised recently.

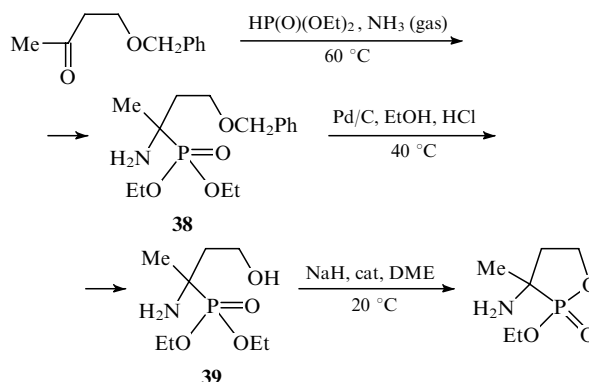


R¹ = H; R² = CH₂Ph, (CH₂)₂Ph, 2-pyridyl; R¹ = R² = CH₂Ph.

The use of appropriate bifunctional amines in the Kabachnik–Fields reaction allows the synthesis of heterocyclic compounds. For example, chiral phosphorylated oxazolidine is formed in a one-pot procedure from (*R*)-(-)-phenylglycinol, formaldehyde and dimethyl phosphite in boiling methanol.¹⁵⁰

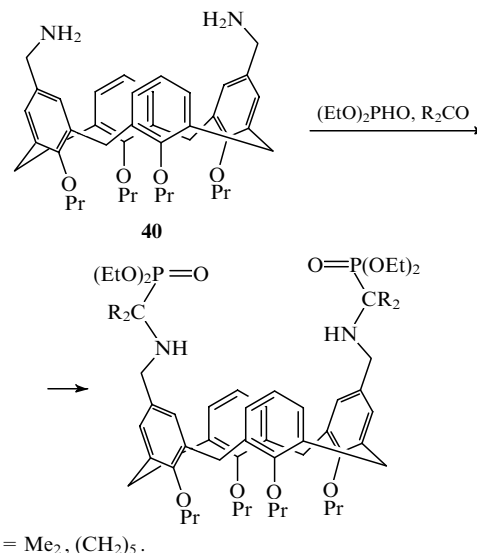


Heterocyclisation was successfully used in the synthesis of 3-amino-2-oxo-1,2-oxaphosphacyclanes.¹⁵¹ A one-pot synthesis of AP **38** from 4-benzyloxy-2-butanone, ammonia and diethyl phosphite followed by its hydrogenolysis results in alkanol **39**. Intramolecular transesterification of the latter gives the 1,2-oxaphospholane.

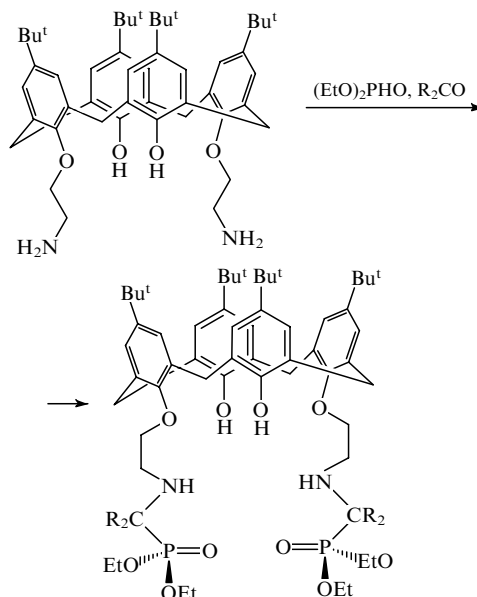


AP used in membrane extraction were obtained recently from calix[4]arene. Modified calix[4]arene platforms with (phosphorylalkyl)aminoalkyl fragments in the top and bottom rings were prepared from dialkyl phosphites and the appropriate carbonyl compounds.^{60, 64}

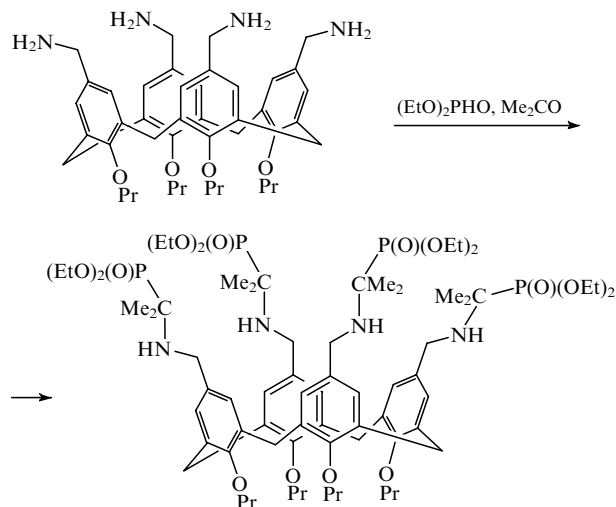
Regiospecific amination of calix[4]arene gave compound **40**, and in the 'top' rim of its platform two phosphorylalkyl groups were introduced.



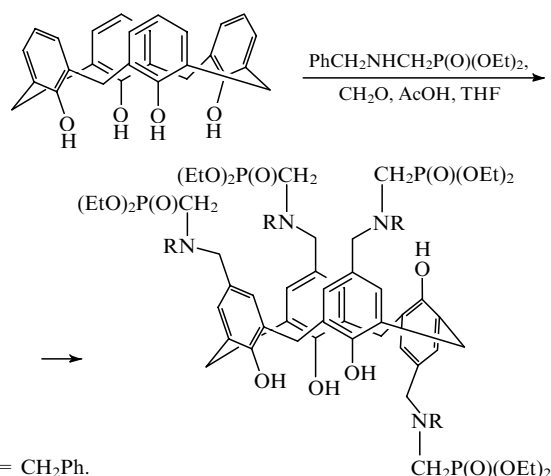
The amino phosphonate fragments in the 'bottom' rim were obtained using a calix[4]arene platform carrying β-aminoethoxy groups.



Four amino phosphonate groups were introduced in a similar way using a tetrakis(aminomethyl) derivative of calix[4]arene. As a result of the reaction, all phosphorus-containing fragments were located in the 'top' rim.

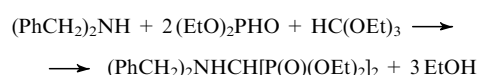


Modification of calix[4]arene with diethyl *N*-benzylamino-methylphosphonate gave a tetrasubstitution product in the 'partial cone' conformation.



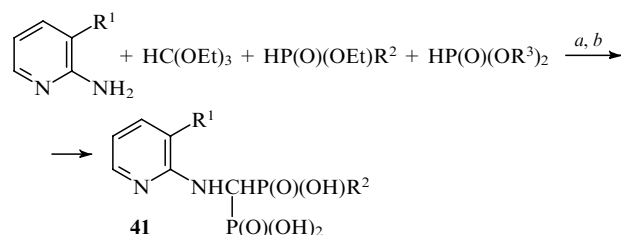
$\text{R} = \text{CH}_2\text{Ph}$.

Orthoformate was successfully used instead of carbonyl compounds in the classical version of the Kabachnik–Fields reaction. In this case, two phosphoryl groups rather than one can be attached to the carbon atom. Condensation of dibenzylamine and diethyl phosphite with orthoformate (1 : 3 : 1.2, refluxing for 24 h) gives dibenzylaminomethylenediphosphonate (yield 58%).¹⁵²



The reaction of benzylamine with one equivalent of $\text{HC}(\text{OEt})_3$ and four equivalents of diethyl phosphite at 160°C with subsequent acidification of the reaction mixture gave diaminomethylphosphonate $(\text{PhCH}_2\text{NH})_2\text{CHP}(\text{O})(\text{OEt})_2$ in 34% yield.¹⁵²

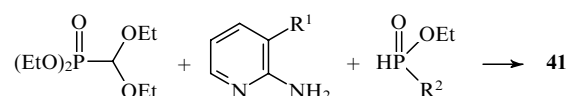
This version of the reaction makes it possible to introduce organophosphorus groups of different structures into an AP during one chemical process. For example, a phosphite and a phosphonite participate in a one-pot synthesis of phosphonato-phosphinate **41**.¹⁵³



(a) Δ ($-\text{EtOH}$); (b) H_2O , Δ ($-\text{R}^3\text{OH}$); $\text{R}^1 = \text{H}, \text{Me}$; $\text{R}^2 = \text{Me}, \text{Bu}$;

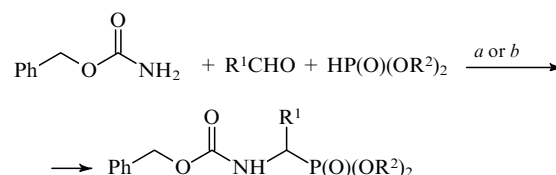
$\text{R}^3 = \text{Et}, \text{Pr}^i$.

The drawback of this method is that it gives, along with asymmetrical phosphonato-phosphinates, a small amount of symmetrical bisphosphonates and bisphosphinates. This can be avoided if phosphorus-containing groups are introduced successively. For example, α -phosphonoacetal, alkylphosphonite and aminopyridines react under these conditions to give compound **41** exclusively.



The scope of the classical version of the Kabachnik–Fields reaction is expanded if carbamates, amides of carboxylic and phosphorus acids and some other compounds are used as the amine component.

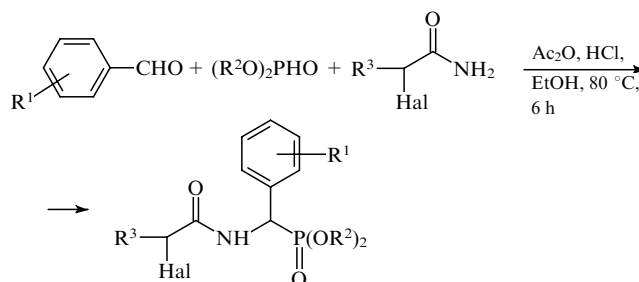
Benzyl carbamate, an aliphatic or aromatic aldehyde and diethyl phosphite react at room temperature in the presence of a mixture of acetic acid and thionyl chloride [method (a)] or acetyl chloride [method (b)] to give moderate to high yields of AP containing an *N*-benzyloxycarbonyl group, which can easily be removed if necessary.¹⁵⁴



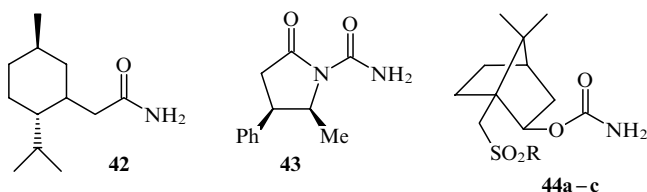
(a) AcOH , SOCl_2 , 20°C , 20 min, Δ , 2–12 h;

(b) AcCl , 0–5 $\rightarrow$ 20°C (43%–98%).

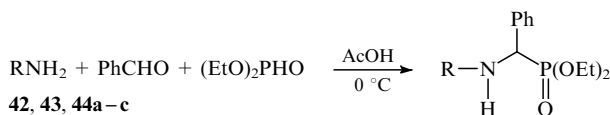
A modification of this method was suggested for the Kabachnik–Fields reaction with α -halocarboxamides.¹⁵⁵ Their condensation with aromatic aldehydes and hydrophosphoryl compounds occurs in the presence of an alcoholic solution of HCl or *p*-toluenesulfonic acid in acetic anhydride.



The diastereoselectivity of condensation of chiral cyclic carbamates and ureas according to the scheme of the Kabachnik–Fields reaction depends largely on the nature of the cyclic compound. The highest diastereomeric excess (*de*) in the one-pot synthesis of AP from diethyl phosphite, benzaldehyde and compounds **42**–**44a–c** containing an amino group is reached for derivatives of camphorsulfonic acid **44a–c**.¹⁵⁶



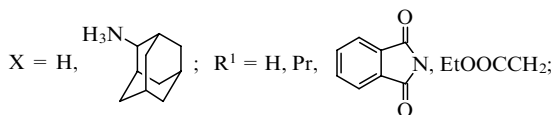
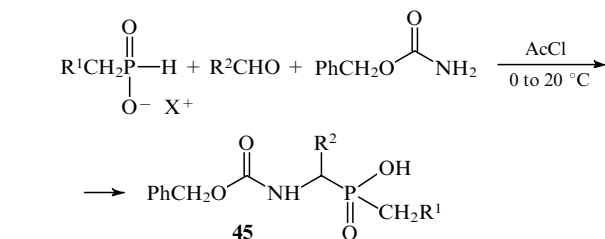
R = N(cyclo-C₆H₁₁)₂ (**a**), NPr₂ⁱ (**b**), C₆H₄OMe-4 (**c**).



Starting compound	42	43	44a	44b	44c
Yield of AP (%)	71	84	75	73	77
de (%)	14.4	34.1	99	96.4	96.2

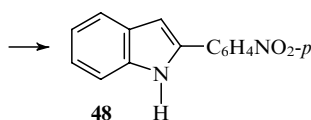
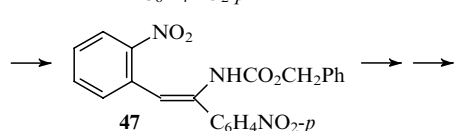
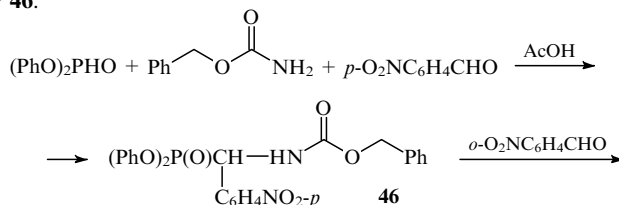
If benzaldehyde is replaced by other aldehydes (anisaldehyde, α -naphthaldehyde or *p*-tolualdehyde) in the reaction with carbamates **44**, the *de* remains at about 99%. The *de* is small (56%) only in the case of cyclohexanecarbaldehyde.

It is noteworthy that both hydrophosphoryl compounds and their salts can participate in this condensation.¹⁵⁷



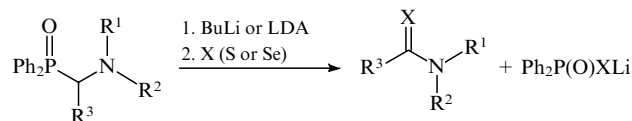
R² = H, Me, Et, Buⁱ, Ph, *p*-MeOC₆H₄.

The AP **45** obtained this way were used as synthons in the development of a new approach to the synthesis of functionalised indoles.¹⁵⁸ The reaction between diphenyl phosphite, benzyl carbamate and *p*-nitrobenzaldehyde in acetic acid results in the AP **46**.



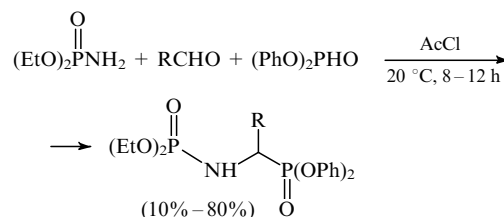
Dephosphonylation of amino phosphonate **46** by the Horner–Wittig–Emmons reaction with *o*-nitrobenzaldehyde gives the enamine **47**, which is converted in two steps to the C-substituted indole **48**. The use of α -aminophosphine oxide

provides a convenient method for the synthesis of thio- and selenoamides.¹⁵⁹ In this reaction, generation of a carbanion is followed by cleavage of the P–C bond under the action of two equivalents of sulfur or selenium.



R¹, R² = Me, Ph, (CH₂)₂O(CH₂)₂; R³ = H, Alk, alkenyl; X = S, Se.

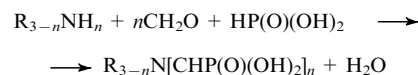
The use of acetyl chloride as the condensation agent makes it possible to introduce an organophosphorus radical to the amine centre of AP if *O,O'*-diethyl phosphoramidite is used as the amine component.¹⁶⁰



R = Pr, Prⁱ, Ph, *p*-MeC₆H₄, *p*-MeOC₆H₄, *p*-Me₂NC₆H₄.

b. Reaction of inorganic phosphorus acids

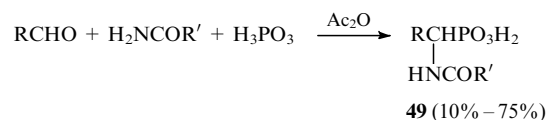
This version of the Kabachnik–Fields reaction is also named¹⁶¹ the Moedritzer–Irani reaction in the name of the researchers who were the first to use inorganic phosphorus acids of the lowest oxidation state for the synthesis of APA in a three-component system 'hydrophosphoryl compound–carbonyl compound–amine'.⁷¹



Reaction of orthophosphorous acid with formaldehyde is known to occur almost quantitatively. Since both primary and secondary amines can be involved, the Mannich reaction mechanism is considered most probable for these reactions,⁷¹ although other mechanisms are not ruled out either.

Attempts at expanding this version of the Kabachnik–Fields reaction to aliphatic aldehydes and ketones failed.¹⁶² The 'imine' version of the reaction is preferable for these compounds (see below).

Acylamides readily undergo condensation with aldehydes and phosphorous acid under the action of acetic anhydride.¹⁶³

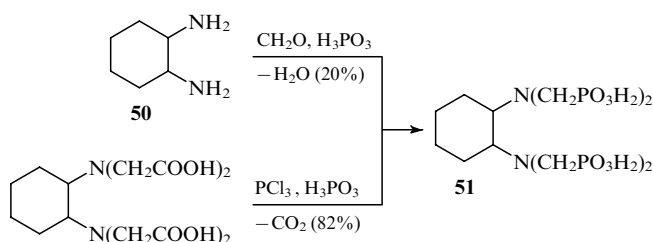


R = Me, Prⁱ, Ph, 3-NO₂C₆H₄, 4-ClC₆H₄, 4-MeC₆H₄;

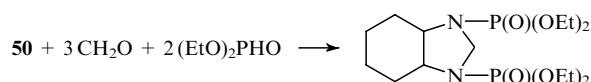
R' = PhCOO, PhCO, Ac.

Presumably, the condensation of an aldehyde with an amide is followed by decomposition of the condensation product to APA **49**.¹⁶³

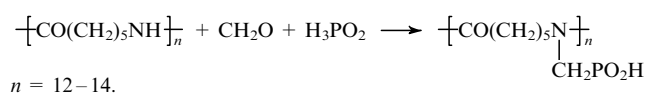
The reaction of 1,2-cyclohexanediamine **50** with formaldehyde and phosphorous acid occurs in a low yield.¹⁶¹ The yield of tetraphosphonate **51** increases considerably if 1,2-cyclohexanediaminotetraacetic acid is phosphorylated with a mixture of H₃PO₄ and PCl₃.



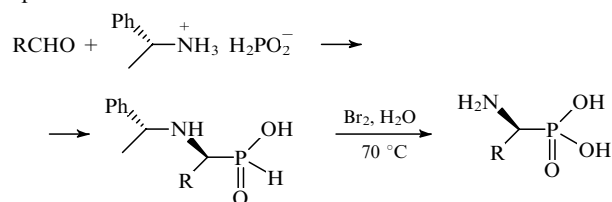
The reaction of 1,2-cyclohexanediamine **50** with formaldehyde and diethyl phosphite results in a bicyclic bisphosphonate.¹⁶¹



Hypophosphorous acid in a mixture with formaldehyde undergoes polymer-analogous Kabachnik–Fields reaction with polycaprolactam. This method has been used for the synthesis of materials with low flammability.¹⁶⁴



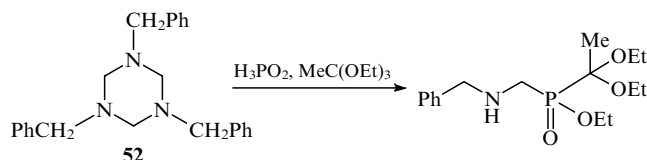
Salts of hypophosphorous acid with (*R*)-(+)- or (*S*)-(–)-1-phenylethylamine react with aldehydes in boiling ethanol to form homochiral APA.¹⁶⁵ The protective group at the nitrogen atom is easily removed by a standard method, and the intermediate phosphonous acid is converted into the APA.



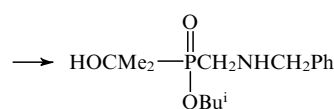
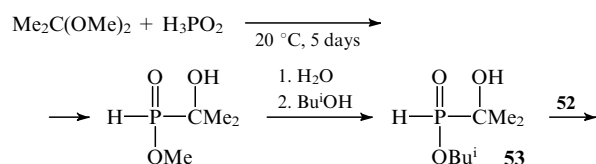
$\text{R} = \text{Pr}^i, \text{Bu}^i, \text{cyclo-C}_6\text{H}_{11}, \text{Ph}, \text{PhCH}_2.$

Recently, an efficient method for the synthesis of AP has been developed in which 80%–90% aqueous solutions of hypophosphorous acid is used as the hydrophosphoryl compound. In this case, orthoesters and acetals were used instead of carbonyl compounds, and 1,3,5-tribenzylhexahydro-1,3,5-triazine **52** was chosen as the amine component.

The reaction of triazine **52** with triethyl orthoacetate and H_3PO_3 gives an amino phosphinate under very mild conditions and in high yield.¹⁶⁶



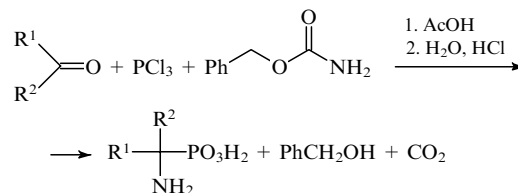
A three-step synthesis of a phosphinate containing both an α -hydroxy and an α -amino group in different *P*-alkyl substituents simultaneously¹⁶⁷ involves the initial formation of a phosphonite from 2,2-dimethoxypropane and hypophosphorous acid, its subsequent transesterification to the more hydrolytically stable isobutyl phosphonite **53** and the reaction of the latter with triazine **52** to give the AP.



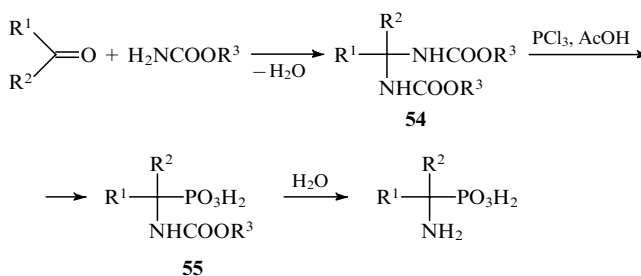
In these cases, commercial 50% hypophosphorous acid can be used following its concentration *in vacuo*. The efficiency of this approach in comparison with the methods based on the use of anhydrous H_3PO_2 is noteworthy (see Ref. 166 and references cited therein).

2. Reactions of trivalent phosphorus chlorides

This version of the Kabachnik–Fields reaction based on phosphorus trichloride was used in the synthesis of APA in 1978.¹⁶⁸

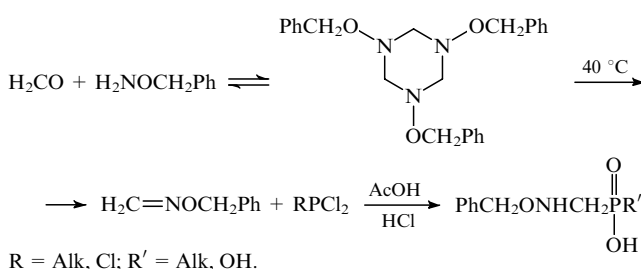


The method is equally applicable to alkyl(aryl)dichloro- and dialkyl(aryl)chloro-phosphines.^{169, 170} It is considered¹⁷⁰ that the process starts with condensation of an amide with a carbonyl compound. The alkylidenebisamide **54** thus formed is phosphorylated to AP **55**, hydrolysis of which results in an APA.

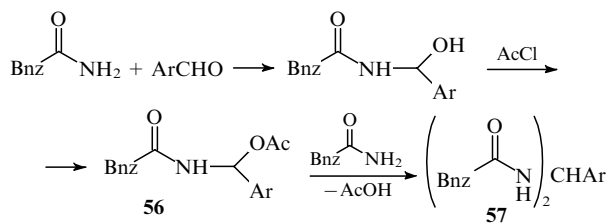


The method was expanded to a wide set of amides, carbonyl compounds and P(III) chlorides (see Ref. 171 and references cited therein). Another interpretation of aminomethylation of P(III) chlorides is considered in detail in Ref. 171.

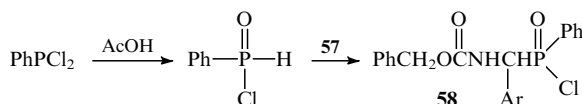
The method based on the use of PCl_3 was applied successfully to the synthesis of α -aminoarylalkylphosphonic acid³⁶ and its monoesters,¹⁷² as well as a large number of APA containing fluorinated aryl substituents.¹⁷³ Aminomethylol synthons¹⁷⁴ or hexahydrotriazine derivatives were also used as aminoalkylating agents.^{174, 175} The latter compounds have repeatedly been used in the synthesis of AP. *N,N,N*-Tribenzylhexahydrotriazine is reversibly formed in the condensation of formaldehyde with *O*-benzylhydroxylamine and undergoes conversion to *O*-benzylformaldoxime on gentle heating, which reacts with P(III) chlorides in acidic medium to give the corresponding APA.¹⁷⁵



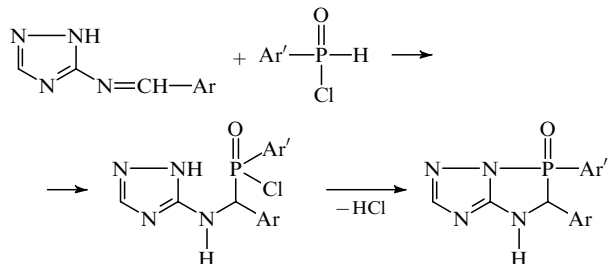
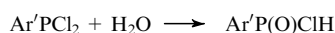
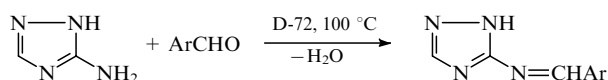
The mechanism of aminomethylation of P(III) chlorides is rather complex. It can be different in each particular case. For instance, in the system 'benzyl carbamate–aromatic aldehyde–phenyldichlorophosphine–acyl chloride',¹⁷⁶ the addition of the amide to the aldehyde occurs first, and then acylation of the resulting acylaminoalkanol produces compound **56**.



The reaction of the acylated carbamate **56** with the starting amide gives the diamide **57**. The acetic acid evolved converts phenyldichlorophosphine into phenylphosphinic chloride. The latter cleaves the N–C bond in diamide **57** and converts it into the final amidomethylphosphinic chloride **58**.



A similar reaction of aryldichlorophosphines, aromatic aldehydes and 5-amino-1,2,4-triazole occurs in the presence of cation-exchange resins (D-72, Amberlyst-15) and results in 6-phospha-4,5,6-trihydroimidazo[2,3-*e*]-1,2,4-triazole. It is believed¹⁷⁷ that the Schiff's base is formed first and then adds aryphosphinic chloride.



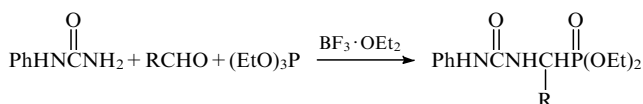
Intramolecular dehydrochlorination of the addition product results in the final bicycloamidophosphinate.

3. Reactions of neutral phosphites and their analogues

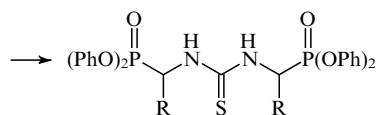
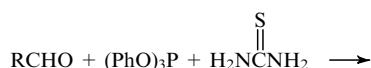
Reactions of natural α -amino acids with trialkyl and triaryl phosphites have long and successfully been used in peptide synthesis. As a rule, the non-classical Arbuzov reaction occurs in this case (see, *e.g.*, Ref. 178).

A three-component system 'phosphite–carbonyl compound–amine' was successfully used in a number of syntheses of AP derivatives of urea and thiourea.

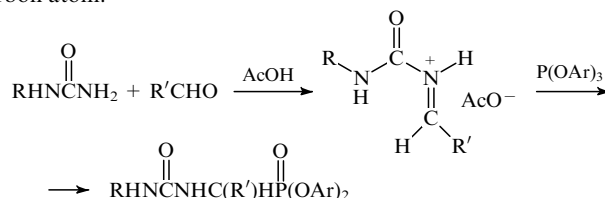
Triethyl phosphite undergoes condensation with an aldehyde and phenylurea in the presence of boron trifluoride etherate on refluxing in toluene to give the corresponding AP.¹⁷⁹



A similar reaction of a thiourea¹⁸⁰ and *N*-substituted thioureas¹⁸¹ occurs with triphenyl phosphite in the presence of glacial acetic acid. Under certain conditions, both amino groups of thiourea can be involved in this reaction.

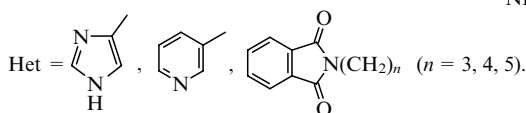
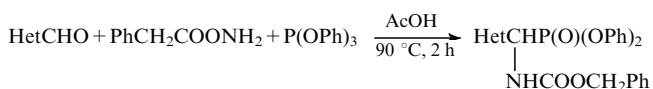


The stereochemistry of condensation of chiral carbamates and thioureas with benzaldehyde or aliphatic aldehydes and triaryl phosphites in the presence of acetic acid depends on the chirality of the starting amine: (+)-AP are obtained from chiral (+)-carbamates and ureas; accordingly, (–)-AP are formed from (–)-amides.¹⁸² The reaction occurs *via* an immonium salt with subsequent *syn*- or *anti*-attack of the phosphite on the iminium carbon atom.

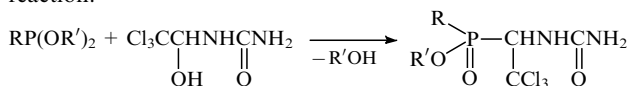


Ar = Ph, 2-MeC₆H₄.

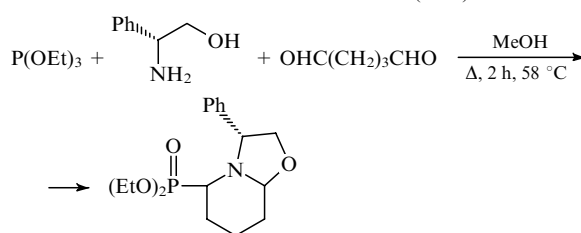
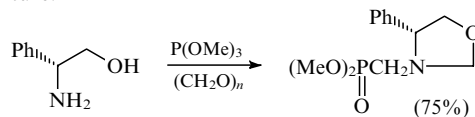
The 'triphenyl phosphite' version of the Kabachnik–Fields reaction was successfully used for the synthesis of C-hetaryl derivatives of AP.^{183–185}



The mechanism of these reactions has not been discussed in detail. However, in this case the reaction begins most probably with the interaction of the aldehyde with the amino component. The smooth reaction of phosphinites and phosphonites with chloralurea¹⁸⁶ can probably serve as a model of the second step of the 'trialkyl phosphite' version of the Kabachnik–Fields reaction.

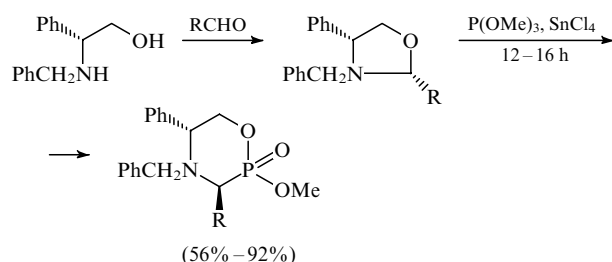


As in the classical version of the Kabachnik–Fields reaction, in this case it is possible under certain conditions to carry out cyclisation by the one-pot technique, for example, in the *N*-phosphonoalkylation of (*R*)-(–)-phenylglycinol;^{187, 188} in the latter case glutaraldehyde replaces formaldehyde in a three-component mixture.¹⁸⁸

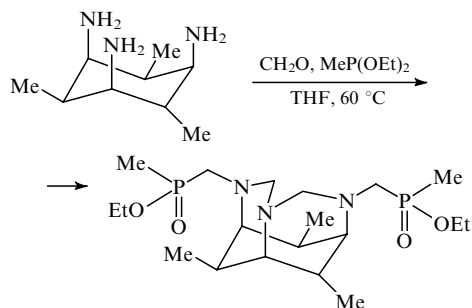


The reaction can also be carried out stepwise.¹⁸⁷ For example, *N*-benzylphenylglycinol reacts with an aldehyde to form oxazolidine with high diastereomeric excess. The latter reacts with

trimethyl phosphite in the presence of SnCl_4 to give an oxazaphosphorinane.



Polydentate ligands, *viz.*, bisphosphinate triaminocyclohexanes, were obtained by the ‘phosphonite’ version of the Kabachnik–Fields reaction with diethyl methylphosphonite and paraform.¹⁸⁹



It is possible to introduce two phosphorylmethylene groups into a 1,3,5-triamino-2,4,6-trimethylcyclohexane molecule due to the fact that all of its methyl groups occupy the equatorial positions, while all amino groups occupy the axial ones.

4. Reactions in two-component systems

As discussed above, reactions in two-component systems resulting in APA and their esters and involving interactions in the pairs hydrophosphoryl compound–imine and hydroxy phosphonate–amine are, in essence, separate steps of the Kabachnik–Fields reaction. It is often impossible to distinguish between three- and two-component systems. This can depend on the order of mixing the reactants.

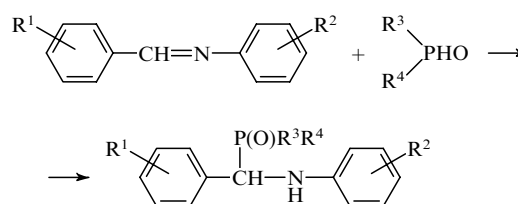
On the other hand, it has repeatedly been noted that it is often preferable to carry the reaction out in a stepwise way rather than to use a one-pot three-component process: the chemical yield and *de* of the AP are generally higher in two-component processes. The methods that have been developed most extensively recently include enantioselective addition of hydrophosphoryl compounds to imines and replacement of the hydroxy group in hydroxy phosphonates by the amino group under the Mitsunobu reaction conditions.¹⁹⁰ We shall give these processes the most attention in our review.

a. Addition of hydrophosphoryl compounds to imines

The addition of hydrophosphoryl compounds to imines, discovered simultaneously with the Kabachnik–Fields reaction, corresponds to the Pudovik reaction type²⁰ and has been covered rather comprehensively in reviews.^{6,10} Some examples of asymmetric synthesis of AP in the ‘imine’ version are discussed in another review.¹⁸ However, many new studies have been published in recent years which are to some extent relevant to the problem under discussion. Important data on the mechanism of the ‘imine’ method and the catalytic effects observed have been obtained.

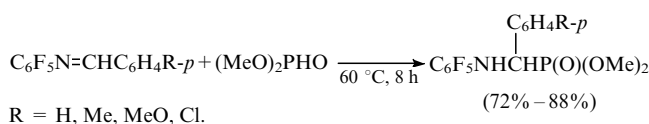
The ‘imine’ method should be preferred when choosing the strategy for the synthesis of AP if it is necessary, first, to reach the maximum diversity of functional groups at the N and C atoms in the target AP and, second, to enable conditions for the maximum stereoselectivity of addition of hydrophosphoryl compounds to the $\text{C}=\text{N}$ bond.

The reaction of hydrophosphoryl compounds with the Schiff’s bases studied in detail by Pudovik²⁰ continues to draw the attention of researchers due to the simplicity of the procedure and useful properties of the AP obtained in this way.



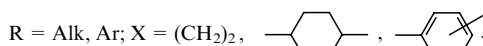
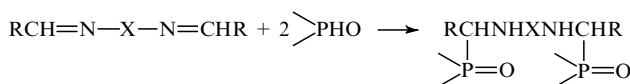
The reaction occurs in a condensed phase or in a solution in the presence of acidic and basic catalysts or without them at all, sometimes upon simple mixing of the reagents.^{191,192}

The reaction of hydrophosphoryl compounds with the Schiff’s bases containing fluorine atoms in the *N*- and/or *C*-aryl fragments ($\text{Ar} = 2\text{-}, 3\text{-}, 4\text{-FC}_6\text{H}_4$; $2\text{-}, 3\text{-}, 4\text{-F}_3\text{CC}_6\text{H}_4$; $2\text{-}, 4\text{-F}_3\text{CCOC}_6\text{H}_4$; $3,4\text{-F}_2\text{C}_6\text{H}_3$ and others)^{193–195} allows one to obtain biologically active fluorinated AP. The reaction occurs on heating of the starting reagents to 90–110 °C without a catalyst. *N*-Pentafluorophenylaldimines add dimethyl phosphite even more readily.¹⁹⁶



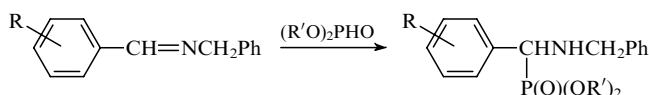
Aryl-substituted AP are formed as a mixture of diastereomers (chiral α -carbon atom). The presence of each of the stereoisomers is confirmed by analysis of ^1H and ^{13}C NMR spectra. In some cases, these diastereomers could be separated by column chromatography.

Bisamino phosphonates of various structures were synthesised by addition of hydrophosphoryl compounds to bisimines.^{192–195}



The NMR and mass spectroscopic, as well as other characteristics of bisamino phosphonates have been studied.^{197–199}

Numerous *N*-substituted AP derivatives, mainly *N*-benzyl ones, were obtained for use in peptide synthesis. The addition of hydrophosphoryl compounds to *N*-benzylbenzylideneimines occurs very readily. Lower dialkyl phosphites react at room temperature to give the corresponding AP in very high yields.^{36,200,201}

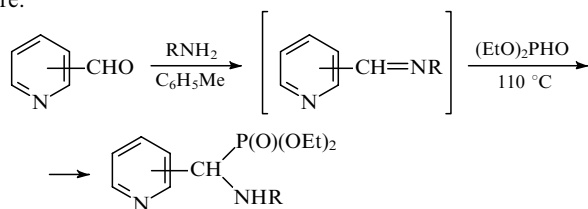


Longer reaction time and higher temperature are needed with the lengthening of the alkyl chain in the hydrophosphoryl compound (R'). For example, at $\text{R} = n\text{-C}_5\text{H}_{11}$, the reaction at 80 °C takes 8 h or longer. A similar effect is caused by replacement of the *C*-aryl group by C_6F_5 (however, there are exceptions: see Ref. 196).

N-Protected alkylideneimines,²⁰² perfluoroisopropylidene-*N*-acylimine,²⁰³ *N*-tritylmethylenimine,⁷⁵ and many other compounds (see the review¹⁸ and references cited therein) also add hydrophosphoryl compounds rather easily, usually on heating in the absence of catalysts, giving AP in high yields.

The ‘imine’ method is widely used in the synthesis of hetaryl derivatives of AP. In this case, the structures of heterocyclic

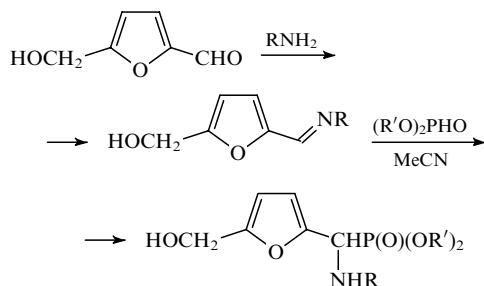
fragments can be varied widely. An array of *C*-pyridine derivatives have been obtained by addition of diethyl phosphite *in situ* to the appropriate Schiff's bases.²⁰⁴ 1-, 2- and 3-formylpyridines readily react with amines in a toluene solution, forming the corresponding aldimines, which are hydrophosphorylated in a one-pot procedure.



R = Bu, Ph, CH₂Ph, CHPh₂.

One-step syntheses of 1-(2-aminoethyl)pyridyl-1-arylmethylphosphonates²⁰⁵ and analogous APA monoesters were carried out in a similar way.²⁰⁶ It is noteworthy that the addition of dialkyl phosphites to the Schiff's bases containing a pyridine fragment under mild conditions (at room temperature, in the absence of catalysts) has been reported.²⁰⁷

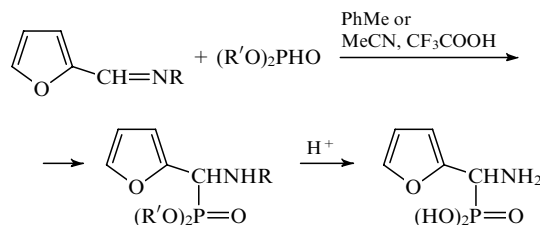
The results obtained in a study of the reaction of hydrophosphoryl compounds with imines containing furan and thiophene rings are also worth noting. 5-Hydroxymethylfurfural readily reacts with ethyl- and benzylamines to give the corresponding aldimines.



R = CH₂Ph, CH₂-furan, Bu^t, (*R*)- and (*S*)-CHMePh; R' = Et, CH₂Ph.

Subsequent addition of diethyl phosphite gives (in the case of chiral amines) a diastereomeric mixture of AP in 2:1 ratio.²⁰⁸ When pure enantiomeric amines are used, the resulting imines react with dibenzyl phosphite to give a mixture of AP, from which individual stereoisomers can be isolated by chromatography.

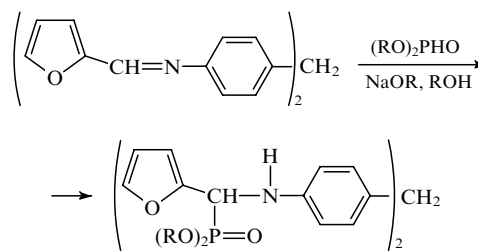
The same scheme was used for the synthesis of (2-furyl)aminomethylphosphonic acid.²⁰⁹



R = CH₂Ph, CPh₃; R' = Et, CH₂Ph.

N-Benzylated imines add hydrogen phosphites in toluene without catalyst or in acetonitrile with a catalytic amount of CF₃COOH. *N*-Tritylated imines give an AP just upon mixing the reagents. It was reported that an attempt at detritylation of an AP resulted in destruction of the AP with cleavage of the P–C bond. Similar fragmentation of AP has also been observed in other cases.^{203, 204, 210}

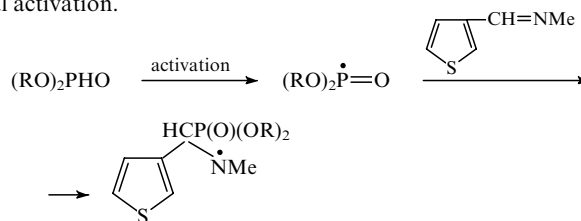
Bis(amino phosphonates) containing terminal 2-furyl groups were obtained and used as monomers for the synthesis of polymeric materials with low flammability.^{211, 212}



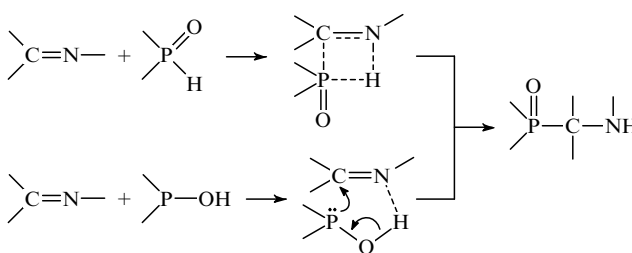
The addition of the hydrophosphoryl compound occurs at room temperature in the presence of catalytic amounts of sodium alkoxide.

Important observations related to the activation of addition of dialkyl phosphites to hetarylimines with an *N*-thiophene or *N*-pyrrole fragment were obtained.^{213, 214} The addition of a hydrophosphoryl compound can occur on prolonged heating (72–96 h) of a mixture of the reactants at 60 °C. The process is accompanied by formation of side products. Attempts to optimise conditions of the synthesis of AP by carrying out the reaction in various solvents failed in general: this only increased the time of conversion.

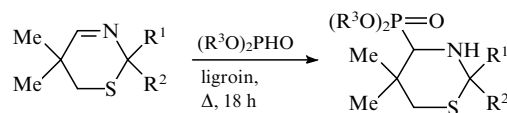
On the other hand, sonochemical (ultrasonic) activation of the addition reaction was found to be rather efficient. Both in a condensed phase and in a solution, even short sonication increases abruptly the temperature of the reaction mixture, hence the yield of AP increases and the reaction time is decreased to 5–120 min. This phenomenon was explained²¹³ using EPR spectroscopy with a spin trap: phosphinyl radicals were detected during sonochemical activation.



The uninitiated reaction occurs by a concerted mechanism with a four- or five-centred transition state. This mechanism agrees with the stereochemical result of addition to furfuraldimine.²⁰⁸



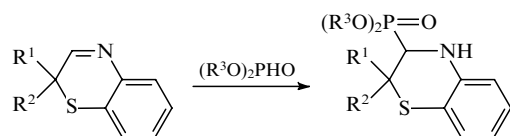
A method for the introduction of heterocyclic fragments into an AP molecule by addition of a hydrophosphoryl compound to the endocyclic C=N bond in unsaturated five- and six-membered cyclic imines was developed. In these cases, the amino phosphonate fragment C–N is included in the heterocycle. Chiral 2*H*-5,6-dihydro-1,3-thiazines react with dialkyl phosphites to give diastereomeric AP in a ratio from 52:48 to 88:12, depending on the substituents in the imine and in the phosphite.²¹⁵



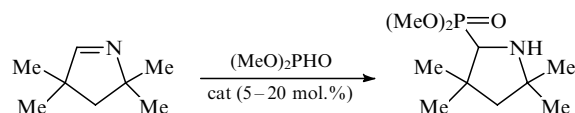
R¹ = H, Me, Et; R² = Me, Et, Bu^t, CMe₂CH₂Cl;

R¹, R² = (CH₂)₄, (CH₂)₅; R³ = Me, Et.

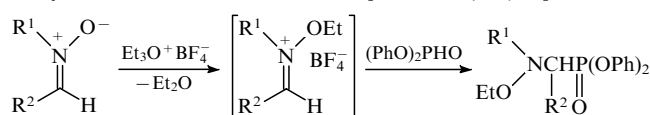
The addition of hydrophosphoryl compounds to 2*H*-1,4-benzothiazines and 2*H*-1,3-oxazolidines occurs under the same conditions.¹⁰⁰



Hydrophosphorylation of cyclic imines catalysed by chiral lanthanide catalysts results in a high *de* (up to 98%).²¹⁶ In the presence of chiral titanium catalyst, the reaction is nonstereospecific. The mechanism of asymmetric induction of cyclic imines has not been discussed.

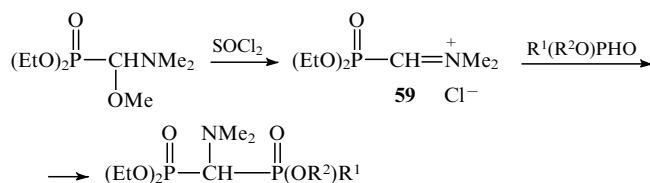


Hydrophosphorylation of oximinium salts, which is a version of the ‘imine’ method for AP synthesis, has been performed in only a few cases. In our opinion, this is rather a promising method. The addition of diphenyl phosphite to the C=N⁺ bond of a nitron is carried out in the presence of an alkylating agent, *viz.*, triethyloxonium tetrafluoroborate, at room temperature in 3 h.²¹⁷ The processes is nonstereospecific; however, rather high enantioselectivity is observed for chiral nitrones [R¹ = CH(Me)Ph].



R¹ = Me, CH(Me)Ph; R² = Ph, MeOC₆H₄; R¹, R² = (CH₂)₃.

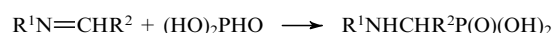
The addition of alkyl phosphinites to phosphonyliminium salt **59** also occurs nonstereospecifically.²¹⁸ In this case, two chiral centres are induced in the AP, *viz.*, the α-carbon atom and the phosphinate phosphorus atom.



R¹ = Me, Ph; R² = Et, Bu.

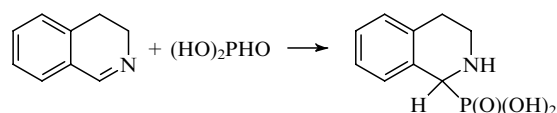
Broad diversity of possibilities for the synthesis of AP by the ‘imine’ pathway is due to the variability of the substituents not only in the imine but also in the phosphorus-containing addend. Inorganic phosphorus acids and various silylated organophosphorus compounds have been used for the synthesis of APA.

It has already been noted¹⁶² that attempts to use phosphorous acid in the classical three-component version of the Kabachnik–Fields reaction was not always successful. The ‘imine’ method turned out to be more efficient.¹⁶²

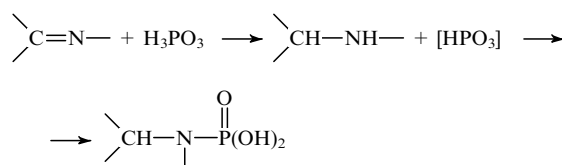


R¹ = Me, Et, Bu^t, PhCH₂; R² = Prⁱ, Ph, 4-ClC₆H₄, 2-HOC₆H₄.

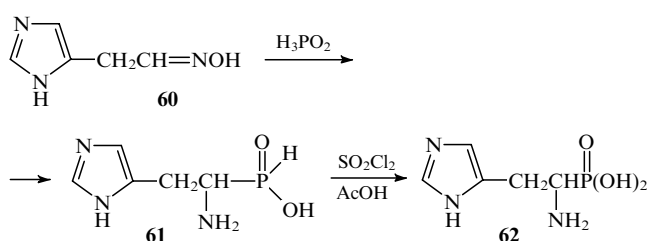
The addition to the intracyclic bond of 3,4-dihydroisoquinoline, resulting in 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid, occurs successfully.¹⁶² It is believed that the reaction occurs in an autocatalytic mode with preliminary protonation of the nitrogen atom.



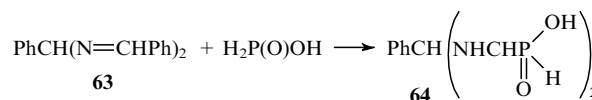
Under certain conditions, phosphorous acid can be a reducing agent with respect to an imine. In this case, it is not the AP that is formed as the final product but rather an isomeric amido phosphate, which is believed¹⁶² to result from the reaction of the intermediate amine with metaphosphoric acid.



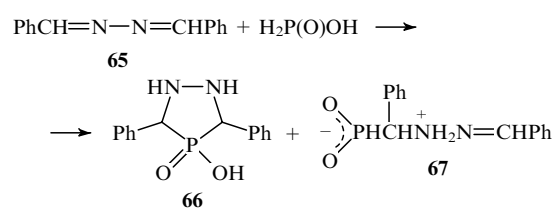
The phosphorus analogue of histidine **62** was obtained by the addition of hypophosphorous acid to the oxime **60**. The phosphinic acid **61** obtained in 19% yield was transformed in an almost quantitative yield into the target product **62** by oxidation with sulfonyl chloride in glacial acetic acid.²¹⁹



The addition of inorganic phosphorus acids to both C=N bonds of bisimines was carried out. The reaction of geminal diimine **63** with hypophosphorous acid²²⁰ gives, contrary to expectations, bisphosphinic acid **64** rather than a cyclic phosphonic acid.



A similar reaction of diimine **65**, which is carried out by prolonged storage of the reaction mixture (20 °C, 20–25 days), gives a five-membered cyclic phosphinic acid **66**²²¹ and a linear product **67** formed due to addition to one of the C=N bonds.

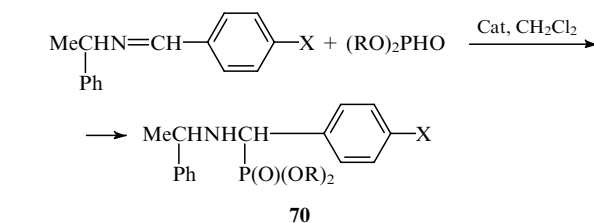


It is of note that the ratio of products **66**:**67** in a crystalline state is 1:4, whereas their ratio is 1:1 in dioxane solution, according to ³¹P NMR data.²²¹ The possibility of mutual transformation of compounds **66** and **67** during dissolution and isolation from the solution cannot be ruled out.

Silyl ethers of phosphorus acids of low oxidation states behave in reactions with imines similarly to phosphorous acid, its esters and other hydrophosphoryl compounds. For example, tris(silyl) phosphite in the presence of Lewis acids (ZnCl₂, BF₃·OEt₂) or strong protic acids (CF₃COOH, *p*-MeC₆H₄SO₃H) forms a product of phosphonosilylation of imines.²²² On refluxing in methanol, desilylation of the adduct occurs, resulting in the corresponding APA isolated as a hydrochloride.

For example, the substituents in the benzene ring weakly affect both the chemical yield and the *de* in the reaction of imines obtained from 1-phenylethylamine and *para*-substituted benzaldehydes with dialkyl phosphites²³⁴ (Scheme 5).

Scheme 5



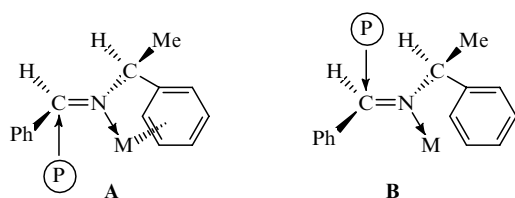
X	H	Me	OMe	Cl	Br	F
Yield of 70 (%)	80	84	72	79	77	80
<i>de</i> (%)	61	54	60	56	54	56

R	Me	Et	Pr ⁱ	Bu ⁿ	Bu ⁱ	Ph
Yield of 70 (%)	85	85	61	74	72	78
<i>de</i> (%)	43	61	83	68	71	80

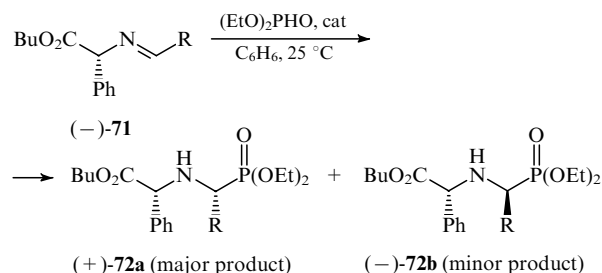
Catalyst	AlCl_3	$\text{BF}_3 \cdot \text{OEt}_2$	ZnCl_2	TsOH	—
Yield of 70 (%)	77	80	75	72	65
<i>de</i> (%)	70	61	−30	−50	−16

The increase in the volume of substituents at the phosphorus atom decreases the chemical yield but increases the *de*. The yield and *de* are considerably affected by catalysts used for this purpose, such as Lewis acids. A negative *de* upon changing the catalyst means the predominance of the other enantiomer, *i.e.*, the change in the direction of stereoinduction.

In the general case, a pronounced effect of catalysis is observed: the degree of conversion increases in comparison with non-catalysed addition. However, a catalyst basically affects the ease of the reaction. A catalysed process occurs at room temperature, while a non-catalysed one requires heating of the reaction mixture to 140 °C. The different effect of AlCl_3 and BF_3 on *de*, on the one hand, and ZnCl_2 and TsOH , on the other, is explained²³⁴ by the different character of the donor-acceptor interaction between the imine and the catalyst. Whereas Lewis acids form A-type chelate complexes due to the transfer of *n*- and π -electron density to the vacant orbitals of the central atom with *s-cis*-arrangement of the C=N fragment and aryl substituent, ZnCl_2 and TsOH interact only with the imine nitrogen atom, causing a P-nucleophile to attack an imine in conformation B.



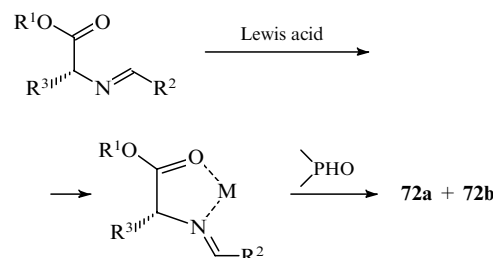
The effect of catalysts⁷² and of the way of the phosphite anion generation²³⁵ on the stereochemistry of the hydrophosphorylation of imines containing a complementary functional group that can provide chelation has been studied in detail. The imine **71** adds diethyl phosphite without a catalyst in 120 h. In the presence of Lewis acids or CF_3COOH , the reaction occurs faster. In all cases, a mixture of diastereomers **72a** and **72b** with low *de* is formed.



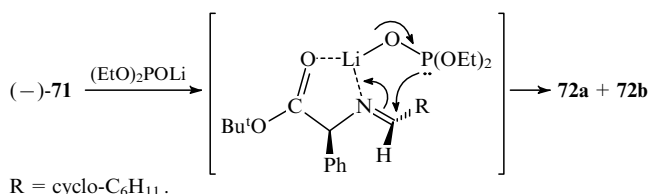
R = cyclo- C_6H_{11} .

Catalyst	Time /h	Yield (%)	<i>de</i> (%)
—	> 120	87	38
ZnCl_2	7	84	48
MgCl_2	> 48	40	38
CF_3COOH	> 48	48	14

It is believed that the stereocontrolling role of Lewis acids consists in the formation of chelates. However, this effect appears to be insufficient to ensure high diastereoselectivity of the hydrophosphorylation step.



At the same time, high diastereoselectivity is reached if lithium diethyl phosphite is used.

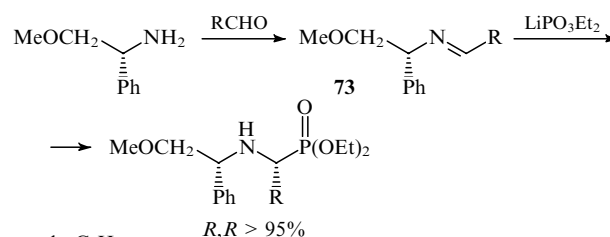


R = cyclo- C_6H_{11} .

Conditions	Yield (%)	<i>de</i> (%)
$(\text{EtO})_2\text{PHO}$, Bu^iOLi , CH_2Cl_2 , −70 to 25 °C	38	94
$(\text{EtO})_2\text{PHO}$, BuLi , THF, −78 to 25 °C	75–80	94–96

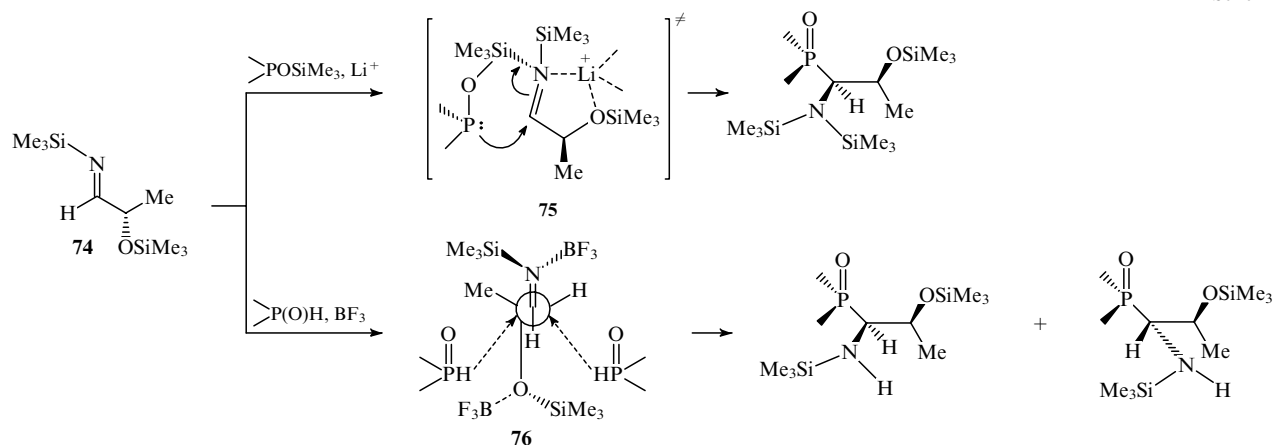
The chelate structure of the intermediate with *trans*-arrangement of the nucleophile and the stereo-controlling phenyl group is responsible for this impressive stereochemical result. The yield of the adduct depends on the reaction conditions and the method of generation of the phosphite anion. The best result was achieved using butyllithium as the base.

The stereochemically individual imine **73** obtained by the condensation of the appropriate amine with cyclohexanecarbaldehyde adds lithium diethyl phosphite to give the *R,R*-isomer of an *N*-protected AP with *de* > 95%.²³⁶

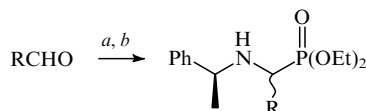


R = cyclo- C_6H_{11} .

Scheme 6



The reaction of the same aldehyde with diethyl phosphite and (*S*)- α -phenylethylamine is less stereospecific: a mixture of diastereomeric AP (ratio *S,S*:*S,S* = 5:1) is formed (see Ref. 236).

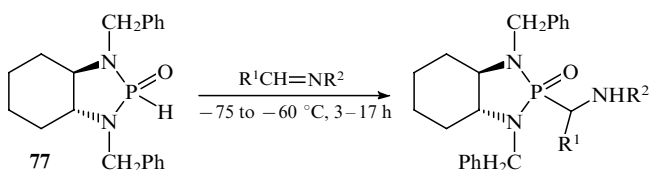


R = cyclo- C_6H_{11} ;

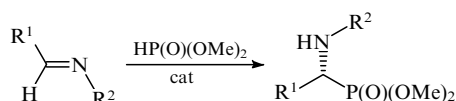
(a) (*S*)- $\text{PhCH}(\text{Me})\text{NH}_2$, MeOH; (b) 3 HP(O)(OEt)_2 , 3 days, 25 °C.

High stereospecificity of reactions was achieved by addition of phosphites to bis-silylated imine **74** in the presence of lithium ions (Scheme 6).²³⁷ Enantiofacial preference of attack on the imine carbon by the P(III) atom is due to the formation of a highly-organised cyclic transition state **75** due to chelation by a Li^+ ion. The addition of dialkyl phosphites to the imine **74** catalysed by BF_3 is not accompanied by formation of a cyclic transition state and/or intermediate. In this case, the attack by a phosphite in acyclic complex **76** can occur on the two sides with equal probability. This causes the formation of a diastereomeric mixture of products.

The absence of stereoselectivity was also noted in the case of boron trifluoride-catalysed addition of chiral cyclic diamidophosphite **77** to imines.²³⁸ The reaction occurs under very mild conditions; it is also possible to use TiCl_4 as the catalyst, while SnCl_4 chlorinates the cyclophosphite to the corresponding chlorophosphate.



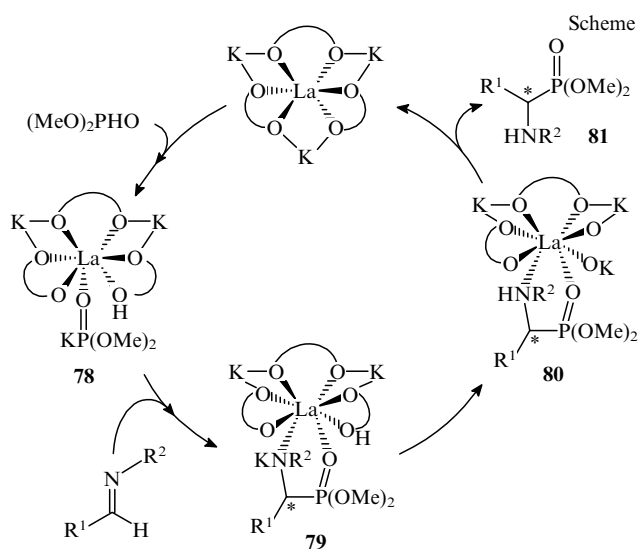
Catalytic asymmetric synthesis of AP with the use of a wide range of imines and dimethyl phosphite was carried out in the presence of an asymmetric lanthanide-based catalyst.³³



$\text{R}^1 = \text{Me}, \text{Et}, \text{Pr}^i, \text{PhCHMe}, n\text{-C}_5\text{H}_{11}, \text{cyclo-C}_6\text{H}_{11}$;

$\text{R}^2 = \text{Tr}, \text{CHPh}_2, 4\text{-MeOC}_6\text{H}_4$.

The reaction occurs with excess of a hydrophosphoryl compound in THF at room temperature or on gentle heating (50–60 °C). A chelate heterobimetallic complex involving a lanthanide, the chelating ligand BINOL³³ and potassium ions (potassium carbonate) is used as the catalyst. The catalytic cycle is presented in Scheme 7.



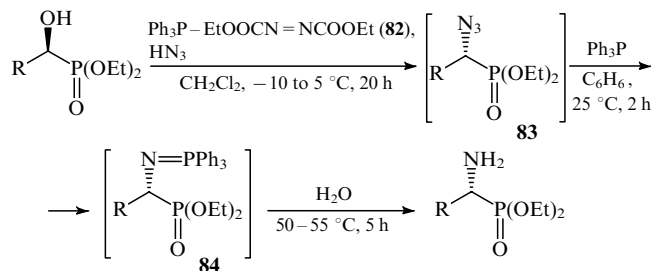
The first step of the process is deprotonation of the phosphite and generation of potassium dimethyl phosphite, which is coordinated by the lanthanide with formation of the complex **78**; the latter reacts with the imine to give the optically active K salt of AP **79**. Replacement of the K^+ ion by a proton at the amine centre results in the complex **80**. In the final step, the product of catalytic asymmetric synthesis **81** is liberated from the coordination sphere. In this process, the lanthanum complex acts as a polyfunctional asymmetric catalyst of AP synthesis with high *de* (96%). A drawback of the method is the rather small number of catalytic cycles. This is probably due to the too high acceptor ability of the lanthanum complex with respect to AP.

b. Reaction of hydroxy phosphonates with amines

As noted above, the reaction of hydroxy phosphonates with amines is a model of the 'hydroxy phosphonate' pathway of the Kabachnik–Fields reaction. It has been studied in much more detail than the alternative 'imine' route, *i.e.*, hydrophosphorylation of imines. Relatively little convincing evidence has been obtained that the Kabachnik–Fields reaction occurs through the step of formation of α -hydroxyalkylphosphoryl intermediates. Moreover, as already mentioned, in certain cases the formation of hydroxy phosphonates is undesired for successful use of the Kabachnik–Fields reaction for preparative purposes.

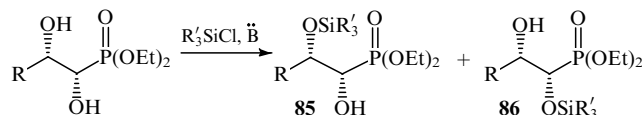
Nevertheless, there are many examples of transformation of hydroxyalkylphosphoryl synthons to the corresponding aminoalkylphosphoryl products by the reaction of hydroxy phosphonates with amines (see Refs 13 and 122 and references cited therein). In recent years, conditions for carrying out this process in a preparative and stereocontrolled way have been found.

The condensation under the action of the azodicarboxylate–triorganylphosphine system (the Mitsunobu reaction¹⁹⁰) has found use for replacement of the hydroxy group by the amino group in a one-pot procedure.^{239–242} Hydroxy phosphonates and phosphine oxides obtained by the Abramov reaction from the appropriate hydrophosphoryl and carbonyl compounds by treatment with the Mitsunobu reagent **82** and HN₃ are converted with inversion of the configuration to α -azido phosphonate **83**. The reaction of triphenylphosphine with phosphonate **83** by the Staudinger reaction results in phosphimine intermediate **84**. The latter is hydrolysed to the target AP.

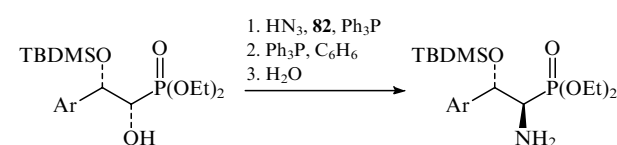


In the one-pot procedure, the intermediate azide and phosphimine are not isolated. Since the Mitsunobu reaction with secondary alcohols, including the above hydroxy phosphonates, occurs stereospecifically by the S_N2 mechanism, the formation of the azido phosphate involves inversion of configuration of the α -carbon atom. Subsequent phosphimination and hydrolysis do not involve this centre.

The Mitsunobu reaction described here, which enables conversion of hydroxy phosphonates to the corresponding azides, has been used²⁴³ for the stereoselective conversion of monosilylated α,β -dihydroxy phosphonates. Optically active silyloxy phosphonates result from the reaction of *threo*- α,β -dihydroxy phosphonates with chlorosilane in the presence of bases.

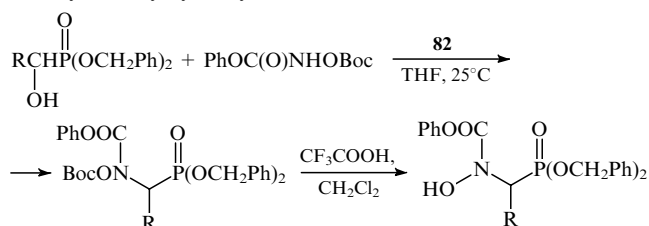


Depending on the nature of the substituents R and R' and the base used, the ratio of β - and α -silylated products **85** : **86** is from 1 : 1 to 99 : 1. Most often, the regioisomer **85** predominates ($>90\%$). Its amination²³⁹ involves exclusively the carbon atom carrying the hydroxy rather than the silyloxy group and is accompanied by inversion of configuration.



$Ar = 4-MeOC_6H_4$, TBDMS = Bu^tMe_2Si .

The Mitsunobu reaction is used in the synthesis of potential haptens, *viz.*, *N*-hydroxy- α -amino phosphonates, for the condensation of hydroxy phosphonates with *N*-phenoxycarbonyl-*O*-*tert*-butoxycarbonylhydroxylamine.²⁴⁴



As a rule, the reaction goes only in one direction, *viz.*, with the formation of AP (40%–75%). α -Hydroxy-2-phenylethylphosphonate is an exception, it undergoes intramolecular (rather

than intermolecular) dehydration to give 62% of styrylphosphonate $PhCH=CHP(O)(OCH_2Ph)_2$.

V. Conclusion

Despite the impressive progress in the synthesis and studies of properties of AP, not all the problems have been solved. The problem of stereocontrol in the 'imine' method for the synthesis of AP is still urgent, to say nothing about the enantioselective synthesis using a three-component system in the one-pot version. It is easy to predict that the basic efforts in studying the AP chemistry will be concentrated in this direction, and the Kabachnik–Fields reaction is promising for solving these problems.

The prospects of chemical modification of AP with introduction of new, more and more complex groups, including those with definite configurations, to C-, N- and especially P-centres are far from exhausted.

This aspect of AP chemistry is closely related to the problem of the effect of phosphorus-containing groups on the adjacent reaction centre.^{96,97} The attention to α -functionalised organophosphorus compounds has increased abruptly in recent years. This is evident, for example, from recent publications on the chemistry of α -phosphorylated alcohols (α -hydroxy phosphonates),^{97,245} α -halogeno phosphonates,²⁴⁶ α -oxo phosphonates,²⁴⁷ and α -phosphonoalkyl phosphites.²⁴⁸ Reactions that occur at the α -carbon centre and formally do not involve the phosphorus atom are still largely controlled by the phosphorus-containing fragment. It not only determines the type and rate of the reaction but also, in some cases, changes the reaction rate by a few orders (see, for example, Ref. 249) and even changes the reaction mechanism.⁹⁷ A large number of studies deal with the problem of the quantitative estimation of the effect of phosphorus-containing groups (see Refs 250–252 and references cited therein). This problem still remains the focus of attention of experts in quantitative organic and organometallic chemistry.²⁵³ The quantitative estimation of the dependence of the reaction pathway both of AP and components of the Kabachnik–Fields reaction on the structure is an important problem which is waiting for solution.

One may believe that the area of the application of AP will be much expanded. In addition to the search for new biologically active compounds of high efficiency among APA, their derivatives and analogues, an abrupt growth of interest should be expected to the prospects of practical application related to their complex-forming properties. These applications may primarily include the use of AP as recognising agents (synthetic receptors) and chiral ligands in metal complexes, as well as selective highly-efficient complexones, extraction agents and analytical reagents.

Analysis of the data presented above allows one to consider the discussed area of chemistry as not only rather topical but also having wide prospects in the future.

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Physicochemical properties of technetium acido clusters

S V Kryutchkov

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Abstract. The review is concerned with the electronic and molecular structure and physicochemical properties of all types of technetium clusters with acido ligands described to date. As a typical cluster-forming metal, technetium possesses a number of specific, anomalous cluster-forming properties that can be interpreted in terms of greater capability of outer diffuse $5s(5p)$ AOs to participate in the formation of additional M–M bonds in technetium acido clusters as compared to analogous clusters of other transition d -elements. Theoretical interpretation of the electronic and molecular structure and properties of technetium clusters has been confirmed by experimental data (X-ray analysis, magnetochemistry, and EPR, optical, X-ray photoelectron and X-ray emission spectroscopy). The experimentally observed increased stability of technetium clusters with odd numbers of ‘metallic’ electrons and a decrease in the effective charge on Tc atoms upon formation of the M–M bonds are discussed. Recently found ‘anomalous’ properties of technetium and rhenium compounds with ferrocenium cations (in particular, unusual low-temperature electron emission on X-ray irradiation) are also considered. The bibliography includes 101 references.

I. Introduction

Compounds with metal–metal bonds (clusters) were first isolated and structurally characterised early in the 1960s. Several thousands of clusters are known to date.¹ Among all compounds of transition elements belonging to this type, only about 80 technetium-containing clusters with acido ligands have been described.² This is mainly due to difficulties encountered in the synthesis of complexes of radioactive elements. However, a great interest has been expressed in such technetium clusters, because they possess a set of ‘anomalous’ structural and other physicochemical properties.³ In the present review, generalisation of experimental data on the known technetium acido clusters[†] has been made with primary emphasis on studies of physicochemical characteristics of these compounds (optical spectra in the visible, UV, and IR

regions, magnetochemistry, X-ray emission spectra, X-ray photoelectron spectra, ^{57}Fe Mössbauer spectra, electric conductivity and other properties) and comparison with those of mononuclear technetium complexes. All fundamental physicochemical properties of technetium acido clusters insufficiently covered in previous reviews^{1–3} are considered in particularly great detail.

All technetium acido clusters known to date have been systematised according to their electronic and molecular structure and to the method of their synthesis.² The nuclearity of the cluster, *i.e.*, the number of metal atoms forming direct metal–metal (M–M) bonds in the metal core of a cluster, is the basis of classification. In accordance with this principle, all technetium clusters are subdivided into di- and polynuclear clusters. Further classification is based on the electronic structure of the M–M bonds in the metal core of clusters and their molecular structure (*e.g.*, dinuclear d^4-d^4 clusters of the ‘lantern’ structural type or trigonal-prismatic hexanuclear clusters with metal–metal bonds of high order). The main structural types of technetium clusters are shown schematically in Fig. 1. The most important physicochemical properties of these clusters will be considered below.

II. Optical spectra of technetium clusters in the visible, UV, and IR spectral regions

1. Electronic spectra

No information on systematic studies of the optical spectra of technetium clusters has been reported to date. At best, spectral parameters of particular compounds were reported, and their qualitative assignment was made by analogy, *e.g.*, with rhenium compounds.^{4–7} This is first of all due to difficulties in recording and interpreting the spectra, since this requires rigorous quantum-chemical calculations and precise spectroscopic measurements on single crystals in polarised light. The most precise spectroscopic studies have been carried out only for two clusters, *viz.*, $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ ⁸ for which scattered-wave self-consistent field (SCF– X_{α} –SW) quantum-chemical calculations⁹ have been performed, and for $[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$ (where 2-PyO is the 2-hydroxypyridine alcoholate)¹⁰ for which it has been possible to obtain suitable single crystals with all molecules oriented along the z axis of the tetragonal unit cell. The results of these studies have been described in detail;¹ therefore, it is hardly reasonable to repeat

S V Kryutchkov Institute of Physical Chemistry, Russian Academy of Sciences, Leninskii prosp. 31, 117915 Moscow, Russian Federation.
Fax (7-095) 335 17 78. Tel. (7-095) 335 20 04

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[†] Here, we are dealing with compounds with metal–metal chemical bonds and weak crystal field ligands that are anions of mineral acids: Cl^- , Br^- , I^- , SO_4^{2-} , *etc.*

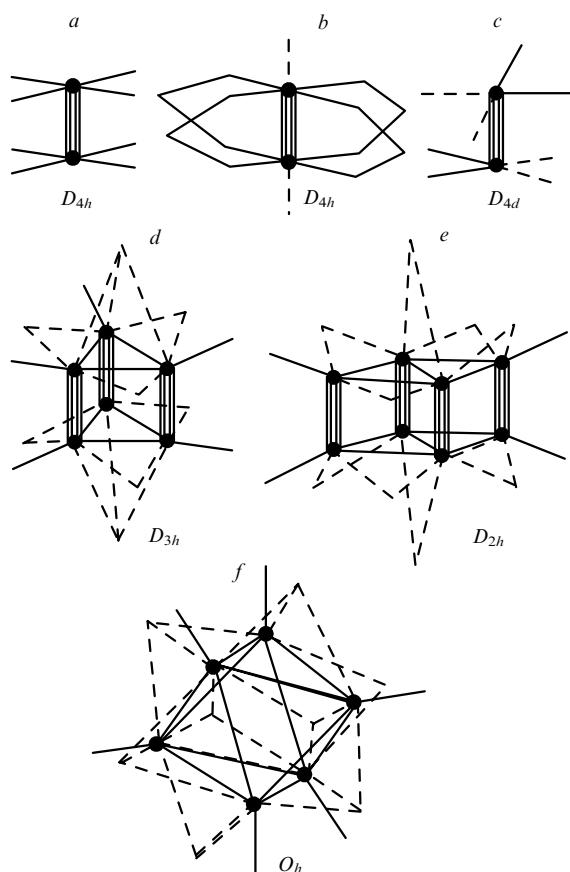


Figure 1. The main structural types of technetium acid clusters:² (a) $[\text{Tc}_2\text{X}_8]^{n-}$ ($\text{X} = \text{Cl}, \text{Br}; n = 2, 3$); (b) $\{[\text{Tc}_2\text{L}_4\text{X}_m]^{n-}$ ($\text{L} = \text{SO}_4^{2-}, \text{AcO}^-, \text{Bu}^t\text{COO}^-, 2\text{-PyO}^-; \text{X} = \text{Cl}, \text{Br}, \text{H}_2\text{O}, m = 1, 2; n = 0, 1, 2$); (c) $[\text{Tc}_2\text{X}_6]^{2-}$ ($\text{X} = \text{Cl}, \text{Br}$); (d) $[\text{Tc}_6(\mu\text{-X}_6)\text{X}_6]^{n-}$ ($\text{X} = \text{Cl}, \text{Br}; n = 0, 1, 2$); (e) $[\text{Tc}_8(\mu\text{-X}_8)\text{X}_4]^{n-}$ ($\text{X} = \text{Br}; n = 0, 1$); and (f) $[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]^{2-}$. The positions of bridging or axial ligands are shown by dashed lines.

them in this review. We consider in brief only the most important conclusions drawn in these studies.

The optical spectra of the cluster $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ in the region of the $\delta\text{-}\delta^*$ transition have been recorded at 300 and 3.7 K.⁸ They belong to the lowest-energy electronic spectra. Fine structure associated with vibronic interaction and caused by progression in the $\nu'(\text{M-M})$ frequency (320 cm^{-1} for the electronically excited state), i.e., $\nu', 2\nu', 3\nu', \text{etc.}$, is observed in these spectra. Since the M-M bond in the excited state is weaker than that in the ground state, the frequency ν' is about 50 cm^{-1} lower than the frequency of the ground electronic state $\nu(\text{M-M})$. It should be noted that the $\nu(\text{M-M})$ frequency is observed in the Raman spectra and is symmetry-forbidden in the IR spectra. The spectra of the $[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$ single crystal at 5 K in the region of the $\delta\text{-}\delta^*$ transition as well as in other regions appear to be much more complicated, since not only a progression based on the $\nu'(\text{M-M})$ frequency (339 cm^{-1}), but also vibrations of the Tc-O and Tc-N bonds with frequencies ν'_2 and ν'_3 (264 and 298 cm^{-1} , respectively) are observed.¹⁰ Thus, the O-O band is followed by peaks corresponding to the ν'_1, ν'_2 and ν'_3 frequencies. Moreover, not only the expected extension of progressions to all possible overtones of frequencies ν'_1 and ν'_2 , but also progressions based on combination frequencies are observed in the spectra. Thus, Cotton *et al.*¹⁰ have identified vibrations with frequencies $5\nu'_2, 4\nu'_2 + \nu'_1, 3\nu'_2 + \nu'_1, 2\nu'_2 + 3\nu'_1, 2\nu'_2 + 4\nu'_1$, and $5\nu'_1$ in the fifth group of peaks (see also Ref. 8).

Electronic absorption spectra of solutions of potassium octachloroditechnetate in hydrochloric acid in the UV and visible regions have been studied,^{4,11} and the results (the dependence of the extinction coefficients ϵ_{max} on the HCl concentration) are

listed in Table 1. As can be seen, the HCl concentration affects strongly the positions of the lines and the extinction coefficient in spectra of octachloroditechnetate ions, which is due to additional complexation and hydrolysis (see below).

Table 1. Dependence of the extinction coefficients of $[\text{Tc}_2\text{Cl}_6]^{3-}$ on the HCl concentration.^{4,11}

$[\text{HCl}]$ / mol litre ⁻¹	λ_{max} / nm	$10^3 \epsilon_{\text{max}}$ / litre mol ⁻¹ cm ⁻¹	λ_{max} / nm	$10^3 \epsilon_{\text{max}}$ / litre mol ⁻¹ cm ⁻¹
11.4	647	0.33	322	3.6
10.2	643	0.32	320	3.5
7.6	640	0.29	320	3.6
6.5	638	0.29	320	3.0
5.9	635	0.26	318	2.7
4.8	630	0.25	318	2.5
3.0	618	0.19	315	2.2

Table 2 presents the assignment of bands in the spectra of $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ and $[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$.^{8,10} An appreciably larger splitting between δ and δ^* MOs due to shortening of the Tc-Tc bonds in the oxopyridine complex is the major feature of the electronic spectra of these compounds.

Table 2. Electronic spectra of $[\text{Tc}_2\text{Cl}_8]^{3-}$ and $[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$ and the band assignment.^{1,8,10}

$[\text{Tc}_2\text{Cl}_8]^{3-}$			$[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$		Transition
$10^3 \nu_{\text{max}}$ / cm ⁻¹	ϵ_{max}^a	$10^3 E_{\text{calc}}$ / cm ⁻¹	$10^3 \nu_{\text{max}}$ / cm ⁻¹	I_{rel}	
<u>5.9</u>	630	6.0	13.0	m	$\delta\text{-}\delta^*$
<u>13.6</u>	35	15.8	18.0	vw, br	$\pi\text{-}\delta^*$
<u>15.7</u>	172	15.8	17.0	w, br	$\delta^*\text{-}\pi^*$
<u>20.0</u>	10	17.7	—	—	$\delta^*\text{-}d_{x^2-y^2}$
		20.2			$\delta^*\text{-}\sigma^*$
		21.3			$\delta\text{-}\pi^*$
		23.0			$\delta\text{-}d_{x^2-y^2}$
<u>31.4</u>	3900	28.3	25.0	s	LMCT
		29.1			LMCT
		31.2			$\pi\text{-}\pi^*$
		32.5			$\pi\text{-}d_{x^2-y^2}$
<u>37.2</u>	5600	~42	—	—	LMCT
		~41			LMCT
		~44			LMCT

Note. E_{calc} is the calculated transition energy, I_{rel} is the relative intensity, and LMCT denotes the bands with ligand to metal charge transfer. The bands with electric dipole transitions are underlined.

^a Measured in litre mol⁻¹ cm⁻¹.

Selected parameters of the electronic absorption spectra of technetium clusters are listed in Table 3. These data are far from being complete and thus can be used mainly for qualitative analysis. It is likely that the only exception is the $\pi\text{-}\delta^*$ transition ($\lambda_{\text{max}} \approx 600\text{--}700\text{ nm}$) that can be identified for all $d^4\text{-}d^5$ complexes by analogy with the $[\text{Tc}_2\text{Cl}_8]^{3-}$ ions. The absorption bands of this optical transition correlate well with the quantity $10Dq^4$ characterising the strength of the crystal field of the ligand environment in the dinuclear complexes in question. It should be noted that an analogous tendency is also observed for most of other bands.

The electronic spectra of polynuclear technetium clusters are characterised by the absence of clearly defined absorption bands and by a monotonic increase in the optical density with increase

Table 3. Electronic absorption spectra of technetium clusters.

Cluster	$\lambda_{\max}$ / nm ($\epsilon_{\max}^a$ or I_{rel})	Note	Ref.
$[\text{Tc}_2(\mu\text{-O})_2(\text{H}_2\text{EDTA})_2]$	~ 500 (2000), ~ 600 (<200)	aqueous solution	14
$[\text{Tc}_2(\mu\text{-O})_2(\text{H}_2\text{EDTA})_2]^-$	~ 610 (s)	ditto	14
$[\text{Tc}_2(\mu\text{-O})_2(\text{TCTA})_2]^{2-}$	~ 510 (s)	"	14
$[\text{Tc}_2(\mu\text{-O})_2(\text{TCTA})_2]^{3-}$	592 (s)	"	14
$[\text{Tc}_2\text{Cl}_8]^{2-}$	~ 680 (w), 391 (m), 303 (m), 238 (s)	TBA salt in CsCl pellet at 10 K	5
$[\text{Tc}_2\text{Cl}_8]^{3-}$	676 (w), 388 (w, sh) 337 (m), 308 (w, sh)	ditto	5
$[\text{Tc}_2\text{I}_8]^{3-}$	760 (~ 250)	solution in HI (conc.)	4
$[\text{Tc}_2\text{Br}_8]^{3-}$	690 (400)	solution in HBr (conc.)	15
$[\text{Tc}_2(\text{AcO})_4\text{Cl}_2]^{2-}$	620 (~ 200)	solution in AcOH	4
$[\text{Tc}_2(\text{SO}_4)_4]^{2-}$	700 (~ 300)	solution in H_2SO_4	16
$[\text{Tc}_2\text{Cl}_6]^{2-}$	460 (~ 600)	solution in HCl	4
$[\text{Tc}_2\text{Br}_6]^{2-}$	~ 480 (~ 600)	solution in HBr	4

Note. TBA is tetra-*n*-butylammonium, EDTA is ethylenediaminetetraacetate and TCTA is 1,4,7-triazacyclononane triacetate.

^a Measured in litre mol⁻¹ cm⁻¹.

in energy.⁴ This is due to a large number of allowed electronic and vibronic transitions close in energy in the molecules of these compounds, which precludes their experimental observation because of limited resolution of spectrometers.

Despite the small number of reliable theoretical assignments of electronic spectra of technetium clusters, they are successfully employed by experimentalists, *e.g.*, in studies of the mechanism and kinetics of reactions in solutions.^{2,4,11,15,17} Typical changes in the absorption spectra of potassium octachloroditechnetate in hydrochloric acid solutions in the presence and in the absence of atmospheric oxygen are shown in Fig. 2. Based on these data, the kinetics and mechanisms of acid hydrolysis, complexation, disproportionation with the cleavage of M–M bonds, oxidative addition of atmospheric oxygen to a multiple M–M bond and cycloaddition of multiple M–M bonds with the formation of polynuclear clusters occurring in the system under consideration and characterising the stability of octahalotechnetate ions in solutions of hydrohalogenic acids have been studied. Each reaction dominates under particular conditions depending on the chemical nature of the solvent, concentration of dinuclear complexes and complexing agent, temperature, *etc.* Based on kinetic experiments on the stability of octahaloditechnetate ions in solutions of hydrohalogenic acids, it has been possible to calculate the effective rate constants for some of the reactions listed above and, in particular, to establish that the stability of these ions in solutions and their thermal stability in the solid state is determined by the strength of the M–M bonds and decreases in the series Cl > Br > I.²

2. Vibrational spectra

The vibrational spectra of technetium clusters have been studied somewhat more thoroughly. However, most of them are not very informative, since the fundamental vibrational modes of cluster fragments themselves are observed in the long-wave region. Moreover, the most interesting $\nu(\text{M} - \text{M})$ vibrations are forbidden in the IR spectra due to the centrosymmetric structure of most of the clusters and are allowed in the Raman spectra that cannot be

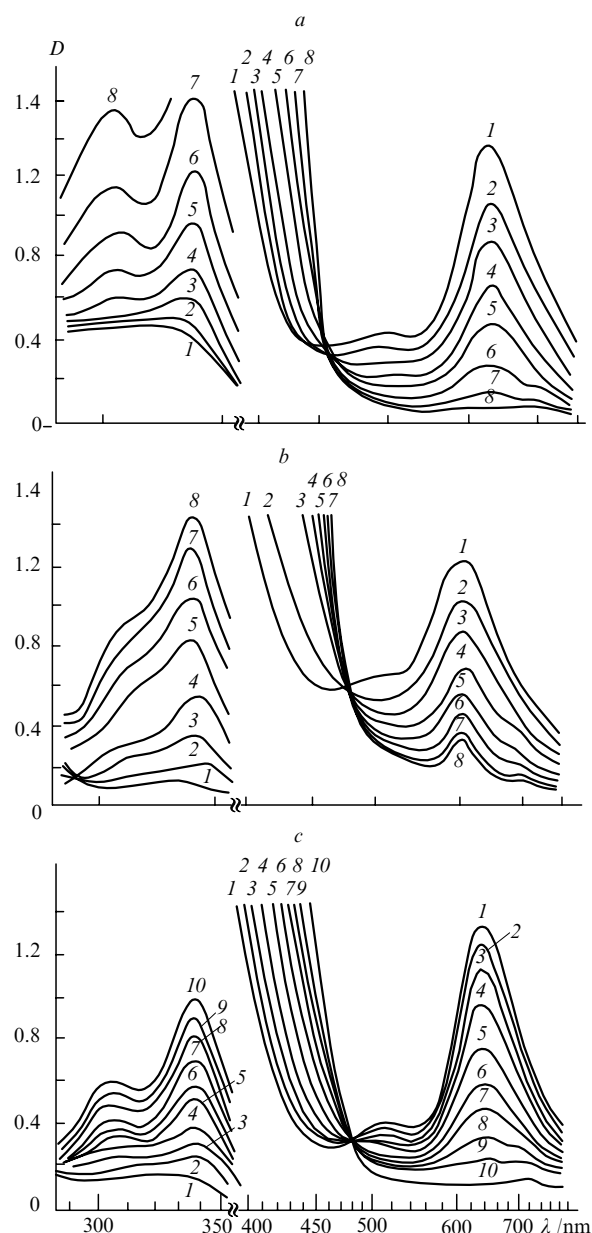


Figure 2. Typical changes in the absorption spectra of solutions of $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot \text{H}_2\text{O}$ in hydrochloric acid in the absence (a) and in the presence of atmospheric oxygen (b, c) at initial concentrations of octachloroditechnetate(II, III) ions of less than 5×10^{-4} mol litre⁻¹ (a, b) and more than 5×10^{-3} mol litre⁻¹ (c). The duration of the oxidation of $[\text{Tc}_2\text{Cl}_8]^{3-}$ with oxygen (b, c) and of disproportionation of $[\text{Tc}_2\text{Cl}_8]^{3-}$ (a) increases uniformly in the order of increasing the numbers of spectra in the series (1–10).^{4,17}

recorded in many cases because of an intense dark colour of the compounds. Thus, only the IR spectra containing bands corresponding to stretching and bending vibrations of the atoms in cations or to characteristic vibrations of the Tc–X bonds (X is a ligand) can be observed for most of the technetium clusters. In this case, the Tc–X type of vibrations can be isolated from a set of more complex normal vibrations only by convention, since these can hardly be considered as characteristic ones because of large masses and strong mutual influence of the ligands. As has been mentioned in the previous Section, vibronic spectra can serve as yet another source of information on the cluster vibrational modes. However, vibrational progressions observed in this case will be characteristic of the electronically excited state of the cluster rather than of its ground state.¹⁸

Table 4. Frequencies and relative intensities of the bands of bending (δ) and stretching (ν) vibrations of OH groups in the IR spectra of technetium clusters (in KBr pellets).¹⁹

Compound	$\delta(\text{H}-\text{OH}) / \text{cm}^{-1}$			$\nu(\text{OH}) / \text{cm}^{-1}$	
	$\delta(\text{H}-\text{OH})_{\text{H}_3\text{O}^+}$	$\delta(\text{HO}-\mu\text{-H})$	$\delta(\text{H}-\text{OH})_{\text{H}_2\text{O}}$	H_3O^+	H_2O
$\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}\} \cdot 2\text{H}_2\text{O}$ (1)	—	—	1620 (m)	—	3520 (br, s)
$[\text{H}(\text{H}_2\text{O})_2]\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}\}$ (2)	1030 (w)	1410 (m)	1620 (m)	3150 (vw)	3540 (br, s)
$[\text{H}(\text{H}_2\text{O})_2]_2\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}_2\}$ (3)	1040 (m)	1420 (m)	1620 (m)	—	3550 (br, s)
$[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$ (4)	1045 (m)	1400 (m)	1618 (m)	—	3550 (br, s)
$[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6] \cdot 4\text{H}_2\text{O}$ (5)	1035 (m)	1420 (s)	1620 (s)	—	3550 (br, s)
$[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6] \cdot n\text{H}_2\text{O}$ (6) ^a	980 (s)	1322 (m)	1390 (m)	—	2800 (vw)
	1040 (s)	1350 (m)	1620 (s)	—	2930 (w)
	—	1420 (s)	—	—	3020 (w)
$(\text{H}_3\text{O})_2[\text{TcBr}_6]$ (7)	1030 (m)	—	—	3150 (m)	—
$\text{K}'_{3-x}\text{K}''_x(\text{H}_3\text{O})_x[\text{Tc}_2\text{Cl}_8]_3 \cdot n\text{H}_2\text{O}$ (8) ^b	—	—	1610 (m)	2965 (w)	3550 (br, s)
	—	—	—	2930 (w)	—
	—	—	—	2865 (w)	—

^a Partially deuterated specimen. ^b K' denotes K^+ ions in special three-fold position in the structure (on the two-fold axis) and K'' denotes K^+ ions in general position in the structure.

Thus, all available information on the vibrational spectra of technetium clusters is reduced mainly to characteristic atomic vibrations in the cations in the region $4000\text{--}400\text{ cm}^{-1}$ and to vibrations of cluster anions (or molecules) themselves in the region $400\text{--}50\text{ cm}^{-1}$. Since the anions of different chemical nature have little effect on the cations, the absorption bands corresponding to characteristic vibrations of the same cations in different compounds differ insignificantly in most of spectra. In this connection, the IR spectra in the region $4000\text{--}400\text{ cm}^{-1}$ can be used mainly for qualitative analysis, and it makes no sense to consider them in this review, since they are rather characteristic of the cations themselves. Apparently, the IR spectra of differently hydrated hydroxonium cations and certain bridging bidentate (*e.g.*, carboxylate or sulfate) ligands are the exceptions, since they can contain essential information on the formal charge and on the electronic and molecular structure of the cluster fragments. Let us consider the results obtained from these spectra in more detail.

The absorption bands corresponding to stretching and bending vibrations of the OH groups in technetium clusters with differently hydrated hydroxonium cations¹⁹ are listed in Table 4. The results obtained indicate that the pattern of the IR spectra depends on the character of bonding of the OH groups in crystals of the compounds in question. For instance, since only isolated H_3O^+ ions are present in the crystals of compound **7**, only two bands corresponding to the $\nu(\text{OH})_{\text{H}_3\text{O}^+}$ and $\delta(\text{H}-\text{O}-\text{H})_{\text{H}_3\text{O}^+}$ vibrations are observed in its IR spectrum (see Table 4). Only water molecules of crystallisation are present in the cluster **1**; therefore, only absorption bands due to the $\nu(\text{OH})_{\text{H}_2\text{O}}$ and $\delta(\text{H}-\text{O}-\text{H})_{\text{H}_2\text{O}}$ vibrations are observed in the IR spectrum of this compound. As can be seen, their positions differ considerably from those of corresponding absorption bands of hydroxonium cations.

Several bands due to stretching and bending vibrations of the OH groups are simultaneously observed in the IR spectra of compounds **2–5** and **8** (see Table 4). This is probably due to the fact that the bridging hydrogen atoms in the $[\text{H}(\text{H}_2\text{O})_2]^+$ and $[\text{H}_3\text{O}(\text{H}_2\text{O})_3]^+$ cations are closer to one of the oxygen atoms while to the other oxygen atom they are bonded by a strong hydrogen bond. Therefore, the absorption bands corresponding to vibrations of both H_3O^+ ions and H_2O must be observed in the IR spectra of hydrated hydroxonium cations. It should be noted that in this case the frequencies of $\delta(\text{H}-\text{O}-\mu\text{-H})$ absorption bands must be intermediate between those of the $\delta(\text{H}-\text{O}-\text{H})_{\text{H}_2\text{O}}$ and $\delta(\text{H}-\text{O}-\text{H})_{\text{H}_3\text{O}^+}$ vibrations. A much larger number of bands corresponding to bending vibrations must be observed in the case of partially deuterated differently hydrated hydroxonium ions (see Table 4). Thus, IR spectra, as well as the experiments on thermal

dehydration and magnetic measurements, can be used to establish¹⁹ the structure of clusters if their crystals contain differently hydrated hydroxonium cations, whereas X-ray analysis provides no unambiguous solution of this problem. Yet another example of this type is provided by the IR spectra of compound $(\text{Bu}_4\text{N})_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$ in which no absorption bands corresponding to vibrations of the OH groups are observed. In contrast to the initial assumptions,²⁰ this indicates that the $[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]^{2-}$ anion contains no OH groups.

The IR spectra of μ -acetato dinuclear $d^4\text{--}d^5$ technetium complexes have been studied and all absorption bands have been assigned.²¹ Previously,⁷ the IR spectra of analogous dinuclear $d^4\text{--}d^4$ technetium and rhenium clusters have been studied; however, no complete assignment of the absorption bands has been performed. From comparison of the results obtained it follows that, in contrast to analogous dinuclear complexes of other elements (*e.g.*, copper acetates), the splitting (Δ) between the frequencies of symmetric $\nu_s(\text{C}-\text{O})$ and antisymmetric $\nu_{as}(\text{C}-\text{O})$ vibrations of the bridging acetate anions in technetium clusters is extremely small ($\sim 20\text{ cm}^{-1}$). It should be noted that a tendency for the Δ value to decrease is observed on going from monodentate acetate ions to bidentate ones and that the anomalously small value of this splitting is probably due to a specific influence of strong Tc—Tc bonds. The frequencies of the $\nu(\text{Tc}-\text{X})$ vibrations are appreciably shifted towards the long-wave region relative to analogous frequencies of other halide technetium complexes without bridging ligands. This indicates appreciable weakening of the Tc—X bonds in μ -acetato technetium complexes as compared to analogous bonds in other halide Tc complexes (Table 5). From these data altogether it has been suggested²¹ that the compounds under consideration have the ‘lantern’ type of structure (see Fig. 1*b*), *viz.*, two technetium atoms form a strong Tc—Tc bond, four bridging acetate ions additionally bind Tc atoms to one another, while two halide ions are in axial positions with respect to the M—M bonds and are in essence ionically bonded to the technetium atom. This assumption has been completely confirmed by X-ray analysis.^{22–24}

Using the IR spectra, the structures of sulfate dinuclear technetium complexes have also been determined.¹⁶ The parameters of the IR spectra and the assignment of bands of two sulfate dinuclear technetium complexes, $\text{K}_2[\text{Tc}_2(\text{SO}_4)_2] \cdot 2\text{H}_2\text{O}$ and $\text{K}_4(\text{H}_3\text{O})_2[\text{Tc}_2(\text{SO}_4)_6]$, are listed in Table 6. The IR spectrum of the former compound contains absorption bands in the region $330\text{--}3530\text{ cm}^{-1}$ with maxima at 3450 and 1655 cm^{-1} corresponding to stretching and bending vibrations of coordinated water molecules, respectively. Four groups of bands each split by the crystal field are observed in the regions of both stretching and

Table 5. Frequencies of absorption bands (cm^{-1}) in the long-wave IR spectra of technetium halide clusters and their assignment.^{28, 29}

Cluster	$\nu(\text{M}-\text{M})$,	$\nu(\text{M}-\text{X})$,	$\delta(\text{XMY})$, $\delta(\text{MMX})$
$[\text{Tc}_2(\text{AcO})_4\text{Cl}]$	—	~ 180	—
$[\text{Tc}_2(\text{AcO})_4\text{Br}]$	—	~ 120	—
$[\text{Tc}_2(2\text{-PyO})_4\text{Cl}]$	383 ^a (337 ^b) ¹⁰	—	—
$[\text{Tc}_2\text{Cl}_8]^{2-}$	—	362, 342	179, 170
$[\text{Tc}_2\text{Br}_8]^{2-}$	323 ^a 5	269, 249 ⁵	—
$[\text{Tc}_2\text{Cl}_8]^{3-}$	370 ^a (320 ^b) ¹	335, 310	184, 157
$[\text{Tc}_2\text{Cl}_6]^{2n-}$	—	~ 310 , 285	183, 175
$[\text{Tc}_6\text{Br}_{12}]$ (see ^c)	324, 302, 298	234, 170	141, 120, 106
$[\text{Tc}_6\text{Br}_{12}]^-$ (see ^c)	349, 335, 298	230, 181	~ 100
$[\text{Tc}_6\text{Cl}_{12}]^-$ (see ^c)	349, 336, 298	253, 233	189, 176, 153, 122
$[\text{Tc}_6\text{Cl}_{12}]^{2-}$	~ 360 (br)	~ 303 (br)	195, 153
		~ 254 (br)	
$[\text{Tc}_8\text{Br}_{12}]$ (see ^c)	355, 290, 266	232, 213	120, 96
$[\text{Tc}_8\text{I}_{12}]$ (see ^c)	342, 283, 243	187, 113	80, 61, 54
$[\text{Tc}_6\text{Br}_{11}]^{2-}$	330, 292	266, 238 (w)	164 (w), 120, 76

^a Data of Raman spectra. ^b Data of vibronic spectra. ^c Axial ligands are omitted.

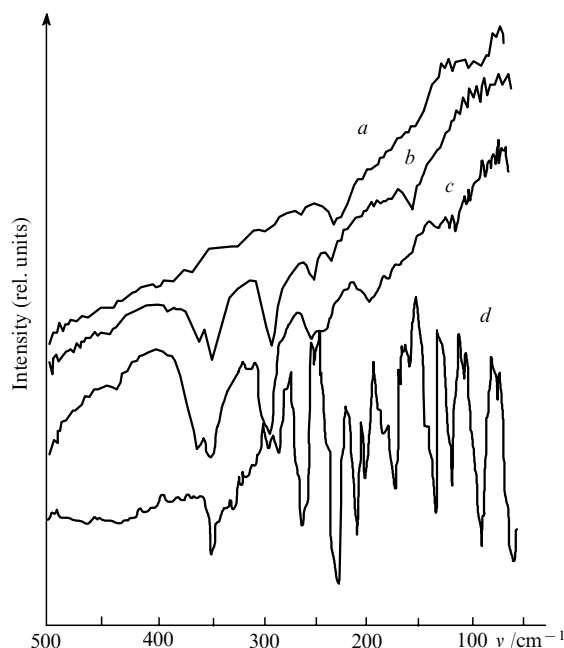
bending vibrations of sulfate ions; this corresponds to distortion of the tetrahedral SO_4^{2-} ion to the idealised C_{2v} symmetry due to the formation of bidentate bridging bonds between the sulfate ions and the Tc_2^{6+} fragment,²⁵ which is analogous to those found in the structure of the $[\text{Re}_2(\text{SO}_4)_4]^{2-}$ anion.^{26, 27}

The IR spectrum of compound $\text{K}_4(\text{H}_3\text{O})_2[\text{Tc}_2(\text{SO}_4)_6]$ is characterised by a more intense absorption band in the region $\sim 2950 \text{ cm}^{-1}$, which can be assigned to the $\nu(\text{OH})_{\text{H}_3\text{O}^+}$ vibrations (see Table 6). Three groups of broad bands are observed in the region of stretching and bending vibrations of the S—O bond in the spectrum of this compound; this is characteristic of monodentate sulfate ions with C_{3v} symmetry.²⁵

Later, the assumptions¹⁶ concerning the structure of compound $\text{K}_2[\text{Tc}_2(\text{SO}_4)_4] \cdot 2\text{H}_2\text{O}$ made on the basis of IR spectra, the results of chemical analysis and data of thermogravimetric analysis and other physicochemical methods were confirmed by X-ray study of a single crystal synthesised by the author of this review.[‡]

The assignment of the absorption bands of a number of di- and poly-nuclear halide technetium clusters is given in Table 5 and the long-wave IR spectra of several polynuclear technetium clusters are shown in Fig. 3. The following major tendencies are observed for compounds of similar structure, *viz.*, the absorption bands corresponding to the $\nu(\text{Tc}-\text{X})$ and $\delta(\text{Tc}-\text{Tc}-\text{X})$ vibra-

[‡] X-Ray analysis has been done by P A Koz'min, M D Surazhskaya, and T B Larin and the results of these investigations have been described in Ref. 2.

**Figure 3.** The long-wave IR spectra of polynuclear technetium clusters:^{28, 29} (a) $(\text{FeCp}_2)_2[\text{Tc}_8\text{Br}_{14}]$; (b) $(\text{FeCp}_2)_3[\text{Tc}_6\text{Cl}_{14}]$; (c) $(\text{Bu}_4\text{N})_3.[\text{Tc}_6\text{Cl}_{14}]$; and (d) $[\text{H}(\text{H}_2\text{O})_2]_2[\text{Tc}_8\text{Br}_{14}]$.

tions are, as a rule, shifted towards the low-energy region as the formal oxidation state of technetium decreases and the replacement of ligands in the series Cl, Br and I occurs. As has already been noted, vibrations of the M—M bonds are symmetry-forbidden and are not observed in the IR spectra of most of dinuclear clusters; however, in polynuclear clusters this exclusion is removed, and certain $\nu(\text{Tc}-\text{Tc})$ and $\delta(\text{Tc}-\text{Tc}-\text{X})$ vibrations can also be observed in the IR spectra. Thus, the stretching vibrations of the M—M bonds of F_{1u} ; E' and A'' ; and B_{1u} , B_{2u} and B_{3u} symmetry types are expected to be observed in the spectra of octahedral, trigonal-prismatic, and tetragonal-prismatic clusters, respectively. For lack of sufficient experimental data, unambiguous assignment of all vibrational frequencies for polynuclear clusters is currently impossible. Therefore, their long-wave IR spectra can be used mainly for qualitative analysis and determination of the structure. Thus, a large number of relatively narrow absorption bands in this spectral region is almost unambiguous evidence for the polynuclear nature of the clusters, while the positions of these lines can be tentative evidence for the formal oxidation state of technetium.

The use of IR spectra of technetium and rhenium complexes with ferrocenium cations for the solution of analytical and structural problems has been described.^{28, 29} The composition

Table 6. Frequencies (cm^{-1}) and relative intensities of bands in the IR spectra of sulfate dinuclear technetium complexes.¹⁶

Compound	$\nu(\text{OH})$	$\delta(\text{H}-\text{O}-\text{H})$	$\nu(\text{S}-\text{O})$	$\nu(\text{Tc}-\text{O})$	$\delta(\text{O}-\text{S}-\text{O})$	Other bands
$\text{K}_2[\text{Tc}_2(\text{SO}_4)_4] \cdot 2\text{H}_2\text{O}^a$	3450 (s, br)	1655 (w)	1295 (s), 1230 (w); 1185 (sh), 1155 (s); 1070 (m), 1041 (m); 915 (s), 850 (m)	698 (m)	698 (s); 600 (m), 585 (m); 532 (sh, w), 522 (w); 465 (m)	381 (m), 335 (s, br) $\delta(\text{O}-\text{Tc}-\text{O})$, 250 (sh, br), 200 (m), 181 (w), 158 (m), 152 (w), 118 (m), 78 (s)
$\text{K}_4(\text{H}_3\text{O})_2[\text{Tc}_2(\text{SO}_4)_6]^b$	2950 (sh, br)		1230 (sh, br), 1155 (s); 1045 (s); 965 (s), 850 (sh)	675 (m)	605 (s); 535 (w); 483 (m)	290 (s, v br) $\delta(\text{O}-\text{Tc}-\text{O})$ 156 (s, v br), 80 (w, br)

^a Sulfate ions have C_{2v} symmetry in the complex $\text{K}_2[\text{Tc}_2(\text{SO}_4)_4] \cdot 2\text{H}_2\text{O}$. ^b Sulfate ions have the C_{3v} symmetry in the complex $\text{K}_4(\text{H}_3\text{O})_2[\text{Tc}_2(\text{SO}_4)_6]$.

and structure of these complexes suggest that the lines corresponding to vibrations of ferrocenium cations, technetium or rhenium anions, and hydrated hydroxonium cations {in the case of compound $(\text{FeCp}_2)_4[\text{H}_3\text{O}(\text{H}_2\text{O})_4]_2 \cdot [\text{TcCl}_6]_3$ } must be observed in their IR spectra. According to the published data,³⁰ if ferrocene and ferrocenium have the $D_{5d}(D_{5h})$ point symmetry, then vibrations of $A_{2u}(A_2'')$ and $E_{2u}(E_2'')$ symmetry types must be active in their IR spectra. It has been shown^{28,29} that all most intense vibrational lines of ferrocene are also observed in the IR spectra of technetium and rhenium compounds with ferrocenium cations. The only exception are the absorption bands in the region $480\text{--}820\text{ cm}^{-1}$, where only one composite line in the region $670\text{--}560\text{ cm}^{-1}$ is observed instead of very intense bands corresponding to the nonplanar $\rho_{\text{CH}}(A_{2u})$ vibrations and $\nu(\text{Fe}-\text{Cp})$ (E_{1u}) stretching vibrations characteristic of pure ferrocene; this line is probably due to the interaction between the above two vibrations. It is known³⁰ that interaction between these types of vibrations [as well as a shift of $\nu(\text{Fe}-\text{Cp})$ towards the high-frequency region] characterises an increase in covalency of the $\text{Fe}-\text{Cp}$ bonds. It should be noted that neither absorption bands corresponding to the $\nu(\text{Fe}-\text{Cp})$ (E_{1u}) vibrations in the IR spectrum of compound $(\text{FeCp}_2)_2[\text{Tc}_8\text{Br}_{14}]$ nor the bands corresponding to bending skeletal $\nu(\text{Cp}-\text{Fe}-\text{Cp})$ (E_{1u}) vibrations in the spectra of all compounds studied are observed. All bands in the IR spectra of compounds containing $[\text{Tc}_6\text{Cl}_{14}]^{3-}$ and especially $[\text{Tc}_8\text{Br}_{14}]^{2-}$ anions are considerably broadened and diffuse (see Fig. 3). Analogous effects have been found for certain specimens preliminarily frozen to $\sim 78\text{ K}$. It has been pointed out that this phenomenon can be due to the effects of vibronic interaction in the molecules.^{29,30}

As to the absorption bands corresponding to stretching and bending vibrations of isolated hydroxonium cations in the cluster $[\text{Fc}(\text{Cp}_2)_4[\text{H}_3\text{O}(\text{H}_2\text{O})_4]_2[\text{TcCl}_6]_3$, it is difficult to identify them because of the superposition of more intense lines of ferrocenium cations. Nevertheless, certain bands in the region of $\delta(\text{H}-\text{O}-\text{H})$ bending vibrations (at $1620, 1555, 1510$, and 1058 cm^{-1}) can be identified unambiguously. The conclusion that the effect of ferrocenium cations on the vibrational spectra of anions is not so significant as the reverse effect of various anions on the vibrations in ferrocenium cations is yet another important result.^{28,29} Nevertheless, this effect persists and manifests itself mainly as a shift of frequencies of these vibrations. Similar shift of the frequencies of stretching and bending vibrations of technetium anions due to the effect of various cations has been found;³¹ it has been shown that the absorption bands of the anions are shifted towards the low-frequency region as the average size of cations increases. For pertechnetate ions, an increase in the cation size is accompanied by a decrease in the splitting of the $\nu(\text{Tc}=\text{O})$ stretching band. Comparison of published data (see Refs 28, 29 and 31) shows that

the extent to which the anions are affected by the ferrocenium cations, the effective radius (R_{eff}) of which is larger than $3\text{ \AA}$, approaches that of $(\text{Me}_4\text{N})^+$ and $(\text{Et}_4\text{N})^+$ having similar R_{eff} . It should be noted that the absorption bands in the long-wave IR spectra of compound $(\text{FeCp}_2)_2[\text{Tc}_8\text{Br}_{14}]$ are also considerably broadened and some of them are missing (see Fig. 3), as is the case of the short-wave IR spectra. This may also be associated with vibronic interactions.^{28,29}

The IR spectroscopic studies of ferrocenium salts with Tc- and Re-containing anions^{28,29} have shown that:

1. All compounds correspond to the expected composition and structure.

2. The absence of additional absorption bands in the IR spectra of the compounds obtained (except for the bands corresponding to anionic and cationic vibrations) indicates that no formation of new types of directed chemical bonds occurs except for those expected from the composition and structure of these compounds.

3. Strong mutual influence of the ferrocenium cations and the technetium (rhenium) anions is observed, which increases in the series of anions $[\text{TcO}_4]^- < [\text{Re}_2\text{Br}_8]^{2-} \approx [\text{Tc}_6\text{I}_{14}]^{3-} < [\text{TcCl}_6]^{2-} < [\text{Tc}_6\text{Cl}_{14}]^{3-} < [\text{Tc}_8\text{Br}_{14}]^{2-}$ and is probably due to the strengthening of vibronic interaction in this series.

The assignment of absorption bands in the long-wave IR spectra of $[\text{Tc}_2\text{X}_8]^{n-}$ ($\text{X} = \text{Cl}, \text{Br}; n = 2, 3$) dinuclear technetium clusters with a simpler structure has been performed.^{1,4,5,8,32} Thus, the IR spectra of these anions contain two absorption bands with E_u and A_{2u} symmetry corresponding to the $\nu(\text{Tc}-\text{X})$ stretching vibrations and one A_{2u} band corresponding to the $\delta(\text{X}-\text{Tc}-\text{X})$ vibrations, while their Raman spectra contain two absorption bands with A_{1g} symmetry corresponding to the $\nu(\text{Tc}-\text{Tc})$ and $\nu(\text{Tc}-\text{X})$ vibrations and one band with E_g symmetry. The frequencies of these bands in the spectra of different anions are listed in Table 5.

Complete normal coordinate analysis for the $[\text{Tc}_2\text{X}_8]^{n-}$ dinuclear complexes ($\text{X} = \text{Cl}, \text{Br}; n = 2, 3$) has been performed, the bands in their IR and Raman spectra (including those of isotope-substituted complexes) have been assigned, and ten force constants have been calculated.⁶ The structural characteristics of these ions used in the calculations and the force constants obtained are listed in Table 7. The assignment of bands in the IR and Raman spectra of analogous rhenium and osmium dinuclear complexes with D_{4h} and D_{4d} symmetry, respectively, has also been performed.⁶ The calculations reproduce well the major regularities expected from the data of X-ray studies. Thus, from Ref. 6 and the data in Table 7 it follows that for all the complexes in question the bond stretching force constants $f_d(\text{M}-\text{M})$ and $f_d(\text{M}-\text{X})$, as a rule, decrease as the ligands are replaced in the series F, Cl, Br and I and n increases. It should be noted that these

Table 7. Bond lengths ($d/\text{\AA}$), bond angles (α/deg) and force constants ($f/\text{mdyn A}^{-1}$) for $[\text{Tc}_2\text{X}_8]^{n-}$ ($\text{X} = \text{Cl}, \text{Br}; n = 2, 3$) ions.⁶

Parameter	$[\text{Tc}_2\text{Cl}_8]^{2-}$	$[\text{Tc}_2\text{Cl}_8]^{3-}$	$[\text{Tc}_2\text{Br}_8]^{2-}$	$[\text{Tc}_2\text{Br}_8]^{3-}$
$d(\text{Tc}-\text{Tc})$	2.15	2.11	2.15	2.13
$d(\text{Tc}-\text{X})$	2.32	2.36	2.47	2.51
$\alpha(\text{Tc}-\text{Tc}-\text{X})$	103.80	104.60	103.90	104.00
$f_d(\text{Tc}-\text{Tc})$	3.79	4.86	2.67	3.15
$f_d(\text{Tc}-\text{X})$	1.79	1.47	1.48	1.31
$d^2(\text{X}-\text{Tc})f_\alpha(\text{X}-\text{Tc}-\text{X})$	0.67	0.64	1.55	1.60
$d(\text{X}-\text{Tc})d(\text{Tc}-\text{Tc})f_\alpha(\text{X}-\text{Tc}-\text{Tc})$	1.09	0.88	1.37	1.15
$f_{dd}(\text{TcTc}-\text{TcX})$	0.11	0.24	0.05	0.13
$f_{dd}(\text{TcX}-\text{TcX})$	0.42	0.40	0.32	0.36
$d(\text{Tc}-\text{X})f_{dx}(\text{TcX}-\text{XTcX})$	0.03	0.02	0.02	0.01
$d(\text{Tc}-\text{X})f_{dx}(\text{TcTc}-\text{XTcTc})$	0.30	0.30	0.17	0.19
$d(\text{Tc}-\text{X})d(\text{Tc}-\text{Tc})f_{\alpha\alpha}(\text{XTcTc}-\text{XTcTc})$	0.25	0.15	0.23	0.05

Note. The subscripts d and α at the force constants f correspond to stretching and bending vibrations, respectively; the direction of the vibrations is given in parentheses.

changes and changes in analogous interatomic distances due to ligand replacement and the decrease in the formal oxidation state of the metal occur in the opposite directions. Of all the complexes studied, the largest $f_d(M-M)$ value was obtained for the $[Tc_2Cl_8]^{3-}$ anion with a formal $M-M$ bond order of 3.5 for which the shortest $M-M$ distance has been found experimentally.²

In conclusion of this Section, it should be noted that many problems associated with the assignment and interpretation of the optical spectra of technetium clusters remain unsolved due to the complex structure of these compounds, the lack of sufficient experimental data (which is often due to the impossibility of obtaining them with currently available instruments) as well as to the absence of reliable theoretical calculations. However, the available data can well be used for qualitative structural analysis.

III. Magnetochemistry of technetium oxo and halide complexes

Among experimental methods of studying the electronic structure of coordination compounds, magnetochemical measurements occupy a particular place since they make it possible to determine the number of unpaired electrons in the molecule, the magnitude of intermolecular exchange interactions, and in some instances

can even serve as immediate evidence for the relative order of some MOs in the molecules of these compounds. Sometimes, magnetochemistry can be used as an analytical and, to some extent, as a structural investigation technique.³³ However, no information on systematic studies of magnetochemical properties of technetium complexes has been reported so far.³⁴ The results available^{35,36} have not been systematised, contain no data on diamagnetic corrections for technetium and thus are unreliable. In connection with the foregoing, in this review we discuss the magnetic properties of technetium complexes in which Tc atoms have different oxidation states and which have been studied by the static magnetic susceptibility method and by EPR spectroscopy.

The data of magnetic measurements for technetium compounds are listed in Table 8. Since no diamagnetic corrections for technetium ions are known, they were obtained by extrapolating the data on diamagnetic corrections for neighbouring elements in the Periodic Table (Mn, Re, Mo and Ru).³⁴ The results of calculations of the electronic structure of technetium oxo and halide complexes are shown in Fig. 4. As can be seen, in most cases the experimental data are in good agreement with theoretical predictions. Let us consider the most typical cases in detail.

Pertechnetates are tetrahedral d^0 complexes. The recently found distortion of these complexes^{37–44} has virtually no effect on their diamagnetic properties, except for weak temperature-

Table 8. Magnetic properties of technetium oxo and halide complexes.^{18, 28, 34}

Compound	Tc oxidation state	Electron configuration	g_{eff}	μ_{eff}/μ_B		θ/deg	Number of unpaired electrons
				80 K	300 K		
$M[TcO_4]$ ($M = K, NH_4, Bu_4^+N$)	+ 7.0	d^0	—	see ^a	see ^a	—	0
$(FeCp_2)[TcO_4]$	+ 7.0	d^0	2.01	2.78	3.88	–185	1.95–3.00
$M_2[TcOCl_5]$ ($M = K, NH_4$)	+ 5.0	d^2	—	see ^a	see ^a	—	0
$(Bu_4^+N)[TcOX_4]$ ($X = Cl, Br, I$)	+ 5.0	d^2	—	see ^a	see ^a	—	0
$Tc_2O_5 \cdot nH_2O$	+ 5.0	d^2	—	see ^a	see ^a	—	0
$[TcO(NO_3)_3] \cdot H_2O$	+ 5.0	d^2	—	see ^a	see ^a	—	0
$K_3[Tc_2Cl_8O_2]$	+ 4.5	d^2-d^3	—	3.69	4.15	–40	3
$M_2[TcCl_6]$ ($M = K, NH_4$)	+ 4.0	d^3	—	2.79	3.44	–68	3
$1/3 \{[FeCp_2]_4[H_3O(H_2O)_4]_2[TcCl_6]_3\}$	+ 4.0	d^3	2.015	6.94	6.80	9	6.02–5.87
$(Bu_4^+N)_2[TcCl_6]$	+ 4.0	d^3	—	3.78	3.80	0	3
$M_2[TcBr_6]$ ($M = K, NH_4$)	+ 4.0	d^3	—	3.21	3.45	–24	3
$M_2[TcI_6]$ ($M = K, NH_4$)	+ 4.0	d^3	—	2.79	3.34	–60	3
$(Me_4N)_2[TcI_6]$	+ 4.0	d^3	—	3.68	3.67	0	3
TcO_2	+ 4.0	d^3	—	~1.0	1.5	~200	~1
$(Bu_4^+N)_2[Tc_2X_8]$ ($X = Cl, Br$)	+ 3.0	d^4-d^4	—	see ^b	see ^b	—	0
$[Tc_2(RCOO)_4Cl_2]$ ($R = Me, Bu^t$)	+ 3.0	d^4-d^4	—	see ^b	see ^b	—	0
$K_2[Tc_2(SO_4)_4] \cdot 2H_2O$	+ 3.0	d^4-d^4	—	see ^b	see ^b	—	0
$M_3[Tc_2Cl_8] \cdot nH_2O$ ($M = K, NH_4, C_5H_5NH, C_9H_8NH$)	+ 2.5	d^4-d^5	2.09	1.75	1.75	0	1
$M_3[Tc_2Br_8] \cdot 2H_2O$ ($M = K, NH_4$)	+ 2.5	d^4-d^5	2.09	1.74	1.74	0	1
$[Tc_2(AcO)_4X]$ ($X = Cl, Br$)	+ 2.5	d^4-d^5	2.09	1.75	1.73	0	1
$K[Tc_2(AcO)_4Cl_2]$	+ 2.5	d^4-d^5	2.09	1.75	1.75	0	1
$1/2 [Tc_4O_5] \cdot nH_2O$	+ 2.5	d^4-d^5	—	1.77	1.75	0	1
$M_2[Tc_2Cl_6]$ ($M = K, NH_4; X = Cl, Br$)	+ 2.0	d^5-d^5	—	see ^b	see ^b	—	0
$(Et_4N)_2\{[Tc_6(\mu-Br)_6Br_6]Br_2\}$	+ 2.0	$6d^5$	—	0.85	1.16	~0	~0.1
$M_3\{[Tc_6(\mu-X)_6X_6]X_2\}$ ($X = Cl, Br, M = Me_4N, Bu_4^+N$)	+ 1.83 (3)	$5d^5-d^6$	2.00 ($g_{\parallel}$), 1.63 ($g_{\perp}$)	~1.5	~1.7	~1	1
$(FeCp_2)_3\{[Tc_6(\mu-Cl)_6Cl_6]Cl_2\}$	+ 1.83 (3)	$5d^5-d^6$	2.007	5.75	6.01	~0	4.85–5.13
$(Bu_4^+N)_3\{[Tc_6(\mu-Cl)_6Cl_6]Cl_2\}$	+ 1.83 (3)	$5d^5-d^6$	2.00 ($g_{\parallel}$), 1.63 ($g_{\perp}$)	1.50	1.77	~0	1
$(Me_4N)_2[Tc_6(\mu-Cl)_6Cl_6]$	+ 1.66 (6)	$4d^5-2d^6$	1.97	~0.8	~1.1	–60	~0.2
$\{[Tc_8(\mu-Br)_8Br_4]Br\} \cdot 2H_2O$	+ 1.625	$5d^5-3d^6$	—	1.12	1.57	~120	1
$(Bu_4^+N)_3\{[Tc_6(\mu_3-Br)_5Br_6]\}$	+ 1.5	$3d^5-3d^6$	~2.0	0.73	0.91	~0	~0.1
$[H_3O(H_2O)_3]_2[Tc_6(\mu_3-Br)_5Br_6] \cdot nH_2O$ ($n = 0, 4$)	+ 1.5	$3d^5-3d^6$	~2.0	~1.0	~1.2	–80	~0.2
$[H(H_2O)_2]_n\{[Tc_8(\mu-Br)_8Br_4]Br_n\}$ ($n = 1, 2$)	+ 1.5	$4d^5-4d^6$	—	see ^b	see ^b	—	0
$(Bu_4^+N)_2\{[Tc_8(\mu-X)_8X_4]I_2\}$ ($X = 0.5 Br + 0.5 I$)	+ 1.5	$4d^5-4d^6$	—	see ^b	see ^b	—	0
$(FeCp_2)_2\{[Tc_8(\mu-Br)_8Br_4]Br_2\}$	+ 1.5	$4d^5-4d^6$	—	4.82	5.87	–64	3.83–4.96

^a Compounds are diamagnetic. ^b Temperature-independent paramagnetism.

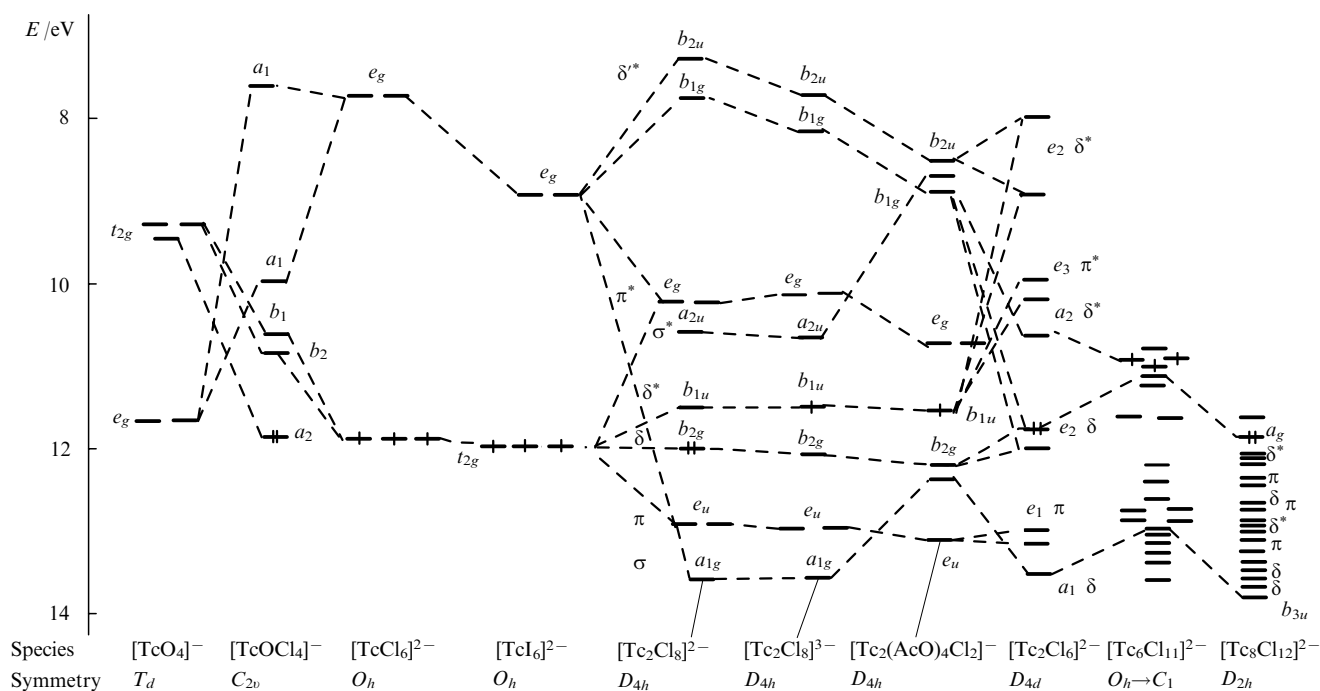


Figure 4. Results of extended Hückel (EH) calculations of the electronic structure of technetium complexes.^{2,34} The presence of electrons in the HOMO is depicted schematically by small double vertical lines.

independent paramagnetism (TIP)[§] observed in some cases (see Table 8 and Fig. 4). It should be noted that according to Fig. 4, the $[\text{TcO}_4]^{2-}$ ions formed in the one-electron reduction of pertechnetates, must possess weak paramagnetism corresponding to one unpaired electron, which is observed experimentally.^{45,46}

Technetium(V) oxohalide complexes are characterised by the d^2 electronic configuration of the central atom. The ground electronic state of the molecules of these compounds must be spin-paired because of a symmetry breakdown in the nearest environment of technetium (e.g., to C_{2v} for $[\text{TcOX}_4]^-$, see Ref. 47); in fact, these compounds also possess diamagnetism or TIP (see Table 8, Fig. 4).³⁴

Technetium(IV) halide complexes are characterised by the d^3 electronic configuration and octahedral structure of the nearest coordination sphere of the Tc atoms. According to theoretical predictions (see Fig. 4), these compounds have a triply degenerate t_{2g} highest occupied molecular orbital (HOMO) and, hence, they must possess paramagnetism corresponding to the spin $3/2$ ($\mu_{\text{eff}} \approx 3.87 \mu_B$).

From the data in Table 8 it can be seen that only for several technetium(IV) compounds are the magnitudes of the effective magnetic moments μ_{eff} close to the pure spin value; in most cases, they are much smaller. Previously,⁴⁸ similar effects of a decrease in μ_{eff} of analogous rhenium halide complexes have been rationalised by intermolecular exchange interactions occurring along the $\text{Re}'-\text{X}'\cdots\text{X}''-\text{Re}''$ chains. It has also been shown⁴⁸ that similar antiferromagnetic interactions can occur at $\text{X}'\cdots\text{X}''$ distances up to $\sim 5 \text{ \AA}$. Thus, antiferromagnetic exchange interactions in technetium(IV) complexes are also the most plausible explanation of the decrease in their effective magnetic moments.

In fact, as can be seen from the data in Table 8, a decrease in the size of the outer-sphere cation and an increase in the anion size (halide ion) leads to an increase (in the absolute value) in the Weiss constant characterising the strength of antiferromagnetic exchange interactions. However, in the case of rather bulky tetraalkylammonium cations, the $[\text{TcX}_6]^{2-}$ anions are 'pushed

apart' by these cations to such an extent that the exchange interactions along the $\text{Tc}'-\text{X}'\cdots\text{X}''-\text{Tc}''$ chains become impossible (the $\text{X}'\cdots\text{X}''$ distances between adjacent $[\text{TcX}_6]^{2-}$ octahedra are $\sim 6 \text{ \AA}$).⁴⁹ An even greater decrease in μ_{eff} is observed for technetium dioxide (see Table 8). According to the published data,⁵⁰ it is assumed that the metal-metal (Tc-Tc) bonds can be formed in the TcO_2 molecule; this may be an additional reason for the decrease in μ_{eff} compared to its pure spin value for technetium(IV).

As can be seen from the data in Table 8, the magnetic properties of most of the compounds considered above are first of all due to the electronic configuration of the Tc atoms, the symmetry of their nearest ligand environment and intermolecular exchange interactions. The magnetic properties of all other technetium compounds listed in Table 8 cannot be explained by these reasons only, since their electronic structures are strongly affected by the M-M bonds localised on pairs of Tc atoms or delocalised over the polynuclear metal core. In these complexes, the M-M interactions result in appreciable shortening of the Tc-Tc distances compared to analogous distances in compact metallic Tc.^{1,2,51} The compounds studied^{2,51} can be divided into two structural types, viz., dinuclear complexes (clusters) with multiple M-M bonds and polynuclear clusters.

Dinuclear d^4-d^4 complexes. Classical quadruple M-M bonds formed by $\sigma(4d_{z^2})$, $2\pi(4d_{xz}, 4d_{yz})$ and $\delta(4d_{xy})$ orbitals of the M-M bonds (see Fig. 4) are characteristic of these compounds.^{1,2,51} These complexes have an eclipsed conformation of ligands (the idealised D_{4h} symmetry, see Fig. 1a,b) and Tc-Tc distances in the range from 2.16 to 2.19 $\text{\AA}$.² All compounds are characterised by the absence of unpaired electrons, therefore their magnetic susceptibility is temperature-independent (see Table 8).

Dinuclear d^4-d^5 complexes are formed as a result of one-electron reduction of the compounds belonging to the preceding group and also have an eclipsed conformation of ligands^{1,2,51} (see Fig. 1a,b). As could be expected from Fig. 4, one unpaired electron is shared by two Tc atoms that form an M-M bond of high order (the Tc-Tc distances in d^4-d^5 complexes lie within the limits 2.10–2.15 $\text{\AA}$)^{1,2,51} in the molecules of these compounds. It has been shown^{3,9,52-54} that this electron occupies the b_{1u} HOMO (the δ^* M-M orbital) formed mainly by the $4d_{xy}$

[§] Unpublished results by K E German (Institute of Physical Chemistry, Russian Academy of Sciences).

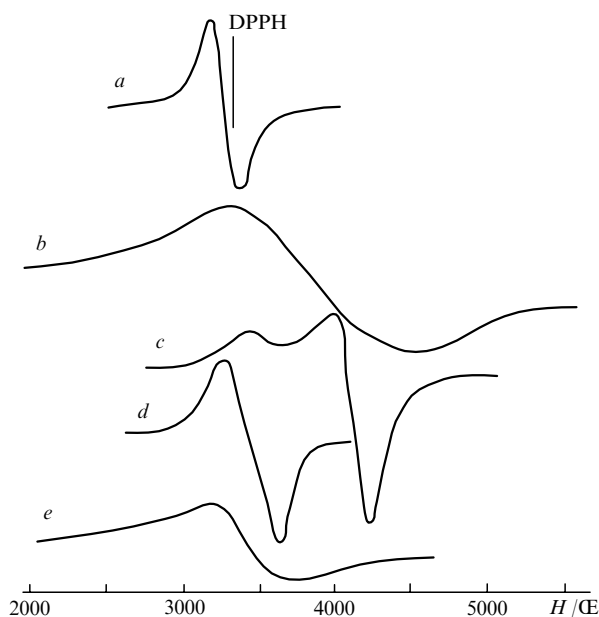


Figure 5. EPR spectra:³⁴ (a) $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ at 78 K (the z crystal axis is perpendicular to the direction of the magnetic field strength); (b, c) $(\text{Me}_4\text{N})_3\{[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]\text{Cl}_2\}$ at 293 and 78 K; (d, e) $(\text{Me}_4\text{N})_2.[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]$ at 78 and 293 K, respectively; DPPH is diphenylpicrylhydrazide.

orbitals of two technetium atoms. Thus, the M—M bonds in these complexes are of formal order 3.5. Let us present the essentials of this proof, since they are of importance for considering the electronic structure of the compounds mentioned.²

EPR signals of all compounds belonging to this type are observed both in the crystalline state and in solutions. Typical EPR spectra of $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ single crystal and $\text{K}_3[\text{Tc}_2\text{Cl}_8] \cdot 2\text{H}_2\text{O}$ solution in hydrochloric acid are shown in Figs 5 and 6, respectively. The EPR spectra of polycrystalline specimens are, as a rule, structureless lines with half-width ~ 500 Γ and effective g -factor $g_{\text{eff}} = 2.09 \pm 0.02$. Clearly defined fine structure is observed in the single-crystal spectra, though their parameters are similar to those listed above. Well-resolved spectra of solutions of these complexes can hardly be obtained because of the impossibility of achieving high technetium concentrations; where it is possible, the spectra are similar to that shown in Fig. 6.⁴ EPR spectra of glassy frozen solutions of d^4 – d^5 complexes have also been studied.^{9, 52–54} It has been established that all dinuclear d^4 – d^5 clusters studied have similar spectral patterns with the parameters coinciding within the limits of experimental error:

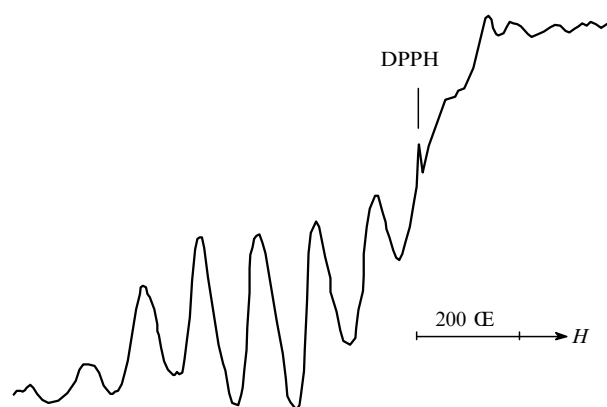


Figure 6. Typical EPR spectrum of Tc_2^{5+} complexes in solutions of HCl at 293 K $\{[\text{Tc}_2\text{Cl}_8]^{3-}$ in 4.0 M HCl $\}$.⁴

$g_{\parallel} = 1.85 \pm 0.03$, $g_{\perp} = 2.13 \pm 0.03$, $A_{\parallel} = -(188 \pm 5) \times 10^{-4} \text{ cm}^{-1}$, $A_{\perp} = -(75 \pm 5) \times 10^{-4} \text{ cm}^{-1}$ and $P = (5 \pm 1) \times 10^{-4} \text{ cm}^{-1}$. The spectra display strong anisotropy: lines of parallel orientation are observed in the region from 1600 to 5550 Γ , while those of perpendicular orientation and, probably, peaks of additional absorption are observed in the region from 2400 to 3900 Γ . From the data in Table 8 it can be seen that despite the chain structure of some of the compounds in question {e.g., $[\text{Tc}_2(\text{AcO})_4]\text{X}$ ($\text{X} = \text{Cl}, \text{Br}$)}, intermolecular exchange interactions have no effect on their magnetic properties (the μ_{eff} values are close to the spin-only value corresponding to one unpaired electron and are temperature-independent).^{2, 22–24, 51}

Thus, even qualitative analysis of the data on the magnetic susceptibility of d^4 – d^5 complexes and their EPR spectra suggests that the only unpaired electron does occupy the $\delta^*(b_{1u})$ MO,⁴ since only in this case can one expect that magnetic parameters will exhibit low sensitivity to the chemical nature of ligands. According to the results of SCF- X_{σ} -SW calculations of the electronic structure of the $[\text{Tc}_2\text{Cl}_8]^{3-}$ ion,⁹ the δ^* MO is the only MO of all unoccupied MOs to which the electrons of ligand atoms make no appreciable contribution (see Fig. 4). A more reliable proof of this fact is known that is independent of the results of theoretical calculations of the electronic structure.^{3, 52, 53} Thus, the possible ground electronic states in the molecules of d^4 – d^5 complexes and values of g -factors predicted by the theory of EPR spectra (the spin Hamiltonian method^{55, 56}) have been considered. All possible ‘reasonable’ energy permutations of the MO levels were taken into account when analysing the experimental values of g -factors (see Fig. 4). From the data obtained it follows that qualitative agreement between theory and experiment can be achieved only if the b_{1u} MO is the highest occupied molecular orbital.

Dinuclear d^5 – d^5 complexes are characterised by extremely short interatomic Tc—Tc distances (~ 2.04 Å), a chain structure, and idealised D_{4d} symmetry of the ligand environment (staggered conformation, see Fig. 1 c).^{57, 58} The molecular and electronic structure of these compounds has been considered in detail.² According to calculations^{2, 18} (see Fig. 4), the e_2 orbital formed by ‘cross’ overlap of the $4d_{xy}$ and $4d_{x^2-y^2}$ orbitals of two Tc atoms in the molecules of these compounds is the HOMO; formally, it is a low-energy δ bonding orbital. Considerable distortion of the idealised D_{4d} symmetry in the complexes results in the removal of degeneracy of the e_2 level and in partial increase in its δ bonding nature. Thus, the formation of formally quintuple M—M bonds in these compounds was first observed⁵⁷ in contrast to, e.g., analogous d^5 – d^5 osmium complexes with triple M—M bonds.^{58, 59} Cotton *et al.*⁵⁸ interpreted the M—M bonds in d^5 – d^5 technetium complexes as triple ones and their shortening as the result of changes in the diffuseness of the σ , π and δ components of these bonds due to changes in the formal technetium oxidation state.

From the data in Fig. 4 it follows that the $[\text{Tc}_2\text{X}_6]_n^{2n-}$ ions must be spin-paired (see Table 8). However, weak EPR signals of polycrystalline specimens of dinuclear d^5 – d^5 technetium complexes are observed in some instances. The parameters of these signals indicate that the specimens contain small amounts ($< 5\%$) of impurities (related paramagnetic d^4 – d^5 complexes).

Polynuclear complexes (clusters). Most of these compounds have an island structure⁵¹ (see Fig. 1 d, e, f), except for two octanuclear $[\text{Tc}_8\text{Br}_{13}]_n^{n-}$ clusters ($n = 0, 1$) with a chain structure.^{60, 61} This would seemingly simplify the interpretation of the magnetic properties of this class of compounds, since in most cases there is no need to take into account intermolecular exchange interactions. However, the interpretation of the results of magnetochemical experiments on polynuclear technetium complexes appeared to be the most complex. This is first of all due to the complexity of the system of M—M bonds and high molecular weights of the compounds in question (and, hence, to the small contribution of spin-only paramagnetism to the magnetic susceptibility and to commensurable contributions of the Langevin diamagnetism and the Van Vleck paramagnetism), large relative

error of magnetic susceptibility measurements in the vicinity of zero values, strong effects of even small amounts of low-molecular-weight paramagnetic impurities as well as to a considerable uncertainty in the values of diamagnetic corrections for this class of compounds. In connection with the foregoing, the results of magnetochemical experiments were interpreted using EPR spectroscopy (as a tool for qualitative and semiquantitative analysis) and the results of theoretical calculations.

Trigonal-prismatic clusters. The following technetium compounds with this structure are known: $(\text{Et}_4\text{N})_2 \cdot \{[\text{Tc}_6\text{Br}_6(\mu\text{-Br})_6]\text{Br}_2\}$, $(\text{Me}_4\text{N})_3\{[\text{Tc}_6\text{X}_6(\mu\text{-X})_6]\text{X}_2\}$ ($\text{X} = \text{Cl}, \text{Br}$), $(\text{Me}_4\text{N})_2[\text{Tc}_6\text{Cl}_6(\mu\text{-Cl})_6]$, $(\text{Bu}_4\text{N})_3\{[\text{Tc}_6\text{Cl}_6(\mu\text{-Cl})_6]\text{Cl}_2\}$ and $(\text{FeCp}_2)_3\{[\text{Tc}_6\text{Cl}_6(\mu\text{-Cl})_6]\text{Cl}_2\}$. The metal core of these clusters has the shape of a trigonal prism with an equilateral triangle as the base (see Fig. 1 *d*). The lateral edges of the prism correspond to the $\text{M}-\text{M}$ bonds of formal order 3.0–4.0 (2.16–2.21 Å), while the edges of the prism base correspond to those of formal order 0.5–1.0 (2.55–2.75 Å). These clusters have the idealised D_{3h} symmetry.

Generally, there is no agreement between the calculated values^{2,54} and the experimental results (see Table 8). In fact, according to extended Hückel (EH) calculations, the $\{[\text{Tc}_6\text{Br}_6(\mu\text{-Br})_6]\text{Br}_2\}^{2-}$ and $[\text{Tc}_6\text{Cl}_6(\mu\text{-Cl})_6]^{2-}$ ions are in a spin-paired ground electronic state; however, experimental studies show that there is ~ 0.1 and ~ 0.2 unpaired electron per each cluster molecule, respectively, and that an EPR signal with $g_{\text{eff}} = 1.97$ is observed (Fig. 5 *d, e*) for a polycrystalline specimen of the latter compound. It should be noted that a weak temperature-dependent paramagnetic component of the total magnetic susceptibility of these clusters can hardly be associated with the presence of mechanical impurities of other paramagnetic polynuclear clusters, since according to X-ray phase analysis data obtained with an accuracy of 5% to 10% (sensitivity of the method), both compounds contain no impurities. Thus, this paramagnetic component can be due to either the nature of the compounds under consideration or the presence of a very small amount of paramagnetic mono- or di-nuclear technetium complexes. However, the fact that EPR signals with such parameters as those of the spectra shown in Fig. 5 *d, e* could not be observed for any of the paramagnetic impurities of mono- or di-nuclear technetium complexes possible in this case is against the latter assumption.

The interpretation of magnetochemical data for the compound with ferrocenium cations appeared to be all the more complex.²⁹ In fact, strong paramagnetism (~ 5 unpaired electrons per molecule) of this compound (see Table 8), the lack of similarity between its EPR spectrum (broad spectra with $g_{\text{eff}} \sim 2$) and spectra of compounds with similar anions and different tetraalkylammonium cations close in their size (Figs 7, 8; *cf.* Fig. 5), temperature-independent behaviour (down to ~ 4 K) of all magnetic parameters as well as physicochemical properties of other technetium and rhenium clusters with ferrocenium cations indicate altogether that their electronic structure is unusual and complex. In this connection, the magnetic properties of all compounds with ferrocenium cations will be considered in Section VI.

To a first approximation, the paramagnetism of $\{[\text{Tc}_6\text{X}_6(\mu\text{-X})_6]\text{X}_2\}^{3-}$ ion corresponding to one unpaired electron per cluster (except for ferrocenium-containing compounds) is well described by theory^{2,34} (see Table 8, Fig. 4). However, no adequate description of EPR spectral parameters of these compounds ($g_{\parallel} \approx 2.00$, $g_{\perp} \approx 1.63$) can be obtained using the EH calculations. In fact, calculations of the electronic structure of trigonal-prismatic technetium clusters^{34,62,63} suggest that the HOMO in these clusters can be either the a'_2 ($\delta_{\text{M}-\text{M}}$) MO or the a'_2 ($\pi_{\text{M}-\text{M}}^*$) MO. However, it has been reported⁶⁴ that none of these variants of the electronic structure as well as all other possible variants based on the energy permutations of the MOs in the HOMO–LUMO region can explain the values of g -factors observed experimentally (the analysis of g -factors was performed

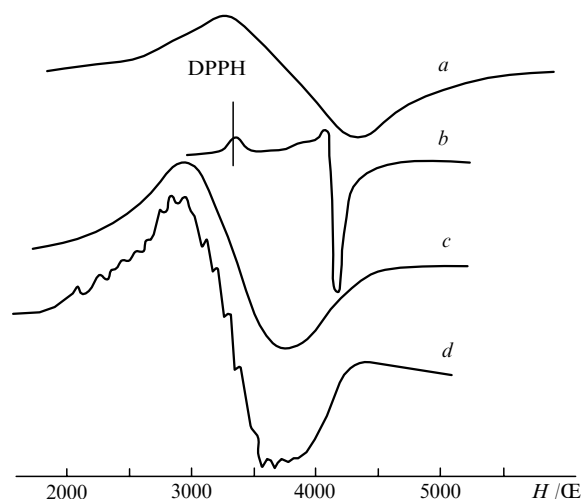


Figure 7. EPR spectra:^{4,18,34} (*a, b*) $(\text{Me}_4\text{N})_3\{[\text{Tc}_6(\mu\text{-Br})_6\text{Br}_6]\text{Br}_2\}$ at 293 and 78 K, respectively; (*c, d*) $(\text{Bu}_4\text{N})_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$ at 293 and 78 K, respectively.

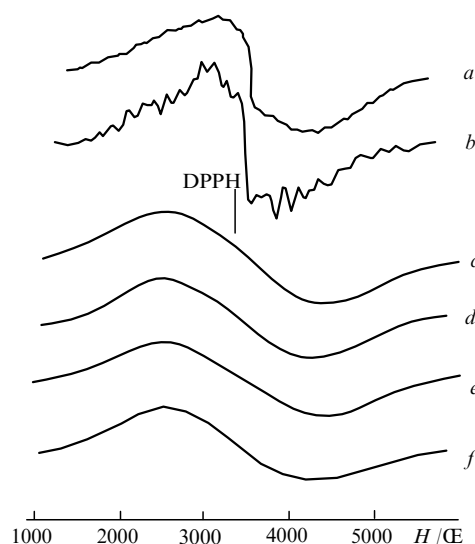


Figure 8. EPR spectra:^{28,29} (*a, b*) $(\text{Bu}_4\text{N})_3\{[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_2]\text{Cl}_2\}$ at 300 and 78 K, respectively; (*c–e*) $(\text{FeCp}_2)_3\{[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_2]\text{Cl}_2\}$ at 300, 78 and 4 K, respectively; and (*f*) $(\text{FeCp}_2)_2[\text{Re}_2\text{Br}_8]$ at 300 and 78 K, respectively.

analogously to that for d^4-d^5 complexes). Thus, magnetochemical experiments show that further refinement of theoretical MO schemes is required.

Such refinements have been carried out and reported.^{18,34,64} According to the results obtained, the experimental magnetic and structural properties of trigonal-prismatic clusters are not contradictory to the idea that there is an MO with a'_1 symmetry between the HOMO and the LUMO of these clusters. This orbital, composed mainly of diffuse $5s$ ($5p$) orbitals of the Tc atoms, is a $2\sigma_g$ bonding orbital in the direction of both vertical and horizontal $\text{M}-\text{M}$ bonds in the metal core of the clusters (see Fig. 1 *d*). In other words, it seems likely that EH calculations^{34,62,63} overestimate the interaction of δ^* and π^* MOs of the dimers in horizontal directions and underestimate the extent of participation of the $5s$ and $5p_z$ AOs in the formation of multiple $\text{M}-\text{M}$ bonds.

In conclusion of this Section let us consider the interpretation of magnetic and other physicochemical properties of certain trigonal-prismatic technetium clusters. For instance, the analysis of the magnetic susceptibility of the cluster $(\text{Me}_4\text{N})_2$.

$[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]$ (see Table 8) shows that it obeys the Curie–Weiss law; a weak signal with a relative intensity of 0.2 of that of the $[\text{Tc}_6\text{X}_{14}]^{3-}$ signal and $g_{\text{eff}} \approx 1.97$ is observed in the EPR spectra of $[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]^{2-}$, which means that the compound under consideration is paramagnetic.³⁴ Since the $[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]^{2-}$ ion has an even number of ‘metallic’ electrons, paramagnetic properties can be manifested if the ground electron state is a triplet. Weak EPR signals and small μ_{eff} values as compared to those expected from the theory for the triplet state suggest that only a part of $[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]^{2-}$ clusters is paramagnetic in real crystals. Assuming that the relative intensity of the EPR signal (0.2) corresponds to the portion of triplet paramagnetic clusters, one can evaluate the magnetic moment of the hypothetical paramagnetic cluster using the formula $\mu^2 = \mu_{\text{eff}}^2/0.2$ (see Ref. 33); the result obtained ($\mu = 2.77 \mu_B$) is rather close to the theoretical magnetic moment of a triplet species with $g_{\text{eff}} = 1.97$. Attempts to explain experimentally observed temperature dependences of the magnetic susceptibility and intensity of the EPR signal by the influence of the Boltzmann population of the triplet excited state, intermolecular exchange interactions or splitting of the triplet state levels in the crystal field have failed.

The simultaneous presence of singlet and triplet $[\text{Tc}_6(\mu\text{-Cl})_6\text{Cl}_6]^{2-}$ clusters in crystals can be explained by sensitivity of the multiplicity of the ground state of the cluster to slight changes in its structure. In real crystals, a transition from the singlet ground state of the cluster to its triplet state can occur due to the presence of defects (vacancies, dislocations, disorder in the ligand environment, etc.) or, which is more probable in our opinion,⁶⁴ due to fast kinetic S – T exchange with involvement of delocalised MOs formed mainly by the $5s(5p)$ orbitals of the Tc atoms.

The latter assumption is also supported by the long-wave IR spectra of trigonal-prismatic technetium clusters (Fig. 3) and unusual physicochemical properties of clusters with ferrocenium cations. In fact, the properties of the last-mentioned compounds taken altogether can be explained^{28,29} as a result of the formation of conduction bands and, perhaps, heavy-fermionic bands formed involving delocalised $5s(5p)$ orbitals of the Tc atoms and $4s$ orbitals of the Fe atoms of ferrocenium cations. The values of the g -factor in the EPR spectra of these compounds, close to that of the free electron, metallic type of the temperature dependence of conductivity, and unusual temperature dependence of the Mössbauer and X-ray photoelectron spectra are evidence for the formation of such bands. A more detailed theoretical interpretation of these properties will be given in Section VI of this review.

Tetragonal-prismatic clusters. This group comprises the following compounds: $\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}\} \cdot 2\text{H}_2\text{O}$, $[\text{H}(\text{H}_2\text{O})_2] \cdot [\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}$, $[\text{H}(\text{H}_2\text{O})_2]_2\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}_2\}$, $(\text{Bu}_4\text{N})_2 \cdot \{[\text{Tc}_8(\mu\text{-Br})_8(\text{Br}, \text{I})_4]\text{I}_2\}$, $(\text{FeCp}_2)_2\{[\text{Tc}_8(\mu\text{-Br})_8\text{Br}_4]\text{Br}_2\}$. Clusters belonging to this type are close in structure to the trigonal-prismatic ones. Their major distinction lies in the fact that in this case the metal core of the cluster is a prism with a rhombus in its base (Fig. 1e). According to the conventional count rule of valence electrons in clusters with acido ligands,^{65,66} the first of the above compounds must have 43, while each of the others must have 44 ‘metallic’ electrons. The calculated electronic structure of a cluster with 44 valence electrons is shown in Fig. 4.^{34,62} As can be seen, these compounds must be spin-paired, whereas the $[\text{Tc}_8\text{Br}_{13}] \cdot 2\text{H}_2\text{O}$ cluster must possess a trivial paramagnetism with μ_{eff} corresponding to one unpaired electron. Indeed, the experimental data (see Table 8) show that only the compound $[\text{Tc}_8\text{Br}_{13}] \cdot 2\text{H}_2\text{O}$ has unpaired electrons; other clusters are characterised by TIP with large χ'_M values due to the high molecular weights of the clusters and their structural peculiarities [$\chi'_M(\text{TIP}) = (570 \pm 150) \times 10^6$ CGSE units].

Magnetic properties of the ferrocenium-containing bromide octanuclear cluster are of particular interest. From the data in Table 8 it can be seen that paramagnetism of this compound

obeys the Curie–Weiss law and corresponds to about two unpaired electrons per ferrocenium cation. No EPR signals of this compound are observed either at room temperature or at a liquid nitrogen temperature. Comparison of experimental results with the magnetic properties of ferrocenium-containing trigonal-prismatic chloride clusters considered above and $(\text{FeCp}_2)_2[\text{Re}_2\text{Br}_8]$ (this compound possesses trivial paramagnetism corresponding to about two unpaired electrons per formula unit and signals with $g_{\text{eff}} = 2.003$ are observed in its EPR spectra^{28,29}) shows that: (1) the EPR signals of all compounds in question are not due to localisation of the unpaired electrons on ferrocenium cations (this is also confirmed by the absence of EPR spectra of ferrocenium chloride and other ferrocenium compounds under the same conditions); (2) the EPR signals of the above clusters cannot also be due to localisation of the unpaired electrons on the cluster fragments, since in this case the recorded EPR spectra would be similar to those of the clusters with tetraalkylammonium cations; and (3) the paramagnetism of ferrocenium cations can affect the overall static magnetic susceptibility. Thus, it is most likely that all experimental facts as well as other unusual properties of the compounds under study,^{28,29} are due to fast dynamic electron transfer from the anion to the cation over distances 5 to 6 Å in a band formed by the overlap of upper $ns(np)$ AOs of the cluster anions and ferrocenium cations (see also Section VI).

Octahedral clusters. This group comprises the following compounds: $(\text{Bu}_4\text{N})_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$, $[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2 \cdot [\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$ and $[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6] \cdot 4\text{H}_2\text{O}$ (see Table 8), which are characterised by octahedral metal cores (see Fig. 1f). However, in contrast to the classical $[\text{M}_6\text{X}_8]^{4+}$ clusters ($\text{M} = \text{Mo}, \text{W}; \text{X} = \text{Cl}, \text{Br}, \text{I}$),⁶⁶ three of the eight positions of the bridging halide ligands in the technetium clusters remain statistically unoccupied. This effect of the distortion of octahedral clusters leads to their stabilisation despite the presence of nine ‘excess’ metallic electrons as compared to the stable electronic configuration of the $[\text{M}_6\text{X}_8]^{4+}$ clusters. The above technetium clusters each contain 33 valence electrons. Their electronic structures are depicted schematically in Fig. 4. It can be seen that these clusters possess trivial paramagnetism with μ_{eff} corresponding to one unpaired electron, which is confirmed by the data in Table 8. A typical EPR spectrum of one of the compounds in question shown in Fig. 7 is characterised by hyperfine structure and $g_{\text{eff}} \approx 2$.

Thus, the magnetochemical studies^{18,34} have shown that it is of crucial importance to know experimental magnetic properties of the maximum possible number of technetium compounds. Magnetochemistry of di- and polynuclear technetium clusters is of particular interest, since the magnetochemical studies of these compounds in combination with other methods of physicochemical analysis and theoretical calculations make it possible, first, to identify the above compounds and reveal the presence of impurities and, second, to study the electronic structure of these clusters that often have no close analogues. It should be noted that in some instances magnetochemical studies in combination with X-ray studies can provide valuable information on the composition and the formal oxidation state of technetium. For example, in such a way the formal charges of cluster anions in the compounds $\{[\text{Tc}_8\text{Br}_4(\mu\text{-Br})_8]\text{Br}\} \cdot 2\text{H}_2\text{O}$, $[\text{H}(\text{H}_2\text{O})_2]\{[\text{Tc}_8\text{Br}_4(\mu\text{-Br})_8]\text{Br}\}$, $[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6]$ and $[\text{H}_3\text{O}(\text{H}_2\text{O})_3]_2[\text{Tc}_6(\mu_3\text{-Br})_5\text{Br}_6] \cdot 4\text{H}_2\text{O}$ ^{9,61,67,68} have been determined. In fact, it was impossible to locate hydrogen atoms in the structures of these clusters using the results of X-ray studies only; however, magnetic measurements made it possible to determine the number of unpaired electrons in the anions and, hence, the number of ‘metallic’ electrons, the oxidation state of technetium and thereby the anionic charges in the clusters.

IV. X-Ray photoelectron study of the structure of technetium complexes

1. Binding energies of the core electrons of technetium atoms

Table 9 presents the binding energies of the core electrons (E_b) in technetium clusters and some mononuclear complexes. It is note-

worthy that the lines corresponding to $E_b(\text{Tc } 3d_{5/2})$ are singlets in all compounds; judging by the half-widths of the lines ($l_{1/2} \leq 2.0$ eV), it is impossible to assign them to two or more chemically or structurally nonequivalent types of the Tc atoms. This conclusion is of particular importance for clusters with fractional oxidation state of technetium and $[\text{Tc}_2\text{X}_6]^{2-}$ anions

Table 9. Binding energies of the core electrons (E_b/eV) of Tc and halogen atoms in the X-ray photoelectron spectra of technetium compounds and the effective charges on Tc atoms calculated by the Pauling electronegativities (EN) and EH methods.^{70–74}

Compound	Tc oxidation state	$E_b(\text{Tc } 3d_{5/2})$	$l_{1/2}$ /eV	$E_b(\text{Cl } 2s_{1/2})$ [$E_b(\text{Br } 3p_{3/2})$] { $E_b(\text{I } 4d_{5/2})$ }	Z_{EN} (Z'_{EN})	Z_{EH} (Z'_{EH})
K[TcO ₄] (9)	+7.0	259.0	1.8	—	1.60 (1.60)	3.854 (3.92)
NH ₄ [TcO ₄] (10)	+7.0	258.9	1.5	—	(1.57)	(3.85)
(FeCp ₂)[TcO ₄] (10')	+7.0	258.9	1.5	—	(1.57)	(3.85)
Na[TcO ₄] · nH ₂ O (11)	+7.0	258.9	1.5	—	(1.57)	(3.85)
Ni[TcO ₄] ₂ · nH ₂ O (12)	+7.0	259.1	1.5	—	(1.63)	(4.00)
Co[TcO ₄] ₂ · nH ₂ O (13)	+7.0	259.2	1.7	—	(1.66)	(4.08)
Ca[TcO ₄] ₂ · nH ₂ O (14)	+7.0	259.2	1.6	—	(1.66)	(4.08)
Ba[TcO ₄] ₂ · nH ₂ O (15)	+7.0	259.0	1.8	—	(1.60)	(3.92)
(Ph ₄ As)[TcO ₄] (16)	+7.0	258.4	1.3	—	(1.41)	(3.46)
(Bu ₄ ⁺ N)[TcO ₄] (17)	+7.0	258.7	1.7	—	(1.49)	(3.70)
Tc ₂ S ₇ (18)	+7.0	254.7	1.4	—	0.31 (0.22)	(0.65)
K ₂ [TcOCl ₅] (19)	+5.0	257.6	1.6	269.0	1.00	—
(Bu ₄ ⁺ N)[TcOCl ₄] (20)	+5.0	257.4	1.5	268.9	1.05	2.312 (2.40)
(Bu ₄ ⁺ N)[TcOBr ₄] (21)	+5.0	256.5	1.6	[181.4]	0.85	(2.00)
K ₃ [Tc ₂ Cl ₈ O ₂] (22)	+4.5	256.8	1.4	268.9	1.08 (0.85)	—
Tc ₂ O ₅ (23)	+5.0	256.6	1.8	—	1.72 (0.80)	—
Tc ₂ O ₅ · nH ₂ O (24)	+5.0	256.0	1.7	—	1.72 (0.65)	—
TcO ₂ (25)	+4.0	255.2	1.8	—	1.52 (0.38)	(0.9)
TcO ₂ · nH ₂ O (26)	+4.0	255.4	2.0	—	1.52 (0.43)	(0.9)
K ₂ [TcCl ₆] (27)	+4.0	257.0	1.3	269.2	0.86	1.793 (1.793)
(FeCp ₂) ₄ [H ₃ O(H ₂ O) ₄] ₂ [TcCl ₆] ₃ (27')	+4.0	257.0	1.5	269.1	0.86	1.793
K ₂ [TcBr ₆] (28)	+4.0	256.2	1.6	[181.4]	0.69	(1.60)
(NH ₄) ₂ [TcBr ₆] (29)	+4.0	256.2	1.5	[181.4]	0.69	(1.60)
[TcPy ₂ Cl ₄] (30)	+4.0	256.8	1.6	268.8	0.83	—
K ₂ [TcI ₆] (31)	+4.0	255.6	1.6	{~48.0}	0.46	0.934 (1.20)
(NH ₄) ₂ [TcI ₆] (32)	+4.0	255.5	1.5	{~48.0}	0.46	0.934 (1.20)
(Bu ₄ ⁺ N) ₂ [Tc ₂ Cl ₈] (33)	+3.0	255.8	1.3	268.5	0.88 (0.54)	1.445 (1.445)
[Tc ₂ (AcO) ₄ Cl] (34)	+2.5	255.8	1.8	268.3	0.91 (0.54)	1.206 (1.30)
K[Tc ₂ (AcO) ₄ Cl ₂] (35)	+2.5	255.8	1.6	268.2	0.92 (0.54)	—
[Tc ₂ (AcO) ₄ Br] (36)	+2.5	255.7	1.6	[181.4]	0.87 (0.49)	—
K ₃ [Tc ₂ Cl ₈] · nH ₂ O (37)	+2.5	255.5	1.8	269.0	0.80 (0.40)	1.065 (1.065)
Tc ₄ O ₅ · nH ₂ O (38)	+2.5	255.9	1.8	—	1.25 (0.58)	—
K ₂ [Tc ₂ Cl ₆] (39)	+2.0	254.9	1.6	268.9	0.73 (0.30)	0.704 (0.704)
K ₂ [Tc ₂ Br ₆] · nH ₂ O (40)	+2.0	254.6	1.7	[181.4]	0.62 (0.20)	—
(Et ₄ N) ₂ {[Tc ₆ (μ-Br) ₆ Br ₆]Br ₂ } (41)	+2.0	254.7	1.2	[181.1], [182.6]	0.60 (0.22)	(0.55)
(Me ₄ N) ₃ {[Tc ₆ (μ-Br) ₆ Br ₆]Br ₂ } (42)	+1.83(3)	254.8	1.2	[181.1], [182.5]	0.60 (0.25)	(0.65)
(Me ₄ N) ₃ {[Tc ₆ (μ-Cl) ₆ Cl ₆]Cl ₂ } (43)	+1.83(3)	255.0	1.3	268.8, <u>270.6</u>	0.70 (0.32)	(0.76)
(FeCp ₂) ₃ {[Tc ₆ (μ-Cl) ₆ Cl ₆]Cl ₂ } (43')	+1.83(3)	255.0	1.3	268.8, <u>270.6</u>	0.70 (0.32)	(0.76)
(Bu ₄ ⁺ N) ₃ {[Tc ₆ (μ-Cl) ₆ Cl ₆]Cl ₂ } (43'')	+1.83(3)	255.0	(1.4)	268.8, <u>270.6</u>	0.70 (0.32)	(0.76)
(Me ₄ N) ₂ [Tc ₆ (μ-Cl) ₆ Cl ₆] (44)	+1.66(6)	255.3	(1.4)	268.9, <u>270.7</u>	0.70 (0.42)	0.597 (0.597)
{[Tc ₈ (μ-Br) ₈ Br ₄]Br} · 2 H ₂ O (1)	+1.625	254.7	(1.2)	[181.1], [182.6]	0.60 (0.22)	(0.55)
[H(H ₂ O) ₂] ₂ {[Tc ₈ (μ-Br) ₈ Br ₄]Br ₂ } (3)	+1.5	254.7	(1.4)	[181.0], [182.5]	0.55 (0.42)	(0.55)
(FeCp ₂) ₂ {[Tc ₈ (μ-Br) ₈ Br ₄]Br ₂ } (3')	+1.5	255.2	(1.4)	[181.0], [182.5]	0.70 (0.42)	(0.60)
[H ₃ O(H ₂ O) ₃] ₂ [Tc ₆ (μ-Br) ₃ Br ₃] · nH ₂ O (6)	+1.5	255.3	(1.8)	[181.1], [182.5]	0.55 (0.42)	(0.90)
(Bu ₄ ⁺ N) ₂ {[Tc ₈ (μ-X) ₈ X ₄]I ₂ } (45) (X = 0.5 Br + 0.5 I)	+1.5	254.6	(1.5)	[181.0], [182.5] {48.4}, {49.8}	0.52 (0.17)	—
{[Tc ₈ (μ-I) ₈ I ₄]I} · nH ₂ O (46)	+1.625	254.5	(1.3)	{48.4}, {49.8}	0.49 (0.17)	—
(FeCp ₂) ₃ {[Tc ₆ (μ-I) ₆ I ₆]I ₂ } (46')	+1.5	254.4	(1.4)	{48.3}, {49.6}	0.49 (0.17)	—
TcC (47)	0	253.9	(1.5)	—	0 (0)	(0)
Tc (metal) (48)	0	253.9	(1.0)	—	0 (0)	0 (0)

Notes. The binding energies are given relative to a peak from adsorbed vapours of diffusion oil [$E_b(\text{Cl } 1s) = 284.3$ eV]. The errors of the binding energy determination are ± 0.2 eV, those of half-widths $l_{1/2}$ are ± 0.1 eV. The binding energies of bridging atoms are underlined. The Z'_{EN} values were determined for compounds with M—M bonds, pertechnetates and binary compounds only from the correlation for mononuclear complexes (curve *a* in Fig. 9). The Z'_{EH} values were determined only for those compounds for which the experimental chemical shifts in X-ray emission spectra^{75–77} and X-ray photoelectron spectra^{70–74} are known.

(see Table 9) in which the Tc atoms formally either have different oxidation state or occupy strongly nonequivalent positions in the structure. Thus, equalisation of the electron density on technetium atoms occurs in all complexes. For most clusters such an equalisation of the electron density due to the formation of multiple M–M bonds could be assumed on the basis of their structural,^{1, 2, 19, 31, 51, 67} magnetic,^{18, 34} spectroscopic^{8, 52, 53, 54} and other physicochemical properties; however, in the case of $[\text{Tc}_2\text{X}_6]^{2-}$ compounds and octanuclear clusters a conclusion that the Tc atoms are structurally nonequivalent would be the most probable.^{19, 57, 67, 69} However, the half-widths of the Tc $3d_{5/2}$ lines in the X-ray photoelectron spectra of these compounds are even smaller as compared to half-widths of the same lines in the spectra of other technetium complexes including mononuclear ones.^{70–74} This indicates strong delocalisation of the electron density in such clusters.

It is known that the chemical shifts in X-ray emission and X-ray photoelectron spectra often correlate with the effective charge on the atom considered.^{75–78} The method based on Pauling electronegativities (EN)^{78–80} is one of the simplest methods used in the effective charge calculations. As a rule, the effective charges (Z_{EN}) calculated using this method correlate almost linearly with binding energies.^{78–80} However, the EN method makes it possible to calculate the Z_{EN} values determined only by conventional valence bonds. If an additional bonding occurs in a compound (*e.g.*, due to hydrogen or π -donor bonds, trans-effect, dative bonds, multiple homopolar bonds, surface effects, *etc.*), then the Z_{EN} values can differ substantially from the experimental effective charges; however, this difference itself will be indicative of such additional effects.^{79, 80} It should be noted^{79, 80} that effective charges determined experimentally by different physicochemical or theoretical methods can differ considerably for the same compound, since each method is characterised by specific ‘sensitivity’ to an effective space region around the atom in question.

Using the EN calculations carried out in the framework of a unified approach,^{70, 74} it has been possible to reveal the reasons for changes in the binding energies of the core electrons of the Tc atoms; this is necessary for determining the oxidation state of technetium in newly synthesised compounds. In other words, this method allows one to understand specific features of the structure of technetium compounds with M–M bonds. It should be noted that, although EN calculations are approximate and arbitrary, this method has some advantages over the traditionally used purely qualitative description of changes in the binding energies of the core electrons depending on the oxidation state of the atom and on the electronegativity of the ligands surrounding this atom, since it relates these two parameters on which the binding energy depends in most instances. Of course, this method lacks sufficient physical grounds characteristic of more rigorous computational methods such as, *e.g.*, the MO LCAO method. However, as a rule, EN calculations make it possible to obtain almost linear correlations between the effective charges^{78–80} and the binding energies, especially, for compounds of similar composition and structure.

The Z_{EN} values were calculated using the following electronegativities (χ) of technetium obtained by interpolating the χ values for Re, Mo, Mn, and Cr in different oxidation states:^{79, 80} $\chi(\text{Tc}^{\text{I}}) = 1.10$, $\chi(\text{Tc}^{\text{II}}) = 1.40$, $\chi(\text{Tc}^{\text{III}}) = 1.60$, $\chi(\text{Tc}^{\text{IV}}) = 1.80$, $\chi(\text{Tc}^{\text{V}}) = 1.95$, $\chi(\text{Tc}^{\text{VI}}) = 2.10$ and $\chi(\text{Tc}^{\text{VII}}) = 2.25$. The Z_{EN} calculations were performed^{70–74} according to the Batsanov procedure^{79, 80} assuming the absence of M–M bonds and other peculiarities of the molecular, crystal and electronic structure capable of affecting the $\chi(\text{Tc})$ value. Thus, it has been assumed *a priori* that in the case of systematic deviations of Z_{EN} values from the experimental effective charges (Z'_{EN}) for the clusters (see Table 9) these deviations must be due to a specific effect of the M–M bonds, since the nature of the M–X bonds in mono-, di- and poly-nuclear clusters remains unchanged in most instances, except for the M– μ -X and M–X_{ax} bonds.

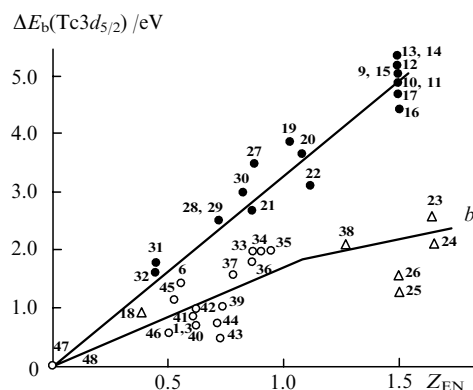


Figure 9. Dependence of the chemical shifts of binding energies of the core electrons [$\Delta E_b(\text{Tc}3d_{5/2})$] in technetium compounds on the effective charge on the Tc atoms (Z_{EN}) calculated by the Pauling electronegativities method (the numbering of points corresponds to that of the compounds in Table 9): (a) correlation for mononuclear complexes (filled circles); (b) correlation for compounds with M–M bonds, di- and polynuclear clusters with acido ligands (open circles) and for binary compounds (sulfides and oxides, open triangles).⁷² For visual aids, correlation lines are drawn.

The dependence of the $\Delta E_b(\text{Tc}3d_{5/2})$ values on Z_{EN} for technetium complexes is shown in Fig. 9. It can be seen that all experimental points fall on two curves. The curve *a* closely resembles an almost straight line and describes the dependence $\Delta E_b(\text{Tc}3d_{5/2}) = \varphi(Z_{\text{EN}})$ for compounds containing no Tc–Tc bonds. The points that obey the dependence $\Delta E_b(\text{Tc}3d_{5/2}) = \varphi'(Z'_{\text{EN}})$ and correspond to the technetium compounds with strong Tc–Tc bonds and to binary compounds fall on curve *b*. The curve *b* in Fig. 9 is much below the curve *a*. This is a direct consequence of neglecting the effect of homopolar multiple Tc–Tc bonds on the electronegativity of Tc atoms, which leads to overestimation of the Z_{EN} values as compared to the ‘true’ effective charges (Z'_{EN}) obtained within the framework of the EN model. Thus, the Z'_{EN} values for technetium clusters can be determined either by introducing some corrections to the technetium electronegativity or from experimental $\Delta E_b(\text{Tc}3d_{5/2})$ values using the correlation curve for mononuclear complexes (see Fig. 9, curve *a*).

Comparison of the curves *a* and *b* in Fig. 9 as well as comparison of Z_{EN} and Z'_{EN} values (see Table 9) shows that the formation of the metal–metal bonds in technetium clusters leads to a decrease in Z_{eff} on the metal atoms. It should be noted that no analogous decrease in Z_{eff} is observed upon the formation of M–M bonds in clusters of other transition *d* elements with similar structures and properties. At first glance, it may appear that this technetium ‘anomaly’ is only a consequence of inadequacy of the procedure for calculating the Z_{EN} values. However, this is not the case. To make sure that Z_{eff} values decrease as the M–M bonds are formed in the case of technetium, it is sufficient to compare the experimental values of changes in the binding energies of the core electrons (ΔE_b) for some transition *d* elements (Table 10); for molybdenum, the opposite is observed (Z_{eff} increase as the M–M bonds are formed), while the Z_{eff} values remain unchanged for rhodium and most of other elements. In fact, from the data in Table 10 and Refs 19, 51, 70–74, 78 and 81–85 it follows that the mean change in the ΔE_b value corresponding to a change of unity in the formal oxidation state of a metal M (M = Tc, Re, and Mo) in complexes with similar stoichiometry and structures is ~ 0.7 eV. Analogous changes in ΔE_b on going from mononuclear d^3 complexes to dinuclear d^4 – d^4 ones are +1.2 eV for Tc, +0.7 eV for Re and –3.3 eV for Mo. Data obtained by X-ray emission spectroscopy^{86–88} allowed one to draw analogous conclusions that Z_{eff} values increase in the case of the Mo–Mo bonds.

Table 10. Chemical shifts of binding energies (ΔE_b) of the core electrons of transition metals in their clusters relative to those of pure metals (averaged values, according to the reported data^{19, 51, 70–74, 78, 81–85}).

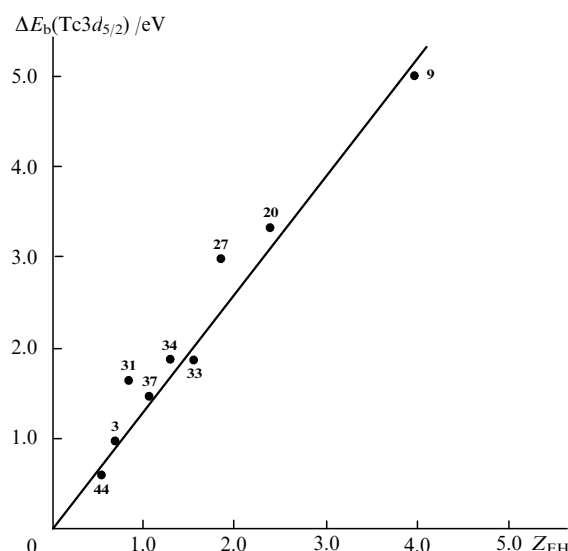
Cluster	ΔE_b / eV	Cluster	ΔE_b / eV
[Re ₂ Cl ₈] ^{2–}	3.0	[Ta ₆ Cl ₁₂] ²⁺	2.6
(ReCl ₃) _n	2.7	[Ta ₆ Cl ₁₂] ⁴⁺	2.6
(ReCl ₂) _n	2.0	[Mo ₂ Cl ₈] ^{4–}	3.6
[Nb ₆ Cl ₁₂] ²⁺	2.6	(MoCl ₂) _n	3.3
[Nb ₆ Cl ₁₄] ²⁺	2.6	[Rh ₂ (AcO) ₄]	2.4
[Tc ₆ (μ-Cl) ₆ Cl ₆] ^{n–}	1.0	[L ₂ Pd(AcO) ₂] ₂	2.7
[Tc ₂ Cl ₈] ^{2–}	1.9	[Cr ₂ Cl ₉] ^{3–}	2.6
[Tc ₂ Cl ₆] ^{2–}	1.1		

It is clear that in the general case the effective atomic charge must depend on the formal order of the bond between this atom and another atom, since a redistribution of the electron density of valence electrons mostly occurs as the bond order increases. This appreciably changes the conditions of shielding of the positive nuclear charge by outer electrons. Simultaneously, when two atoms approach each other as a result of the increase in the order of the interatomic bond, their inner atomic electron shells must undergo an increasing repulsion, which brings about the opposite result, *viz.*, a decrease in the extent of shielding of the positive nuclear charge due to the formation of the multiple bond. Since each physical method is characterised by specific ‘sensitivity’ to an effective space region around the atom M, the net change in Z_{eff} will strongly depend on many factors and can be either positive or negative, or be equal to zero.

A theoretical explanation for the effect of a decrease in Z_{eff} on the Tc atoms in the formation of M–M bonds consists in the following:⁶⁴ in contrast to clusters of other *d* elements, it is highly probable that the outer 5*s* (5*p*) AOs of technetium clusters participate in the formation of ‘metallic’ bonding MOs. Thus, it has been shown experimentally⁶⁴ and theoretically⁸⁹ that the *a*₁′ MO composed mainly of 5*s* (5*p*) orbitals of six Tc atoms represents the HOMO in the trigonal-prismatic technetium clusters [Tc₆X₁₄]^{3–} (X = Cl and Br) (see also Section III). Since these outer AOs possess an increased capability of shielding the positive nuclear charge, their participation in the formation of the M–M bonds results in a decrease in Z_{eff} . It should be noted that an analogous conclusion that Z_{eff} values of the Tc atoms are decreased upon the formation of M–M bonds was drawn on the basis of analysis of changes in the chemical shifts in the K_{α1} X-ray emission spectra of technetium compounds.^{76, 77}

The effective charge on the Tc atoms have also been evaluated using extended Hückel calculations.^{71–73} This semiempirical MO method allows one to take into account the effect of M–M bonds. Therefore, the effective charge obtained by EH calculations (Z_{EH}) can correlate directly with the chemical shifts in the spectra of Tc compounds without introduction of corrections for the M–M bonds. However, a strong parametrisation effect on the results of calculations hampers the use of EH calculations. To diminish this effect, only the results of calculations for the chloride technetium complexes ([TcCl₆]^{2–}, [Tc₂Cl₈]^{2–}, [Tc₂Cl₈]^{3–}, [Tc₂Cl₆]^{2–}, and [Tc₆Cl₁₄]^{3–}) were used. The more detailed consideration of the general procedure for calculations and parametrisation, and the procedure for determination of the effective charge (Z'_{EH}) using EH calculations and the data of X-ray emission spectroscopy (XES) and X-ray photoelectron spectroscopy (XPES) simultaneously is given in Section V. These values are listed in Table 9.

The dependence of $\Delta E_b(\text{Tc } 3d_{5/2})$ on Z_{EH} is shown in Fig. 10. Comparison of the data in Figs. 9 and 10 and the Z'_{EN} and Z'_{EH} values shows that Z_{eff} calculated by the EN and EH methods differ considerably; however, they are related by an unambiguous monotonic dependence. In addition, common to both mononuclear complexes and clusters is the observed dependence of the $\Delta E_b(\text{Tc } 3d_{5/2})$ values on Z_{EH} rather than on Z_{EN} . This is under-

**Figure 10.** Dependence of the chemical shifts of binding energies of the core electrons $\Delta E_b(\text{Tc } 3d_{5/2})$ in technetium compounds on the effective charge on the Tc atoms (Z_{EH}) calculated by the EH method (the numbering of points corresponds to that of the compounds in Table 9).⁷²

standable since the EH calculations (in contrast to the EN calculations) take into account electronic effects due to the formation of the M–M bonds.

2. Binding energies of the core electrons of halogen atoms

Table 11 lists the binding energies of the core electrons of the halogen atoms [$E_b(\text{X})$] in clusters of transition *d* elements. As can be seen, the $E_b(\text{X})$ values vary depending on the nature of the halogen–metal bonds. For technetium clusters, the smallest $E_b(\text{X})$ values have been found for axial halogen atoms in carboxylate dinuclear complexes with the ‘lantern’-type structure (see Table 9). Since the $E_b(\text{X}_{\text{ax}})$ values are close to analogous values for pure ionic compounds,⁷⁸ it can be assumed that all Tc–X_{ax} bonds are ionic. It should also be noted that these types of bonds of halogen atoms are much weaker due to the trans-effect of multiple metal–metal bonds. Previously,^{78, 84, 85} an analogous phenomenon has been observed experimentally for dinuclear Re and Rh complexes.

Table 11. Binding energies (E_b / eV)^a of the core electrons of halogen atoms in clusters of transition *d* elements (averaged values, according to the reported data^{19, 51, 70–72, 78, 81–85}).

Cluster-forming metal	$E_b(\text{Cl } 3p_{3/2})$			$E_b(\text{Br } 3d_{5/2})$			$E_b(\text{I } 4d_{5/2})$		
	ax	eq	brid-ge	ax	eq	brid-ge	ax	eq	brid-ge
Tc	197.2	198.0	199.5	67.7	67.7	69.2	—	48.4	49.8
Re	197.5	198.5	199.7	68.1	68.8	68.8	48.5	49.2	—
Mo	197.3	197.8	199.8	—	67.7	68.8	—	48.5	49.7
Rh	197.4	198.1	—	68.2	68.7	—	—	—	—
Pt	197.5	198.2	—	68.2	68.9	—	48.6	—	—
Nb	—	197.0	198.7	—	67.4	—	—	—	—
Ta	—	197.0	199.1	—	68.0	—	—	—	—
K ^b	197.5	—	—	67.8	—	—	—	—	—

Note. The following notations are used: ax is axial, eq is terminal (equatorial), and br is bridging. ^a The error of binding energy determination is ± 0.4 eV. ^b Potassium halides. The binding energies are given relative to the C1*s* line (284.3 eV).

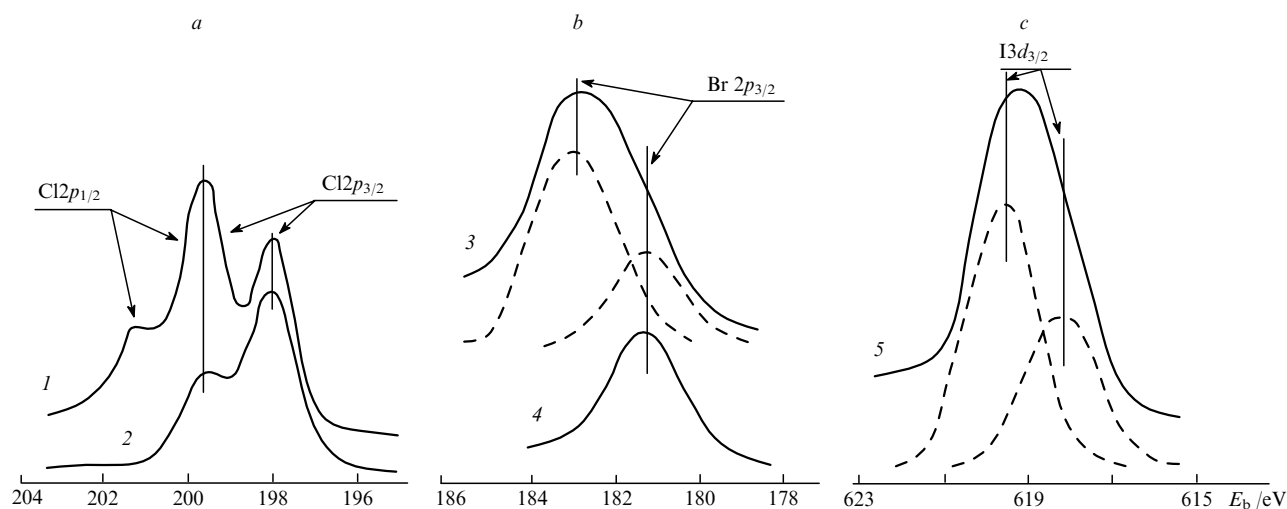


Figure 11. Binding energy X-ray photoelectron spectra of the core electrons of the halogen atoms in polynuclear (1, 3, 5) and mononuclear (2, 4) chloride (a), bromide (b) and iodide (c) complexes: (1) $(\text{Me}_4\text{N})_2[\text{Tc}_6\text{Cl}_{12}]$; (2) $\text{K}_2[\text{TcOCl}_5]$; (3) $[\text{Tc}_8\text{Br}_{13}] \cdot 2\text{H}_2\text{O}$; (4) $(\text{NH}_4)_2[\text{TcBr}_6]$; and (5) $[\text{Tc}_8\text{I}_{13}] \cdot 2\text{H}_2\text{O}$. Dashed lines represent the deconvolution of experimental spectra by the least squares method assuming a Lorentzian shape of single peaks.

The $E_b(\text{X})$ values for the equatorial (terminal) halogen atoms in the technetium clusters correspond to the binding energies of the core electrons of the terminal halogen atoms in mononuclear halide complexes (see Table 9). The $\text{Tc}-\text{X}_{\text{eq}}$ bond lengths are also close to those of the $\text{Tc}-\text{X}$ bonds in halide Tc^{V} and Tc^{IV} complexes.^{1,2,31,90,91} The $E_b(\text{X})$ values for these types of halogens indicate weak ionicity of the $\text{Tc}-\text{X}_{\text{eq}}$ bonds.⁷⁸

The largest $E_b(\text{X})$ values are observed for the bridging halogen atoms in polynuclear clusters (see Table 9); they are close to the $E_b(\text{X})$ for the halogen elements,⁷⁸ which indicates that the $\text{Tc}-(\mu\text{-X})$ bonds are covalent.

As can be seen from the data presented, the structure and composition of technetium complexes can be qualitatively and semiquantitatively judged from the $E_b(\text{X})$ values of the halogen atoms. Indeed, the structures of polynuclear technetium clusters contain all three types of halogen atoms, whereas two lines corresponding to $E_b(\text{X})$ of the terminal and bridging halogen atoms with relative intensities proportional to the stoichiometric amount of these halogen atoms in the cluster are observed in the X-ray photoelectron spectra of these compounds (Fig. 11). It is likely that the peaks corresponding to axial halogen atoms or halide ions are not observed in the spectra due to their low relative intensity.

The 'sensitivity' of the chemical shifts in the X-ray photoelectron spectra to the coordination type of halide ligands can serve as a convenient tool for tentative analysis of the structure. In some instances, the data obtained by X-ray photoelectron spectroscopy significantly complement the information obtained by X-ray analysis and chemical analysis. Thus, an attempt to establish unambiguously the exact stoichiometric composition of a bromide–iodide octanuclear technetium cluster using X-ray analysis⁹² and chemical analysis has failed. Only additionally taking the X-ray photoelectron spectra has made it possible to establish the stoichiometry, composition and structure of the cluster $(\text{Bu}_4\text{N})_2[\text{Tc}_8(\mu\text{-Br})_4(\mu\text{-I})_4\text{Br}_2\text{I}_2]_2$ (see Table 9).

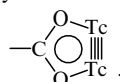
3. Binding energy X-ray photoelectron spectra

The binding energy X-ray photoelectron spectra of a number of technetium compounds have been considered.^{71–73} The experimental spectra have been compared with the results of theoretical SCF-X α -SW calculations for K_2TcCl_6 ⁹³ and $\text{K}_3\text{TcCl}_8 \cdot 2\text{H}_2\text{O}$.⁹ It has been shown that at a qualitative level the calculations represent satisfactorily the fine structure of X-ray photoelectron spectra in most cases. However, the spectra of solids are not always well resolved due to line broadening. The approximate

character of the theoretical calculations makes it possible, as a rule, to determine only the order in which the MOs are arranged on the energy scale rather than the exact absolute values of their vertical ionisation potentials. Despite these drawbacks the following qualitative conclusions were drawn:^{71–73}

1. The high-lying MOs ($\delta_{\text{M}-\text{M}}$ and $\delta^*_{\text{M}-\text{M}}$ orbitals according to the calculations and EPR spectroscopy data^{9,52,53,94}) appear to be separated in energy from other MOs on going from $[\text{TcCl}_6]^{2-}$ to $[\text{Tc}_2\text{Cl}_8]^{3-}$.

2. Replacement of Cl atoms by μ -bridging acetate ions results in a higher degree of mixing in energy between the π -components of the $\text{M}-\text{M}$ and $\text{M}-\text{L}$ bonds; however, the $\delta_{\text{M}-\text{M}}$ and $\delta^*_{\text{M}-\text{M}}$ components remain (though to a lesser extent) separated from other MOs. This is probably due to the formation of cyclic closed π -systems of the type



3. Replacement of the axial ligands in the $\{[\text{Tc}_2(\text{A}-\text{CO})_4\text{Cl}_n]^{(n-1)-} (n = 1 \text{ or } 2)\}$ anion by Br^- does not result in considerable changes in the patterns of the binding energy spectra, which indicates a small contribution of AOs of the axial ligands to the $\delta_{\text{M}-\text{M}}$, $\pi_{\text{M}-\text{M}}$ and $\pi_{\text{M}-\text{L}}$ MOs, since the axial ligands form mainly ionic bonds with the Tc atoms and only due to the trans-effect^{78,84,85} do they somewhat weaken the σ component of the $\text{M}-\text{M}$ bonds, which is hardly observed in this spectral region.

4. There is even greater separation in energy of the δ component of the $\text{M}-\text{M}$ bond from other types of MOs in the complex $\text{K}_2[\text{Tc}_2\text{Cl}_6]$, which is due to specific features of the bond formation in d^5-d^5 complexes with an idealised D_{4d} symmetry. According to the data reported in Ref. 57, the formation of δ bonds in $\text{K}_2[\text{Tc}_2\text{Cl}_6]$ occurs due to 'cross' overlap of the $4d_{xy}$ and $4d_{x^2-y^2}$ orbitals of the Tc atoms. This results in considerable decrease in the vertical ionisation potential of δ MO, since the $4d_{x^2-y^2}$ AOs of technetium participate mainly in the formation of the σ bonds with ligands. It should be noted that this energy separation of the σ MO is not observed in the complex $\text{K}_2[\text{Tc}_2\text{Br}_6]$,¹⁸ since the Br^- ions, being ligands of weaker field and lower electronegativity as compared to the Cl^- ions, do not cause such a substantial decrease in the vertical ionisation potential of δ MOs.

5. The formation of high-lying MOs in polynuclear clusters occurs mainly involving δ MOs and π MOs of dinuclear clusters,^{2,51,62,63,64} which results in an increase in their vertical

ionisation potentials. Therefore, in most cases no low-energy lines corresponding to separated high-lying MOs are observed in the X-ray photoelectron spectra of polynuclear clusters and lines corresponding to all components of the M – M bonds are strongly mixed in energy. The exception is the complex $(\text{Me}_4\text{N})_2[\text{Tc}_6\text{Cl}_{12}]$ and clusters with ferrocenium cations (peaks near the Fermi level are observed in their X-ray photoelectron spectra).²⁹ This is probably due to the formation of a conduction band in these compounds involving high-lying $5s(5p)$ orbitals of the Tc atoms.

V. Chemical shifts in X-ray K_α emission spectra of technetium compounds

In the preceding Section we have considered the X-ray photoelectron spectra of technetium compounds^{70–74} and demonstrated their efficiency for studying the electronic structure of clusters. Here, the results of joint XES and XPES studies of the electronic structure of technetium compounds are presented and the experimental results obtained are compared with those of semiempirical EH calculations.

Table 12 presents the experimental and theoretical results.^{75–77} The interdependence of the experimental chemical

Table 12. Experimental values of the chemical shifts in the X-ray emission spectra ($\delta E_{\text{K}_\alpha}$) and X-ray photoelectron spectra ($\Delta E_{3d_{5/2}}$) spectra of technetium compounds (with respect to metallic Tc) and the calculated effective partial charges on Tc atoms.⁷⁷

Compound	Tc oxidation state	$\delta E_{\text{K}_\alpha}$ / meV	$\Delta E_{3d_{5/2}}$ / eV	Z_{EH}	Q_{5s}	Q_{5p}	Q_{4d}	q_{s+d}	q_s	q_d
(FeCp ₂)[TcO ₄] (10')	7.0	–233(8)	5.0(2)	3.85	1.00	–0.1	2.90	1.73(5)	0.28	1.45
K[TcO ₄] (9)	7.0	–234(4)	5.1(2)	3.854 ^a	0.779 ^a	–0.219 ^a	3.294 ^a	1.73(3)	0.28	1.45
				3.92	1.0	–0.1	3.0			
(Ph ₄ As)[TcO ₄] (16)	7.0	–227(8)	4.5(2)	3.46	0.9	0	2.55	1.69(5)	0.26	1.43
Na[TcO ₄] · <i>n</i> H ₂ O (11)	7.0	–218(3)	–	3.85	–	–	–	1.63(2)	0.28	1.35
(Bu ₄ N)[TcO ₄] (17)	7.0	–198(4)	4.8(2)	3.70	0.97	–0.1	2.78	1.51(2)	0.27	1.24
Tc ₂ S ₇ (18)	7.0	–72(50)	0.8(2)	0.65	0.45	–0.2	0.40	0.7(4)	0.19	0.51
(Bu ₄ N)[TcOCl ₄] (20)	5.0	–91(20)	3.5(2)	2.312 ^a	0.734 ^a	–0.237 ^a	1.815 ^a	0.82(13)	0.19	0.63
				2.40	0.81	–0.25	1.84			
(Bu ₄ N)[TcOBr ₄] (21)	5.0	–47(7)	2.6(2)	2.0	0.71	–0.2	1.29	0.54(5)	0.19	0.35
[TcO ₂ Py ₄ Cl] · 2 H ₂ O (49)	5.0	–154(3)	–	–	–	–	–	1.23(2)	0.24	0.99
Tc ₂ O ₅ (23)	5.0	–104(5)	–	–	–	–	–	0.91(3)	0.20	0.71
TcO ₂ (25)	4.0	–89(2)	1.3(2)	0.90	0.5	–0.25	0.65	0.81(2)	0.19	0.62
TcS ₂ (50)	4.0	–40(3)	–	–	–	–	–	0.50(2)	0.18	0.32
K ₂ [TcF ₆] (51)	4.0	–133(30)	–	2.6	–	–	–	1.09(19)	0.22	0.87
K ₂ [TcCl ₆] (27) ^b	4.0	–51(6)	3.1(2)	1.793 ^a	0.723 ^a	–0.283 ^a	1.353 ^a	0.57(4)	0.19	0.38
(Me ₄ N) ₂ [TcCl ₆] (52)	4.0	–36(5)	–	1.45	–	–	–	0.47(3)	0.18	0.29
(Et ₄ N) ₂ [TcCl ₆] (53)	4.0	–39(3)	–	1.50	–	–	–	0.49(2)	0.18	0.31
(Bu ₄ N) ₂ [TcCl ₆] (54)	4.0	–36(5)	–	1.45	–	–	–	0.47(3)	0.18	0.29
K ₂ [TcBr ₆] (28)	4.0	–14(5)	2.3(2)	1.60	0.84	–0.2	0.96	0.33(3)	0.18	0.15
(NH ₄) ₂ [TcBr ₆] (29)	4.0	6(10)	–	–	–	–	–	0.20(3)	0.18	0.02
(Me ₄ N) ₂ [TcBr ₆] (55)	4.0	21(4)	–	–	–	–	–	0.11(3)	0.18	–0.07
K ₂ [TcI ₆] (31)	4.0	23(4)	1.7(2)	0.934 ^a	0.560 ^a	–0.450 ^a	0.824 ^a	0.09(9)	0.18	–0.09
				1.2	0.67	–0.2	0.73			
(Et ₄ N) ₂ [TcI ₆] (56)	4.0	24(6)	–	–	–	–	–	0.08(6)	0.18	–0.10
(Bu ₄ N) ₂ [Tc ₂ Cl ₈] (57) ^b	3.0	–52(5)	1.9(2)	1.445 ^a	0.648 ^a	–0.235 ^a	1.032 ^a	0.57(4)	0.19	0.38
(Bu ₄ N) ₂ [Tc ₂ Br ₈] (58)	3.0	–48(10)	–	–	–	–	–	0.55(7)	0.18	0.33
K ₂ [Tc ₂ (SO ₄) ₄] · 2H ₂ O (59)	3.0	–42(3)	–	–	–	–	–	0.51(2)	0.18	0.33
[Tc ₂ (AcO) ₄ Cl ₂] (60)	3.0	–42(6)	–	–	–	–	–	0.51(4)	0.18	0.33
[Tc ₂ (AcO) ₄ Cl] (34)	2.5	–17(4)	1.9(2)	1.206 ^a	0.657 ^a	–0.222 ^a	0.771 ^a	0.35(3)	0.18	0.17
				1.30	0.65	–0.25	0.90			
K ₃ [Tc ₂ Cl ₈] · <i>n</i> H ₂ O (37) ^b	2.5	19(8)	1.6(2)	1.065 ^a	0.647 ^a	–0.233 ^a	0.651 ^a	0.12(5)	0.18	–0.06
Py ₃ [Tc ₂ Cl ₈] (61)	2.5	34(10)	–	0.80	–	–	–	0.02(7)	0.18	–0.16
Tc ₄ O ₅ (38')	2.5	–16(16)	2.0(2)	1.40	0.66	–0.2	0.94	0.34(10)	0.18	0.16
K ₂ [Tc ₂ Cl ₆] (39) ^b	2.0	60(3)	1.0(2)	0.704 ^a	0.647 ^a	–0.209 ^a	0.266 ^a	–0.14(2)	0.20	–0.34
(Et ₄ N) ₂ {[Tc ₆ (μ-Br) ₆ Br ₆]Br ₂ } (41)	2.0	40(4)	0.8(2)	0.55	0.62	–0.31	0.24	–0.02(2)	0.18	–0.20
(Me ₄ N) ₃ {[Tc ₆ (μ-Br) ₆ Br ₆]Br ₂ } (42)	1.83(3)	42(4)	0.9(2)	0.65	0.63	–0.27	0.29	–0.03(2)	0.18	–0.21
(Me ₄ N) ₃ {[Tc ₆ (μ-Cl) ₆ Cl ₆]Cl ₂ } (43)	1.83(3)	42(3)	0.5(2)	0.35	0.61	–0.40	0.14	–0.03(2)	0.18	–0.21
(Me ₄ N) ₂ [Tc ₆ (μ-Cl) ₆ Cl ₆] (44) ^b	1.66(6)	0(8)	0.07(2)	0.597 ^a	0.555 ^a	–0.229 ^a	0.271 ^a	0.24(5)	0.18	0.06
{[Tc ₈ (μ-Br) ₈ Br ₄]Br} · 2H ₂ O (1)	1.625	49(3)	0.8(2)	0.55	0.63	–0.3	0.22	–0.07(5)	0.19	–0.26
[H(H ₂ O) ₂] ₂ {[Tc ₈ (μ-Br) ₈ Br ₄]Br ₂ } (3)	1.5	43(6)	0.8(2)	0.55	0.62	–0.3	0.23	–0.04(2)	0.18	–0.22
[H ₃ O(H ₂ O) ₃] ₂ [Tc ₆ (μ ₃ -Br) ₅ Br ₆] (5')	1.5	0(2)	1.4(2)	1.0	0.61	0.20	0.59	0.24(1)	0.18	0.06
[H ₃ O(H ₂ O) ₃] ₂ [Tc ₆ (μ ₃ -Br) ₅ Br ₆] · <i>n</i> H ₂ O (6)	1.5	42(6)	–	–	–	–	–	–0.03(2)	0.18	–0.21
Tc(CO) ₅ Cl (62)	1.0	–46(12)	–	–	–	–	–	0.54(7)	0.18	0.36
Tc(CO) ₅ Br (63)	1.0	–50(12)	–	–	–	–	–	0.56(7)	0.18	0.38
TcC (47)	0	–14(5)	0.02(2)	0	0.18	0	0.18	0.33	0.18	0.15

^a Results of EH calculations. ^b These compounds were used to calculate C_{nl} and δ_{nl} in Eqn (1). The partial charges Q_{nl} and q_l were determined from Eqns (1) and (2) using the Z_{EH} effective charges and the Hartree–Fock approximation, respectively (see text).

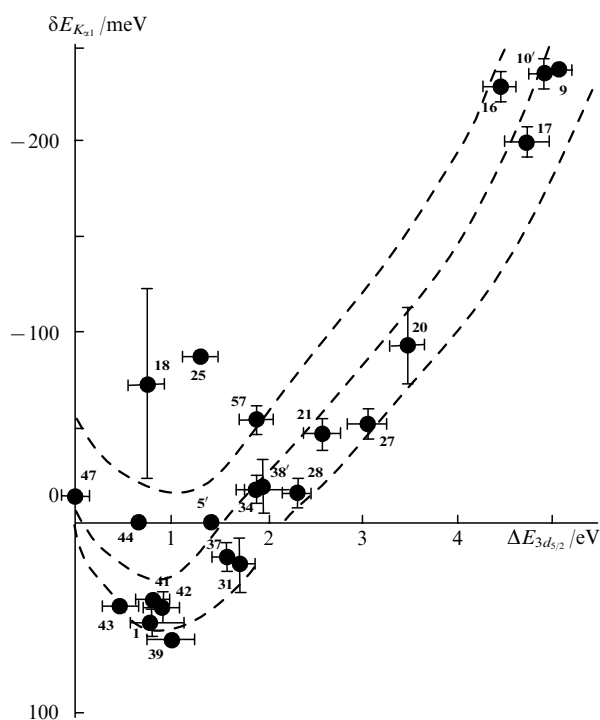


Figure 12. Correlation between the chemical shifts in the $K_{\alpha 1}$ X-ray emission spectra ($\delta E_{K_{\alpha 1}}$) and X-ray photoelectron spectra ($\Delta E_{3d_{5/2}}$) of technetium compounds⁷⁷ (the numbering of points corresponds to that of compounds in Table 12). The scatter of experimental data is shown by dashed lines.

shifts in the X-ray emission (δE) and X-ray photoelectron (ΔE) spectra is shown in Fig. 12.

According to the effective ion model,⁹⁸ the δE and ΔE values depend on the effective charge of the central atom (Q) as follows:

$$\delta E = C_{5s}Q_{5s} + C_{4d}Q_{4d} + Q_{5s}(Q_{5s} - 1)\delta_{5s} + Q_{4d}(Q_{4d} - 1)\delta_{4d} + Q_{5s}Q_{4d}\delta_{5s,4d}; \quad (1)$$

$$\Delta E = Q_{5s}\Delta E_{5s} + Q_{4d}\Delta E_{4d} + Q_{5s}(Q_{5s} - 1)\Delta_{5s} + Q_{4d}(Q_{4d} - 1)\Delta_{4d} + Q_{5s}Q_{4d}\Delta_{5s,4d} + \varphi_M, \quad (2)$$

where Q_{nl} is the partial charge remaining on an atom after the nl -electron has been involved in the formation of a bond, $C_{nl}(\Delta E_{nl})$ is the line shift in the X-ray emission spectrum (or in the X-ray photoelectron spectrum) after abstraction of the nl -electron; δ and Δ are the respective corrections, which correspond to the changes in the electrostatic energy of electrons due to the emission of an X-ray quantum and φ_M is the Madelung constant.

Since for transition d elements $Q = Q_{ns} + Q_{(n-1)d} + Q_{np}$ and Q_{np} is small and remains virtually constant on going from one compound to another (see, e.g., the data of EH calculations for Tc compounds in Table 2), it can be neglected. Then, in the general case, δE and ΔE can be represented as functions of $Q_{5s} + Q_{4d}$. The experimental dependences of δE and ΔE on $Q_{5s} + Q_{4d}$ (obtained from EH calculations) have been reported.⁷⁷ It has been shown that the dependence $\Delta E = f(Q_{5s} + Q_{4d})$ is close to a linear one, whereas the dependence $\delta E = \varphi(Q_{5s} + Q_{4d})$ is less unambiguous. The values of the coefficients C_{5s} , C_{4d} , δ_{5s} , δ_{4s} and $\delta_{5s,4d}$ were determined after substituting the $Q_{5s} + Q_{4d}$ values taken from EH calculations into Eqn (1) and solving the system of five linear equations with five unknowns.⁷⁷ To reduce systematic errors due to inaccuracy in the parametrisation, the data calculated only for the chloride compounds $[\text{TcCl}_6]^{2-}$, $[\text{Tc}_2\text{Cl}_8]^{3-}$, $[\text{Tc}_2\text{Cl}_8]^{2-}$, $[\text{Tc}_2\text{Cl}_6]^{2-}$ and $[\text{Tc}_6\text{Cl}_{12}]^{2-}$ were used.⁷⁷ For comparison, analogous coefficients⁷⁷ calculated by the Hartree–Fock SCF method for the isolated Tc atoms in the approximation of two alternative

configurations ($4d^65s^1$ and $4d^5s^2$) have also been used. It has been shown that, at least except for sign, the values of all the coefficients in question (C_{5s} , C_{4d} , δ_{5s} , δ_{4d} and $\delta_{5s,4d}$) are close. This indicates indirectly that EH calculations provide a good basis for theoretical description of δE at qualitative and semiquantitative levels.

A one-to-one correspondence between the ΔE and $Q_{5s} + Q_{4d}$ values has been established by extrapolating the $\Delta E = f(Q_{5s} + Q_{4d})$ dependence to all other technetium compounds for which the X-ray emission and X-ray photoelectron spectra have been measured.⁷⁷ At this point, it has been assumed that φ_M is independent of $Q_{5s} + Q_{4d}$ or varies monotonically as the latter parameter varies; this has been strictly substantiated only for compounds with similar structure and composition. Then, substituting the $Q_{5s} + Q_{4d}$ value found into Eqn (1) and using the coefficients of this equation calculated in the EH approximation, one could calculate the Q_{5s} , Q_{4d} and Q_{4p} partial charges (see Table 12). To pass to another, more physically well-founded scale of effective charges, the values of coefficients of Eqn (1) calculated by the Hartree–Fock method were used assuming that Z_{eff} of technetium ($Z_{\text{eff}} = q_s + q_d$) in KTcO_4 coincides with the effective charge of ruthenium in RuO_4 and is equal to 1.71.^{96,97} From the fact that the metal atoms in both d^0 complexes have the same oxygen environment and that the electronegativities of the Tc and Ru atoms are almost equal it follows that these charges are approximately equal.^{79,80} Having calculated the partial charges q_s and q_d on technetium atoms in KTcO_4 from Eqn (1) and assuming that the found value of the ratio Q_{5s}/q_s (3.57) remains almost constant, it was also possible to calculate⁷⁷ the q_s and q_d values for all other technetium compounds for which EH data are available (see Table 12). These calculations have shown that all the experimental results can be described by the following equation:

$$\delta E = (37.5 \pm 2.1) - (156.0 \pm 2.9)(q_s + q_d). \quad (3)$$

Since the correlation coefficient of the linear dependence (3) for nine experimental points is 0.999, it was assumed that δE for all other compounds is also described by this equation. Simultaneous solution of Eqns (1) and (3) performed under this assumption allowed one to find q_s and q_d values for all other technetium compounds. The results obtained⁷⁷ are listed in Table 12. The effective charges on the Tc atoms calculated using the two different procedures differ considerably in magnitude. However, all main tendencies and regularities of changes in Z_{eff} on going from one compound to another are the same for both scales of effective charges.^{75–77}

1. The Q_{5p} values and their changes for all compounds are small, which indicates that the extent of participation of the $5p$ AO in the formation of chemical bonds is small. The Q_{5s} (q_s) and Q_{4d} (q_d) values decrease regularly as the formal oxidation state of technetium decreases, which points to increasing covalency of chemical bonds in this series of compounds.

2. A tendency for Z_{eff} to increase with increase in the Tc oxidation state, total electronegativity of ligands in the series $\text{F} > \text{O} > \text{Cl} > \text{Br} > \text{S} \approx \text{I}$ and the polarising capacity of cations $Z_{\text{cat}}/R_{\text{cat}}$ is observed for compounds containing no $\text{M}–\text{M}$ bonds.

3. A ‘loss of sensitivity’ of Z_{eff} to the electronegativity of ligands, the nature of cation and the formal oxidation state of technetium with increase in the number of electrons participating in the formation of $\text{M}–\text{M}$ bonds is observed for compounds with $\text{M}–\text{M}$ bonds. In some cases the Z_{eff} value in technetium clusters changes upon insignificant change in the formal oxidation state of Tc or in the structure of the cluster (see, e.g., compounds **41** and **42**, **43** and **44**, **1** and **3**, **5'** and **5''**, and **25** and **3'** in Table 12).

The partial charges of ligands in technetium compounds (Table 13) have been determined from the analysis of $q_s + q_d$ values, comparison of these values with $Z_{\text{eff}}(\text{Ru})$ ^{96,97} and using the dependence of $q_s + q_d$ on Z_{EH} for the ligands.⁷⁷

The algebraic sums of charges on all atoms in Tc compounds have been calculated from the data in Tables 12 and 13.⁷⁷ These

Table 13. Partial charges on ligands and cations in technetium compounds.⁷⁷

Ligand, cation	Charge	Ligand	Charge	Ligand	Charge
Inorganic cation	+0.82	Cl _{ax}	−0.45	Br _{eq} (clusters)	−0.34
Bulky organic cation	+0.87	Cl _{eq}	−0.36	Br _{bridge}	−0.13
		Cl _{eq} (clusters)	−0.40	I _{ax}	−0.29
F _{eq}	−0.46	Cl _{bridge}	−0.16	S	−0.22(10)
O _{eq} {oxides, [TcOX ₄]} [−]	−0.30(15)	Br _{ax}	−0.37	C	−0.33
O _{eq} {[TcO ₄]} [−]	−0.64(1)	Br _{eq}	−0.32	CO	−0.03

Note. The last significant figures of the maximum deviations from average charge values are given in parentheses.

sums differ considerably from zero for binary compounds, which is probably associated with great differences in the nature of ligand bonding with technetium (apparently, one cannot use the same $q_s + d$ value for the ligands in all these compounds). Systematic deviations of the sums of charges from zero are observed for compounds with M–M bonds (di- and polynuclear clusters). *A priori* this may be due either to the same reasons as for binary compounds or to systematic changes (as a rule, a decrease) in Z_{eff} of the Tc atoms caused by the M–M bonds. The latter assumption seems to be more reasonable, since X-ray photoelectron spectra of technetium compounds indicate that Z_{eff} of halide ligands of the same structural type are constant irrespective of the presence of M–M bonds in the compounds^{67,69,81} (see Section IV).

The averaged deviations of $\Sigma q_s + d$ from zero calculated per two Tc atoms using the above procedure for di- and polynuclear clusters of different structural types are equal to −0.22 (dinuclear d^4 – d^4 clusters), −0.44 (dinuclear d^4 – d^5 clusters), −0.80 (dinuclear d^5 – d^5 clusters), −0.53 (trigonal-prismatic clusters) and −0.17 (tetragonal-prismatic clusters).⁷⁷

As can be seen, the decrease in Z_{eff} due to the formation of M–M bonds is a maximum in the case of dinuclear d^5 – d^5 clusters. This correlates with the shortest M–M distance (2.04 Å) in their molecules.⁵⁷ The influence of relatively long M–M bonds (~ 2.6 Å)² on the Z_{eff} value is minimal. It is likely that the effect of multiple M–M bonds in polynuclear prismatic clusters is more pronounced than, *e.g.*, in d^4 – d^4 complexes, owing to the additional contribution from several weaker M–M bonds.

Thus, the results obtained^{75–77} confirm again that the formation of M–M bonds may cause changes in the effective charges on the metal atoms.^{3,51,70–73,87,88} We believe that this phenomenon is due to the specific effect of the system of M–M bonds on the electronic structure of clusters. Therefore, the M–M bonds in technetium clusters (as well as in a number of clusters of other elements) can be considered as specific additional ligands affecting Z_{eff} on the metal core atoms of the clusters.

Later, another approach to the interpretation of the data on chemical shifts in the $K_{\alpha 1,2}$ and $K_{\beta 1,3}$ lines in X-ray emission spectra of molybdenum, technetium and ruthenium compounds was proposed.^{75–77} These results were generalised by Batrakov *et al.*⁹⁸ who have analysed two independent sets of experimental parameters corresponding to $\delta K_{\alpha 1,2}$ and $\delta K_{\beta 1,3}$ in contrast to the chemical shifts for technetium compounds that we have considered previously. However, a considerable increase in the number of parameters directly determined in the experiments does not allow one to interpret the experimental results unambiguously. Thus, *e.g.*, Batrakov *et al.*⁹⁸ had to make some assumptions on the electron configuration of the reference compound (TcO₂ in the

ionic state 1+ or 3+ has been used as reference compound for technetium compounds). However, from the above discussion it follows that it is just technetium dioxide that can scarcely be used as reference compound, because some of its electronic properties make it different from most other technetium compounds (see also Section IV, Tables 9 and 12 and Figs 9 and 12). Moreover, our calculations performed using a representative random sample of experimental $\delta K_{\alpha 1,2}$ and $\delta K_{\beta 1,3}$ values taken from Ref. 98 and the approach described above in this Section showed that the final conclusions do not differ fundamentally from those drawn in Ref. 77. In this connection it is not expedient to consider the data and, especially, the interpretation of results obtained by Batrakov *et al.*⁹⁸ in detail. We will restrict ourselves to major conclusions only.

The diagram of the chemical shifts of the centres of gravity of the Tc $K_{\alpha 1,2}$ and Tc $K_{\beta 1,3}$ doublets for technetium compounds (see Ref. 98) is shown in Fig. 13. As can be seen, in the coordinate system used all experimental points fall on five curves corresponding to different types of technetium compounds, *viz.*, oxides, iodides, bromides, chlorides and clusters (including metallic technetium). It should be noted that similar dependences have been obtained for technetium compounds⁹⁸ in the coordinates of partial charges Q_{4d} and Q_{5s} which were determined using the approach described above. It was confirmed that the formation of M–M bonds (M = Tc, Mo) results in changes in the effective charges on the atoms of these metals, which is also an important result of this study.

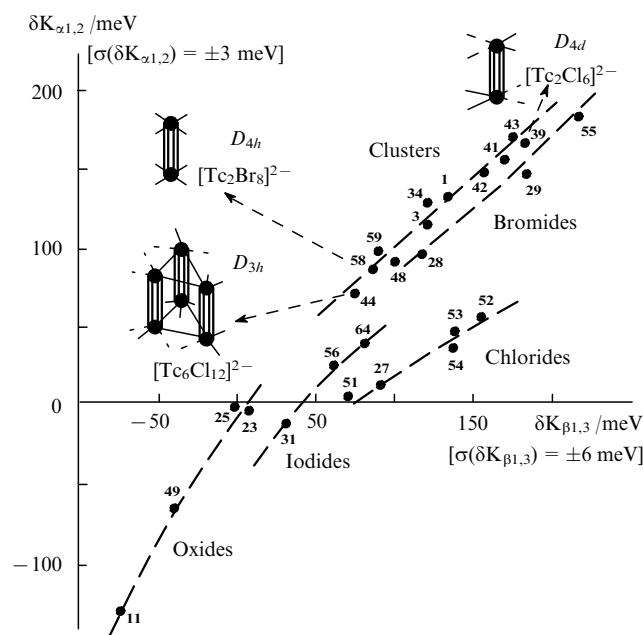


Figure 13. Diagram of the chemical shifts of the centres of gravity of the Tc $K_{\alpha 1,2}$ and Tc $K_{\beta 1,3}$ doublets in the X-ray emission spectra for technetium compounds according to Batrakov *et al.*⁹⁸ The numbering of points corresponds to those of compounds in Tables 9 and 12; the point No. 64 corresponds to (Me₄N)₂[TcI₆].

VI. Compounds with ferrocenium cations

Considering various methods of investigation of technetium clusters, we shall dwell on the ⁵⁷Fe Mössbauer spectroscopy of ferrocenium-containing complexes. Table 14 presents the parameters of the ⁵⁷Fe Mössbauer spectra of compounds with ferrocenium cations. As can be seen, the parameters of the Mössbauer spectra depend strongly on temperature and the chemical nature of the anion. At room temperature, doublet (singlet for two compounds) spectra are observed; the chemical shifts δ in the

Table 14. Parameters of ^{57}Fe Mössbauer spectra (δ , A , Γ / mm s^{-1}) of compounds with ferrocenium cations,^{28, 29}

Compound	T/K	δ	A	Γ	Notes
$(\text{FeCp}_2)[\text{TcO}_4]$	300	0.65	0.74	0.54	doublet
	300 ^a	0.61	0.70	0.60	"
	78	0.75	0.65	0.69	"
	5	0.73	0	1.68	broad singlet
$(\text{FeCp}_2)_4[\text{H}_3\text{O}(\text{H}_2\text{O})_4]_2[\text{TcCl}_6]_3$	300	0.66	0.14	0.36	doublet
	300 ^a	0.62	0	0.60	singlet
	78	0.74 (A)	0.18	0.38	two doublets in the ratio $A : B = \sim 7.6 : 1.0$
	78	0.66 (B)	0.55	0.37	
	5	0.80 (A)	0	0.53	singlet and doublet in the ratio $A : B = \sim 6.6 : 1.0$
	5	0.86 (B)	2.37	0.25	
$(\text{FeCp}_2)_3[\text{Tc}_6\text{Cl}_{14}]$	300	0.66	0	0.50	singlet
	78	0.65 (A)	0	0.60	singlet and two doublets in the ratio $A : B : C = \sim 2.3 : 1.0 : 1.0$
	78	0.80 (B)	2.30	0.40	
	78	0.70 (C)	0.30	0.50	
$(\text{FeCp})_2[\text{Tc}_8\text{Br}_{14}]$	300	0.70	0	0.45	singlet
	78	0.62 (A)	0	0.60	singlet and two doublets in the ratio $A : B : C = \sim 2.0 : 1.0 : 1.0$
	78	0.83 (B)	2.35	0.60	
	78	0.72 (C)	0.35	0.42	
$(\text{FeCp}_2)_2[\text{Tc}_6\text{I}_{14}]$	300	0.68	0.44	0.47	doublet
	300 ^b	0.68	0.46	0.48	"
	78	0.78	0.46	0.53	"
$(\text{FeCp}_2)_2[\text{Re}_2\text{Br}_8]$	300	0.62	0.68	0.59	"
	300 ^b	0.62	0.71	0.67	"
	78	0.72	0.64	0.65	"
$(\text{FeCp}_2)_2\text{PF}_6$	300	0.66	0.30	0.31	"
	78	0.77	0.30	0.30	"
FeCp_2	300	0.60	2.37	0.24	"
	78	0.76	2.38	0.30	"

^a The specimen was preliminarily frozen to 5 K. ^b The specimen was preliminarily frozen to 78 K.

spectra depend slightly on the nature of the anion and the quadrupole splitting A decreases for the anions in the series: $[\text{TcO}_4]^- > [\text{Re}_2\text{Br}_8]^{2-} > [\text{Tc}_6\text{I}_{14}]^{3-} > [\text{PF}_6]^{2-} > [\text{TcCl}_6]^{2-} > [\text{Tc}_6\text{Cl}_{14}]^{3-} \approx [\text{Tc}_8\text{Br}_{14}]^{2-}$. Spectral line broadening is observed as the temperature decreases. Additional lines appear in the spectra of compounds with the $[\text{TcCl}_6]^{2-}$, $[\text{Tc}_6\text{Cl}_{14}]^{3-}$ and $[\text{Tc}_8\text{Br}_{14}]^{2-}$ anions; the parameters of one of these lines are close to those of the Fe^{2+} signal in pure ferrocene³⁰ (see Table 14 and Fig. 14). For cluster anions, this is observed even at 78 K, whereas for ferrocenium hexachlorotechnetate(IV) this is observed only at 5 K (at 78 K, the spectrum of this compound is appreciably broadened and can be deconvoluted into two doublets with small A by the least squares method assuming a Lorentzian lineshape). The spectrum of ferrocenium pertechnetate at 5 K is a broad singlet; however, attempts at its deconvoluting into components failed.

Physicochemical studies^{28, 29} of compounds with ferrocenium cations (see also Sections II–IV) allow one to draw the following principal conclusions:

1. All compounds possess anomalous peculiarities of electronic structure due to the changes in their physicochemical properties with time and temperature.

2. Anomalous properties increase for the series of anions as follows: $[\text{TcO}_4]^- \approx [\text{Re}_2\text{Br}_8]^{2-} \approx [\text{Tc}_6\text{I}_{14}]^{3-} < [\text{TcCl}_6]^{2-} < [\text{Tc}_6\text{Cl}_{14}]^{3-} < [\text{Tc}_8\text{Br}_{14}]^{2-}$.

The following explanation of this anomaly was proposed.^{28, 29} It was shown⁶⁴ that the probability of participation of outer ns (np) technetium (rhenium) AOs in the formation of coordinate bonds formed by this atom increases in the above series of anions (except for the iodide cluster). This is due to the fact that the $4d$ AOs become destabilised to a greater extent than diffuse $5s$ ($5p$)

AOs capable of effective interaction at comparatively long distances ($> 2.5 \text{ \AA}$) as the formal oxidation state of technetium (the effective charge on its atoms) decreases. There are also low-lying MOs formed by diffuse $4s$ ($4p$) orbitals of Fe atoms in ferrocenium cations.⁹⁹ An approach of Fe and Tc atoms within a distance of $\sim 5 \text{ \AA}$ (it is this distance that is observed in ferrocenium complexes of technetium) must result in direct electron overlap of ns (np) orbitals of the Fe and Tc atoms and, hence, in the formation of conduction bands. Indeed, all compounds possess temperature-independent semiconductor-type conductivity. This indicates that the Fermi levels of the ferrocenium cations and technetium (rhenium) anions in these compounds are inside or near the sp conduction bands. This may result in tunnelling of the valence sp electrons between the anions and cations at frequency ω . Such a dynamic electron transfer along the anion–cation chains can be detected using only those physical methods that have a better time resolution than the average lifetime of the valence electron in the proximity of the atom under observation. In other words, these changes can be detected using photoelectron spectroscopy with a time resolution (τ) of $10^{-16} - 10^{-17} \text{ s}$, whereas only an averaged picture can be obtained using such integral methods as static magnetic susceptibility, heat capacity and conductivity measurements, X-ray analysis, *etc.* The results obtained by Mössbauer, EPR, and IR spectroscopy with a time resolution of 10^{-7} s , $\sim 10^{-9} - 10^{-10} \text{ s}$ and $10^{-11} - 10^{-13} \text{ s}$, respectively, will be intermediate due to line broadening in spectra caused by dynamic electron transfer and vibronic interaction.

In the context of the proposed explanation of the properties of compounds with ferrocenium cations,^{28, 29} attention must be focused on the magnetic properties (see Sections III and IV) and changes in the photoelectron spectra of these compounds at low

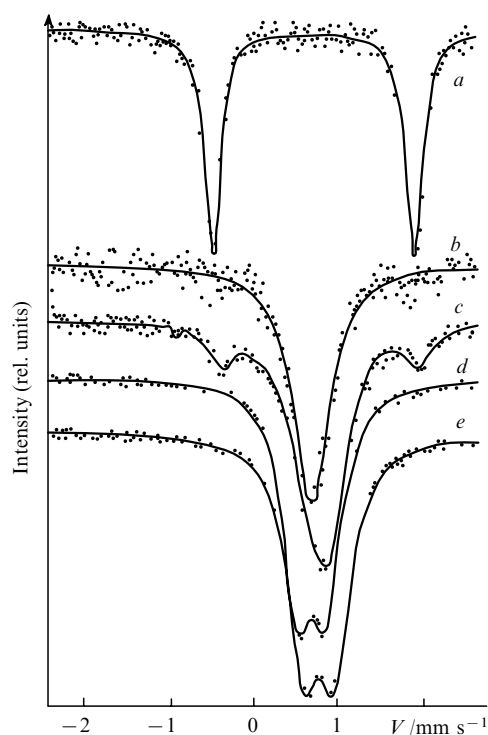


Figure 14. ^{57}Fe Mössbauer spectra of: (a) FeCp_2 at 300 K; (b, c) $(\text{FeCp}_2)_3 \cdot \{[\text{Tc}_6\text{Cl}_6(\mu\text{-Cl})_6]\text{Cl}_2\}$ at 300 and 80 K; (d, e) $(\text{FeCp}_2)_2[\text{PF}_6]$ at 300 and 80 K.

temperatures. Thus, Table 9 presents the experimental parameters of X-ray photoelectron spectra of several technetium and rhenium compounds (see also Refs 28 and 29). From these data it follows that the X-ray photoelectron spectra of the compounds with ferrocenium cations recorded at room temperature for the first time do not differ fundamentally from those of other technetium and rhenium compounds. All major spectral regularities correspond to those described above (see Sections IV.1–IV.3). The only exception is the increased binding energy corresponding to the $\text{Tc } 3d$ line in the case of $(\text{FeCp}_2)_2[\text{Tc}_8\text{Br}_{14}]$. However, anomalous electron emission is observed at a temperature of about 100 K instead of conventional X-ray photoelectron spectra of the compounds with ferrocenium cations and $[\text{TcCl}_6]^{2-}$, $[\text{Tc}_6\text{Cl}_{14}]^{3-}$ and $[\text{Tc}_8\text{Br}_{14}]^{2-}$ anions. No temperature dependence of spectra of other compounds has been found.

The phenomenon of anomalous electron emission consists in the following.^{28,29} The lines of the conventional X-ray photoelectron spectrum (Fig. 15) become diffuse and disappear as the temperature of the specimens decreases below a specific threshold value (~ 100 K). The spectrum of inelastic electrons observed simultaneously with the lines of the X-ray photoelectron spectrum loses its true shape and also disappears against the background of a group of very intense lines; the structure and number of these lines vary substantially on fast freezing of the specimen. The amplitudes of the most intense peaks are approximately 2 orders of magnitude larger than the intensities of the lines in the conventional X-ray photoelectron spectrum, which usually results in overloading of the detector even at the minimum power of the X-ray radiation source (100 W for an HP 5950A spectrometer). Further cooling of the specimens leads to substantial increase in the upper boundary kinetic energy (UBKE) of emitted electrons (from 10 to ≥ 1500 eV). The UBKE changes analogously with the increase in duration of exposure of the specimens in which approximate temperature equilibrium was reached to X-ray radiation. The UBKE decreases slowly until the anomalous emission ceases and the conventional X-ray photoelectron spectrum recovers as the specimens undergo slow unfreezing. The

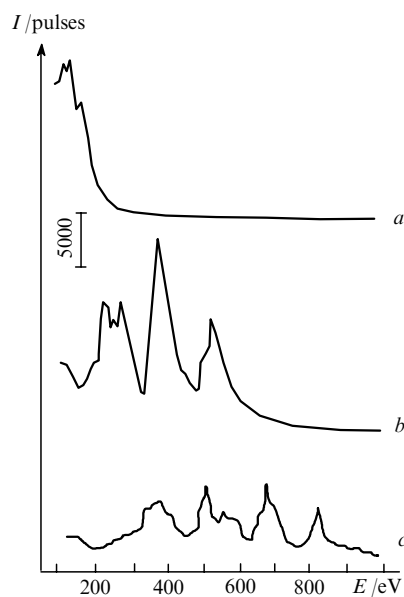


Figure 15. Dynamics of anomalous electron emission for a $(\text{FeCp}_2)_2[\text{Tc}_8\text{Br}_{14}]$ specimen preliminarily cooled to ~ 100 K after switching on the X-ray radiation source (at a beam power of 200 W) during data collection (1000 eV/256 channels) in one scan (data collecting time of 210 s). Start of data collection after switching on the X-ray radiation source: (a) 0 min; (b) 4 min.; and (c) 8 min. (Here E is the kinetic energy of electrons).^{28,29}

qualitative and quantitative spectral pattern is reproduced within short time intervals (~ 5 min) under conditions of relative stabilisation of the specimen temperature. To a first approximation, the intensities of the peaks were found to be proportional to the power of the X-ray tube of the spectrometer. With an accuracy of ~ 0.1 s, no time lag was found on switching off the X-ray tube. The kinetic energy of emitted electrons can exceed the energy of exciting X-ray quanta (1486.6 eV).

The second peculiarity of the X-ray photoelectron spectra of compounds with ferrocenium cations is that the spectra recorded repeatedly at room temperature (after freezing of the specimens to 78 K followed by their unfreezing) can differ from those recorded initially at the same temperature. These differences include^{28,29} the following features: (1) the peaks corresponding to the core electrons of the Fe atoms correspond in the repeatedly recorded spectra to three nonequivalent states of these atoms {compounds with $[\text{Tc}_6\text{Cl}_{14}]^{2-}$ and $[\text{Tc}_8\text{Br}_{14}]^{2-}$ anions} and (2) the same holds for the peaks corresponding to the core electrons of the halogen atoms {the compound with the $[\text{TcCl}_6]^{2-}$ anion}. These data could indicate that the compounds with ferrocenium cations are initially in the metastable state and are stabilised on freezing. However, the temperature dependences of the heat capacity and the magnetic susceptibility of the compounds studied show that no phase transitions occur in the temperature range from 300 to 100 K. Thus, the effects observed are due to pure electronic peculiarities of the structure of the compounds under consideration. It should be noted that the Mössbauer and IR spectra (see Sections II and VI, respectively) of the specimens that were preliminarily frozen repeatedly recorded at room temperature also differ somewhat from those recorded initially.[†]

Phenomena similar to that observed^{28,29} are known: exoelectron emission (see, e.g., Ref. 100) and mechanoemission.¹⁰¹ It is likely that the charges accumulated in the specimen subjected to X-ray radiation are to a great extent responsible for the appear-

[†] Changes in the specimens caused by freezing cannot be due to any chemical processes, since the specimens are stable towards water sorption on the surface; no changes in the chemical composition were found.^{28,29}

ance of anomalous electron emission.⁷⁸ The peculiarities of the low-temperature X-ray photoelectron spectra of some compounds with ferrocenium cations observed in the experiments may be due to the multiphoton photoeffect similar to the laser effect.^{28, 29}

As has been mentioned in Section III, the magnetic properties of compounds with ferrocenium cations are also anomalous. In fact, as can be seen from the data in Table 8, in all cases there is more than one unpaired electron per ferrocenium cation. It is obvious that the effective number of unpaired electrons may be increased due to the partial unpairing of the occupied cationic and anionic MOs composed mainly of *ns(np)* AOs and forming the conduction bands. The effective number of unpaired electrons may also change appreciably due to the changes in the vibronic interaction caused by temperature changes. In this case the paramagnetism of the compound will be the sum of the contributions of *d* electrons of the cations and anions and *s* electrons of the conduction band. Because of the fast dynamic electron transfer (the *s*–*d*–*s* exchange), the lines in the EPR spectra of the compounds will be appreciably broadened or unobservable {as in the case of compound with the [Tc₈Br₁₄]^{2–} anion}. The central, more narrow component of the EPR spectra will correspond mainly to *d* electrons of cations and anions, whereas the broader component will correspond to the electrons of the *s* conduction band.

VII. Conclusion

The experimental and theoretical substantiation of the participation of the outer 5*s* (5*p_z*) orbitals of the Tc atoms in the formation of bonding 'metallic' MOs in technetium clusters with the formal oxidation state of Tc no more than 2.0 is presented in this review. On the one hand, this effect results in strengthening of the M–M bonding in technetium clusters containing a formally 'excess' number of 'metallic' electrons (*i.e.*, the number exceeding that corresponding to the closed shell of the bonding MOs composed of 4*d* AOs). On the other hand, it enhances shielding of the positive nuclear charges (a decrease in *Z*_{eff}) of the Tc atoms in technetium clusters, thus decreasing the Coulomb repulsion in the formation of M–M bonds and increasing the contribution of electron correlation effects to the ground electronic state of the system. Thus, it also leads to an increase in the cluster-forming properties of technetium. This theoretical substantiation agrees well with the descriptions of the 'anomalous' properties of technetium clusters reported earlier.^{3, 51}

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^a — *Russ. J. Coord. Chem. (Engl. Transl.)*

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

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

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

^e — *Organomet. Chem. (Engl. Transl.)*

^f — *Mendeleev Chem. J. (Engl. Transl.)*

^g — *Theor. Exp. Chem. (Engl. Transl.)*

Phosphorus-containing calixarenes

I S Antipin, E Kh Kazakova, W D Habicher, A I Konovalov

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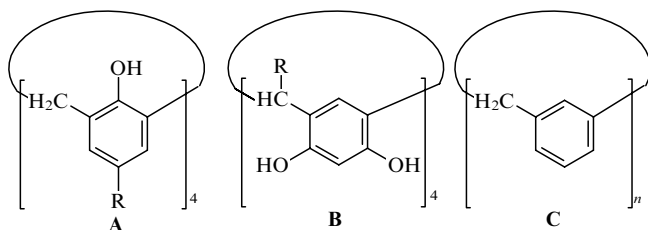
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Abstract. Data on the synthesis, conformational behaviour and complexing properties of calix[4]resorcinolarene and calix[*n*]arene derivatives modified by phosphorus-containing fragments are surveyed. The bibliography includes 123 references.

I. Introduction

The chemistry of calixarenes — cyclic products of condensation of phenols with aldehydes — has vigorously developed during the last 20 years. Calixarenes are readily accessible compounds (many of them can be easily obtained by a one-stage synthesis); they contain reactive sites permitting modification of the structure. In addition, they are capable of forming inclusion complexes of the ‘host–guest’ type both with charged and non-polar molecules.

The first mention of the interaction of phenols with aldehydes¹ dates back to 1872 (A Bayer); however the structure of the reaction products has remained barely known for almost 70 more years. It was not until the 1940s that tetrameric cyclic structures **A** and **B** were ascribed to the products of condensation of *p*-alkylphenols with formaldehyde in an alkaline medium² and to the products of acid-catalysed reaction of resorcinol with aldehydes.³



I S Antipin Kazan State University, ul. Kremlevskaya 18, 420008 Kazan, Russian Federation. Fax (7-843) 275 22 53. Tel. (7-843) 231 54 86.

E-mail: iantipin@ksu.ru

E Kh Kazakova, A I Konovalov A E Arbuzov Institute of Organic and Physical Chemistry of the Kazan Scientific Centre, ul. Arbuzova 8, 420083 Kazan, Russian Federation. Fax (7-843) 275 22 53.

Tel. (7-843) 276 73 74 (E Kh Kazakova). Tel. (7-843) 276 82 54

(A I Konovalov)

W D Habicher Institute of Organic Chemistry of Dresden Technical University, 13 Mommsenstrasse, D-01062 Dresden, Germany.

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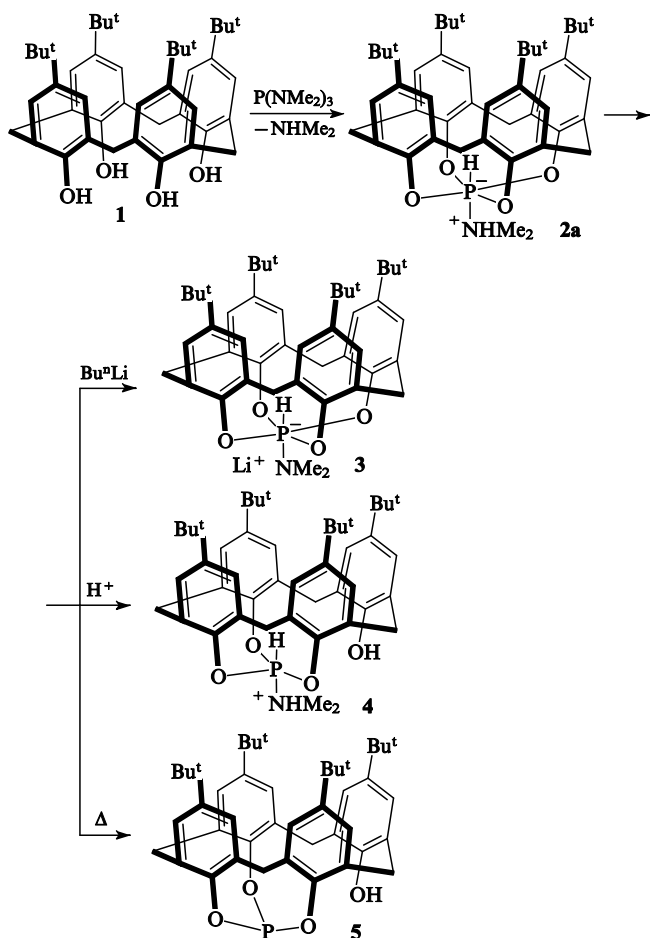
The term ‘calixarene’ was brought into use by Gutsche *et al.*⁴ to characterise the shape of these cyclic tetramers, which resembles a bowl (‘calix’ is the Greek for bowl or cup). Although later it was found^{5–7} that these macrocycles can also exist in other conformations, this term has been adopted to denote the whole class of [1,*n*]-metacyclophanes (including compounds **C**).

Calixarenes are widely used as molecular platforms for the development of pre-organised three-dimensional receptors.^{5–8} Upon functionalisation of the phenolic groups, the aromatic rings and the bridging fragments in the initial macrocycles by appropriate organic or organoelement reagents, the receptor capacity can be increased by a large factor. The number of publications dealing with calixarene derivatives doubles every three years.⁸ The number of patents also swiftly increases, indicating that these compounds are important not only for theoretical studies but also for practical purposes and for industry. The latest achievements in the studies of organic derivatives of calixarenes were summarised in a special issue of the journal *Gazzetta Chimica Italiana* (No. 11 in 1997), which was based on the contributions to the 4th International Conference on Calixarenes held in Parma (Italy) from August 31 to September 4, 1997.

Organic derivatives of phosphorus are of special interest for functionalisation of calixarenes, because phosphorus compounds play an important role in many biological and catalytic properties. The complex-forming ability of organophosphorus groups, the strictly definite size of the molecular cavity in the initial calixarene and the possibility of introducing fragments with a specified spatial orientation open up the way to the synthesis of a new generation of receptors capable of recognising complex molecular images. However, the size and the vicinity of functional groups in the supramolecular systems impart some specific features to their chemical behaviour. This makes development of an efficient methodology for selective functionalisation of calix[*n*]arenes a fundamentally important task. Studies on phosphorylation of calixarenes were started in the late 80s – early 90s. This review is the first attempt to describe systematically experimental data now accumulated along this line.

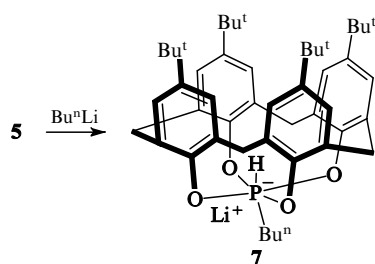
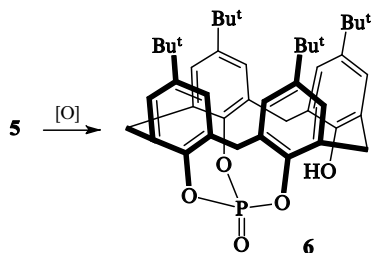
II. O-Phosphorylation of calixarenes by P(III) compounds

The pioneering investigations dealing with the reactions of P(III) compounds with calixarenes were published by a group of American scientists,^{9–13} who accomplished a series of studies dealing with functionalisation of the hydroxy groups in *p*-tert-butylcalix[4]arene (**1**).

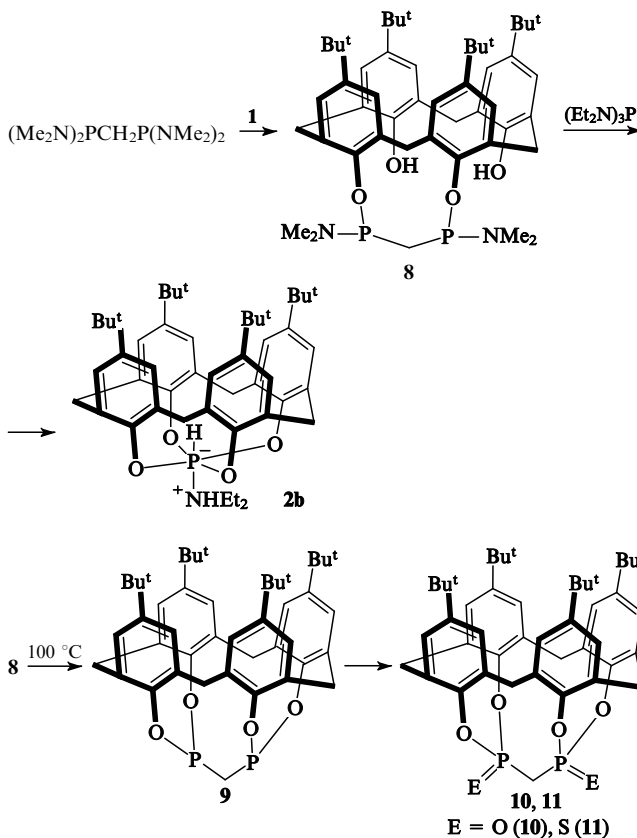


It was shown that the inner cavity of calix[4]arene can stabilise the 'hypervalent' hexacoordinated state of the phosphorus atom. The reaction of the compound **1** with tris(dimethylamino)-phosphine¹⁰ is accompanied by elimination of two dimethylamine molecules and gives spirocyclic zwitter-ionic product **2a** ($\delta_{\text{P}} = -120$ ppm, $J_{\text{P-H}} = 737$ Hz).

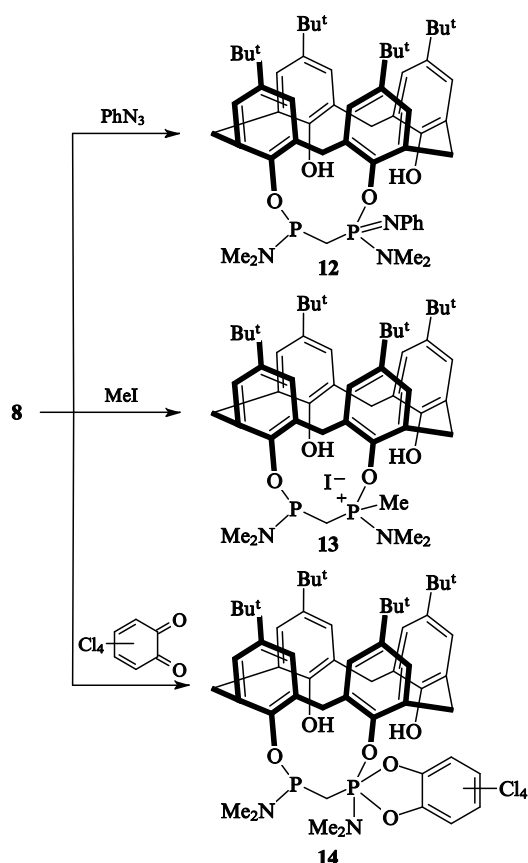
The two apical positions are occupied by an $\text{N}^+ \text{HMe}_2$ group and a hydrogen atom, the bond of the latter with phosphorus being directed inside the aromatic cavity; this was confirmed by NMR spectroscopy and X-ray diffraction analysis.^{12, 13} On treatment of the compound **2** with one equivalent of butyllithium, the dimethylammonium group is deprotonated, which results in the formation of salt **3**. When the zwitter-ion **2** is thermolysed at 200°C or treated with strong acids ($\text{CF}_3\text{CO}_2\text{H}$ or HBF_4), dimethylamine is eliminated and cage phosphite **5** is produced. Spectral studies (^1H and ^{31}P NMR) showed that the reaction with HBF_4 occurs *via* the formation of pentacoordinated phosphorane intermediate **4** ($\delta_{\text{P}} = -22$ ppm). Oxidation of phosphite **5** with *tert*-butyl hydroperoxide affords the corresponding phosphate **6**; according to X-ray diffraction analysis, this product occurs in a conformation intermediate between *1,2-alternate* and *partial cone*. The reaction of the phosphite **5** with one equivalent of *n*-butyllithium gives product **7** with a hexacoordinated phosphorus atom.



The same group of researchers¹⁴ succeeded in the introduction of more than one phosphorus atom in the calixarene platform. Treatment of the compound **1** with di[bis(*N,N*-dimethylamino)phosphino]methane in dichloromethane at room temperature gives rise to disubstituted product **8**.

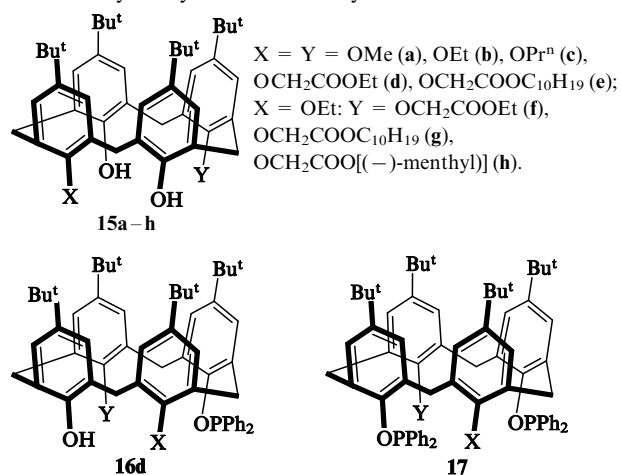


An X-ray diffraction study showed that the compound **8** is the (*R,S*) isomer in relation to the phosphorus atoms. Binding of the remaining hydroxyl groups upon the reaction with tris(diethylamino)phosphine gave the product **2b** and diphosphine. Keeping compound **8** in toluene for 14 h at 100°C resulted in the evolution of two moles of diethylamine and the formation of product **9** containing no free hydroxyl groups. Subsequently this product can be converted into bisphosphonate **10** or bis(phosphonothioate) **11**. NMR monitoring of the formation of the bis(phosphonothioate) **11** showed that reaction consists of two stages. The monothio-derivative formed initially is responsible for two ^{31}P NMR signals, with $\delta_{\text{P}} = 84$ and 179 ppm ($J_{\text{P-P}} = 29$ Hz). To convert this compound into the bithio-derivative, an additional heating for 24 h is required. When the compound **8** is made to react with electrophilic reagents such as phenyl azide, methyl iodide and tetrachloro-1,2-benzoquinone, compounds **12–14** are formed in which only one phosphorus atom of the diphosphino-methylene bridge has changed its coordination. The products **12** and **14** are unstable and rapidly decompose.

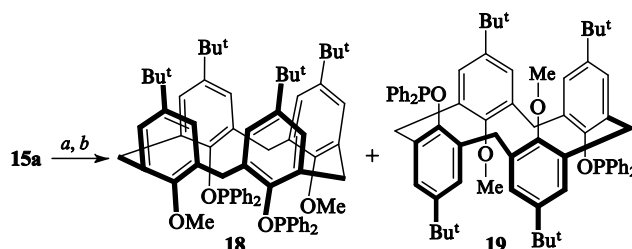


Synthesis of polyfunctional phosphinite derivatives has been reported in several studies.^{15–17} Both *p*-*tert*-butylcalix[4]arene **1** itself and its 1,3-diethers **15** have been subjected to phosphorylation by chloro(diphenyl)phosphine. Treatment of these substrates with lithium diisopropylamide or butyllithium at a temperature below 50 °C followed by reaction with Ph_2PCl results in the selective formation of bis(phosphinites) **17**. These products exist in a *cone* conformation, except for the compound **17a** in which fast interconversion of the *cone* and *partial cone* conformations occurs. When Et_3N is used as the base in boiling THF, the compound **15d** can be converted only into the monophosphinite **16d** having a *cone* conformation. Under the same conditions, the calixarene **1** is converted into 1,3-bisphosphinite as a mixture of two conformers, the *cone* and the 1,2-*alternate*.

The structures of the 1 : 1 complexes formed by **16d** with Au(I) cations and the 2 : 1 complexes with Pd(II) and Pt(II) cations have been studied by X-ray diffraction analysis.¹⁸

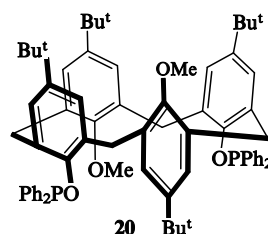


Deprotonation of the dimethyl ether **15a** by Bu^nLi in THF followed by the reaction with Ph_2PCl at room temperature also gives a mixture of conformers, *cone* **18** (25%) and 1,2-*alternate* **19** (60%). At lower temperatures (–78 °C), the content of the conformer **19** increases to 82%; the two possible 1,2-*alternate* structures of this compound undergo fast interconversion.¹⁵



(a) Bu^nLi , THF; (b) Ph_2PCl .

It has been noted¹⁹ that treatment of the calixarene **15a** with two equivalents of KH followed by reaction with Ph_2PCl results in the selective formation of diphosphorylated product **20** in a *partial cone* conformation.



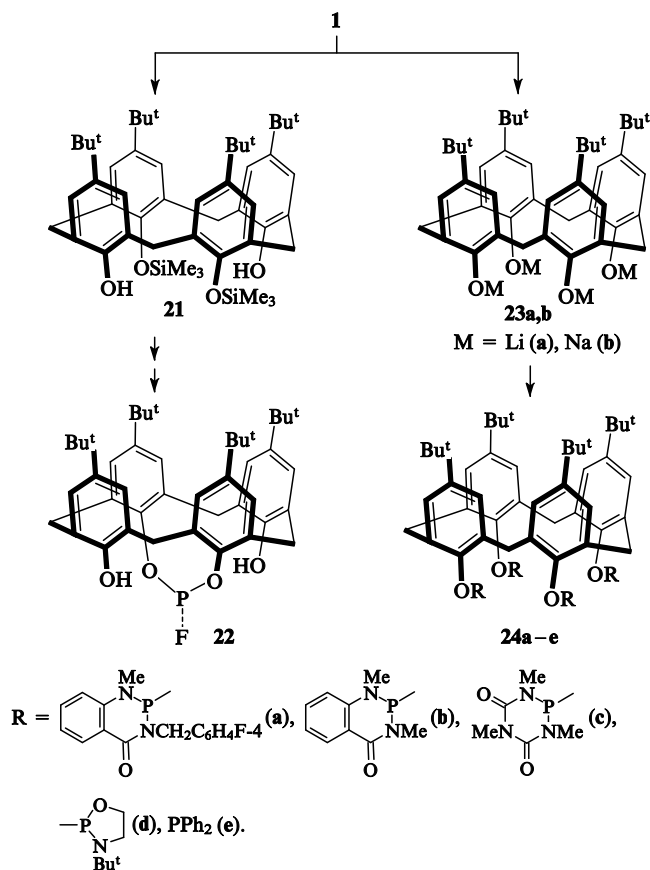
The data of dynamic ^1H NMR in solution point to the occurrence of a dynamic equilibrium between the *cone* **18** and *partial cone* **20** conformations, the former conformer predominating (the ratio **18** : **20** = 2.7 : 1).¹⁶ The number of introduced diphenylphosphinite fragments can be controlled by preliminary methylation of the phenolic hydroxy groups by methyl tosylate in the presence of potassium carbonate.¹⁹

The complex-forming ability of the phosphinite ligands **16d** and **17** in relation to transition metal cations [Pt(II), Pd(II) and Rh(I)] has been studied.^{16,17}

The introduction of P(III) atoms into the lower rim of calix[4]arene by preliminary silylation of hydroxy groups has been described by Schmutzler *et al.*^{20,21} Treatment of the calixarene **1** with hexamethyldisilazane gives rise to 1,3-disubstituted derivative **21**.

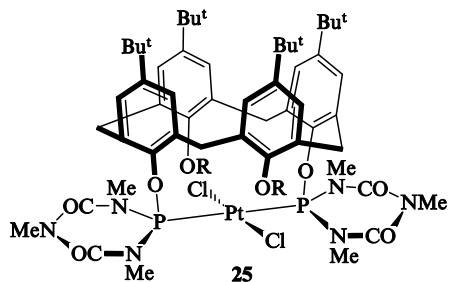
The reaction of this product with PF_2Cl affords mono- and bis-difluorophosphites, which are converted into monofluorophosphite **22** upon elimination of Me_3SiF or PF_3 . The macrocycles **21** and **22** occur in a *cone* conformation.

In order to synthesise completely *O*-phosphorylated calix[4]-arenes, the compound **1** is first converted into the corresponding tetraanion by treatment with a strong base (Bu^nLi or KH). The highly nucleophilic tetraanion is made to react with phosphorus-containing electrophiles with P–Cl bonds. Thus the reaction of the lithium derivative **23a** with *N*-substituted 2-chloro-4-oxobenzotriazaphosphorinanes or 2-chloro-4,6-dioxobenzotriazaphosphorinane yields calixarenes **24a–c**. The macrocycles **24d,e** were synthesised by similar reactions of the sodium derivative **23b** with 3-*tert*-butyl-2-chloro-1,3,2-oxazaphospholidine and chloro(diphenyl)phosphine.^{22–24} The stereochemical outcome of the above reactions is determined by the nature of the organophosphorus group entering the molecule. The compounds **24a,d,e** exist exclusively in a *cone* conformation,²³ whereas for compounds **24b,c** all of the four possible conformers are formed.²¹ Under similar conditions, calix[6]arene is converted into hexakis(diphenylphosphinite),²⁴ while calix[8]-

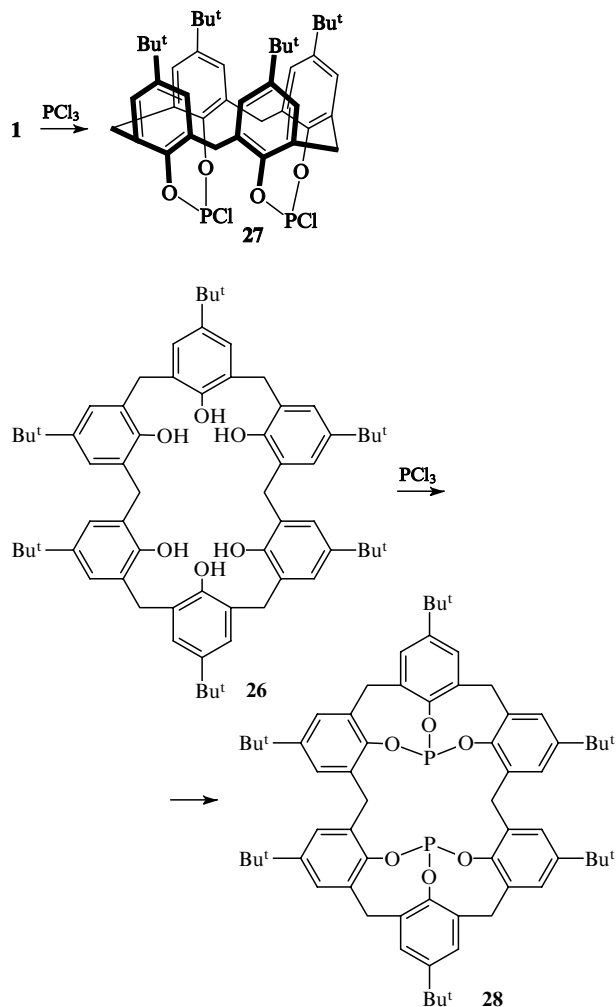


arene gives octaphosphorylated derivatives with diphenylphosphine and 1,3,2-oxazaphospholane fragments.²²

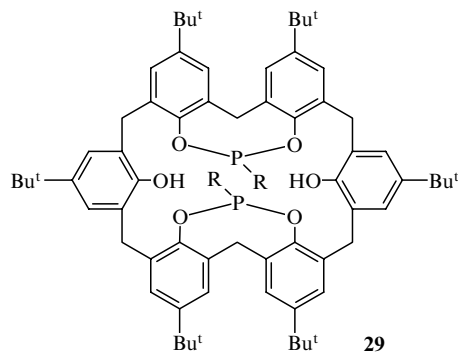
The cyclophane **24c** in a *cone* conformation reacts with dichloro(cycloocta-1,5-diene)platinum(II) giving 1:1 *trans*-complex **25**, in which two phosphorus atoms are coordinated to the Pt(II) cation.²⁰ The tetrakis(phosphinites) **24e** and **24d** also form stable complexes. For example, homodimetal complexes of **24e** with $\text{Fe}(\text{CO})_3$,²³ $[\text{Pd}(\text{COD})\text{Cl}_2]$ and $\text{Pt}[\text{COD}]\text{Cl}_2$ (COD is cycloocta-1,5-diene)²⁵ and a polymeric 1:1 complex of **24d** with copper(I) chloride²³ have been obtained. The tetradentate ligand **24e** is capable of forming both dimeric complexes, for example, $\{(\text{24e})[\text{Rh}(\text{CO})\text{Cl}]\}_2$, and binuclear heterometal complexes, for example, $\{(\text{24e})\{\text{NiCl}_2\}\{\text{Mo}(\text{CO})_4\}\}$.²⁵

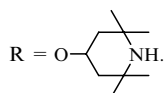
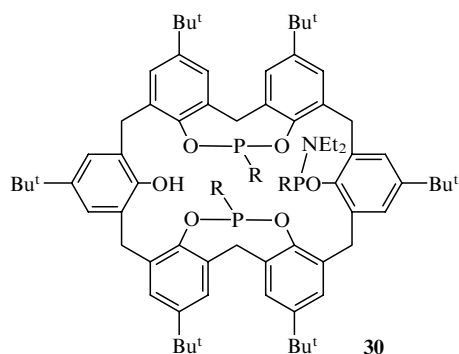


Phosphorylation of the calix[4]arene **1**²⁶ and the calix[6]arene **26**²⁷ with phosphorus(III) chloride (in some cases, in the presence of Et_3N as a base) yields cyclic bisphosphites **27** and **28**.

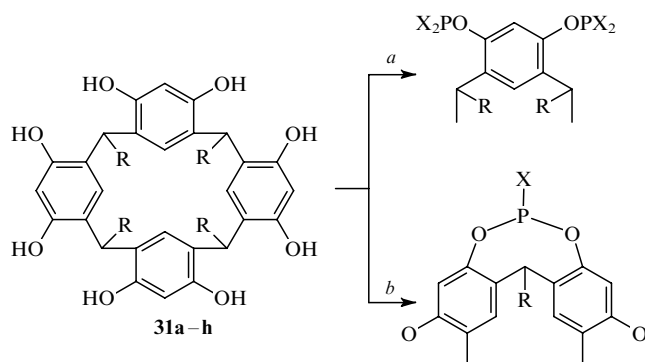


The product **27** is hydrolytically unstable; an attempt to recrystallise it from methanol resulted in the isolation of the initial calixarene **1**. According to X-ray diffraction data, the lone electron pairs of the phosphorus atoms in the compounds **27** and **28** point in the same direction; this makes them promising bidentate ligands for complexation with many *d*- and *f*-metal cations. Thus the compound **28** forms *cis*-complexes with Pd(II), Pt(II) and Re(I). In the complex $[\text{PdCl}_2\text{L}]$, the metal coordinates the bisphosphite fragments at an angle of 90 °C. Calix[6]arene derivatives containing cyclic (**29**) and acyclic (**30**) phosphorus fragments were synthesised by the reaction of calixarene **26** with phosphorous diethylamide.²⁸ These compounds were found²² to exhibit antioxidant properties.





Due to the conformational flexibility of calix[4]resorcinol-arenes **31**,^{29,30} their phosphorylation can follow two major pathways: (a) functionalisation of separate hydroxy groups or (b) cyclophosphorylation of two neighbouring hydroxy groups.

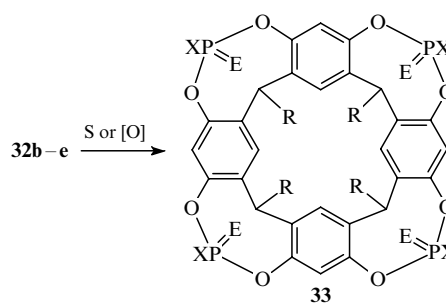
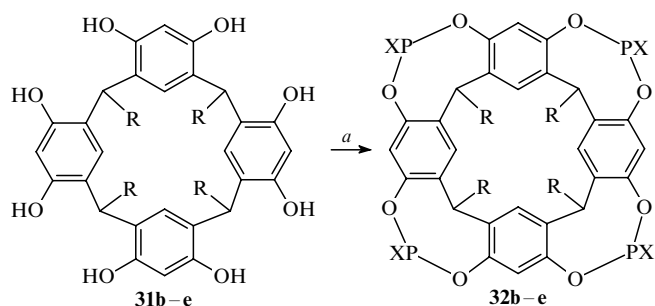


$R = \text{Ph}$ (a), Me (b), Bu^t (c), C_6H_{13} (d), C_7H_{15} (e), C_9H_{19} (f), $\text{C}_{11}\text{H}_{23}$ (g), $(\text{CH}_2)_2\text{Ph}$ (h).

It is obvious that the reaction route depends both on the nature of the phosphorylating reagent (most of all, the number of reaction sites) and on the conformation of the macrocycle. The most favourable conformation of octol **31** for cyclophosphorylation is the *crown* conformation (C_{4v} symmetry). In this conformation, the aromatic rings are directed upwards and form a bowl-like cavity, stabilised by a system of intramolecular hydrogen bonds.^{29,30} Monochlorophosphines, monochlorophosphites, dichlorophosphines and aminophosphines are usually employed as phosphorylation agents.

Phosphorylation using aminophosphines is distinguished by experimental simplicity and mild reaction conditions (room temperature).³¹

A series of P(III)-containing cavitands **32** have been prepared by the reactions of calixarenes **31b-e** with a number of aminophosphines (the reactants were taken in 1 : 4 molar ratio).³²⁻³⁷

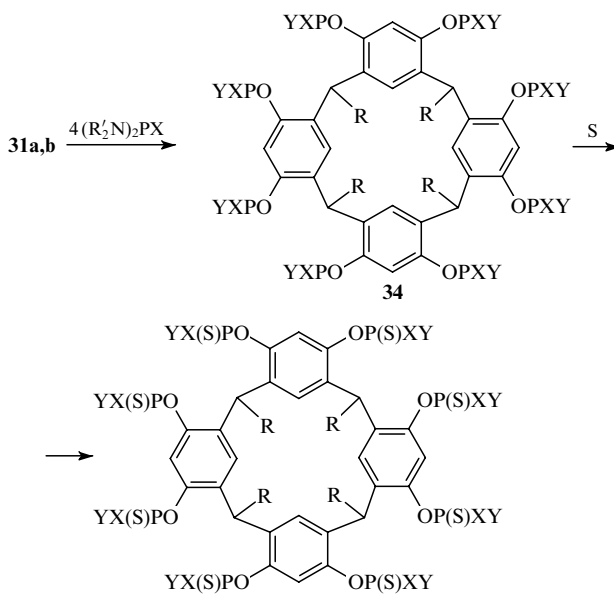


(a) 4 equiv. $(R'_2N)_2PX$; $R' = \text{Me}, \text{Et}$; $X = \text{NMe}_2, \text{NEt}_2$; $E = \text{O}, \text{S}$.

The influence of the nature of the substituent R in the bridging fragment on the reaction route has been studied.³⁶ It was found that the reaction of tris(diethylamino)phosphine with tetraphenyl-octol **31a** mainly follows pathway (a). Even when the ratio of the reactants is 1 : 2, the proportion of the cyclophosphorylation product is only 23%. In the case of tetramethyloctol **31b**, product mixtures containing both cyclic and acyclic phosphorus-containing fragments are formed at various ratios of the reactants. For tetrabutyl-octol, cyclophosphorylation becomes the prevailing process; when the reactant ratio is 1 : 4, only pathway (b) is realised. It was suggested³⁶ that the dependence of the phosphorylation route on the nature of the substituent R is a consequence of the calix[4]resorcinol-arene preorganisation (*i.e.* the position of the conformation equilibrium in the given solvent). Bulky alkyl radicals stabilise the *crown* conformation, due to lipophilic interactions with one another, and thus they promote cyclophosphorylation. The reactions of aminomethylated calix[4]resorcinol-arenes at a 1 : 4 reactant ratio also follow pathway (b).

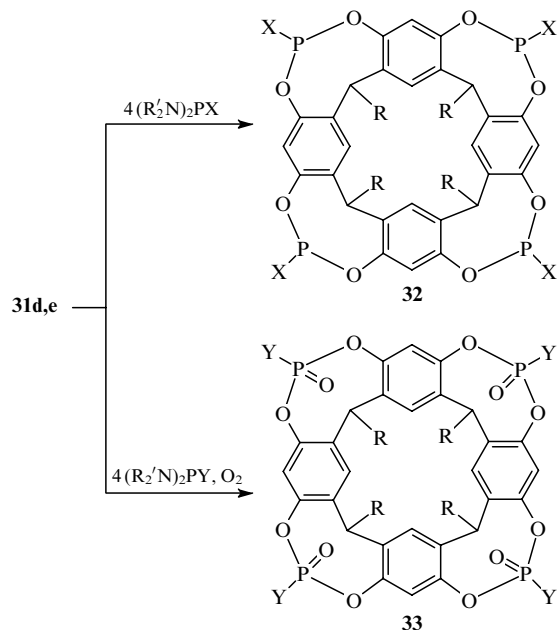
Recently triaminophosphines were used to phosphorylate *p*-*tert*-butylcalix[5]arene. This substrate reacts with $\text{P}(\text{NMe}_2)_3$ to afford monocyclic aminophosphine, *O,O'*-(dimethylaminophosphinediyl)calix[5]arene.³⁸

It is noteworthy that, unlike ordinary aminophosphines, aminophosphine cavitands **32** are stable against alcohols, water and oxygen and add sulfur only under rigorous conditions. Oxidation of these compounds or addition of sulfur gives macrocyclic phosphoroamidates or phosphorothioamidates **33**. Octaphosphorylated macrocycles **34** react with sulfur in a similar way.



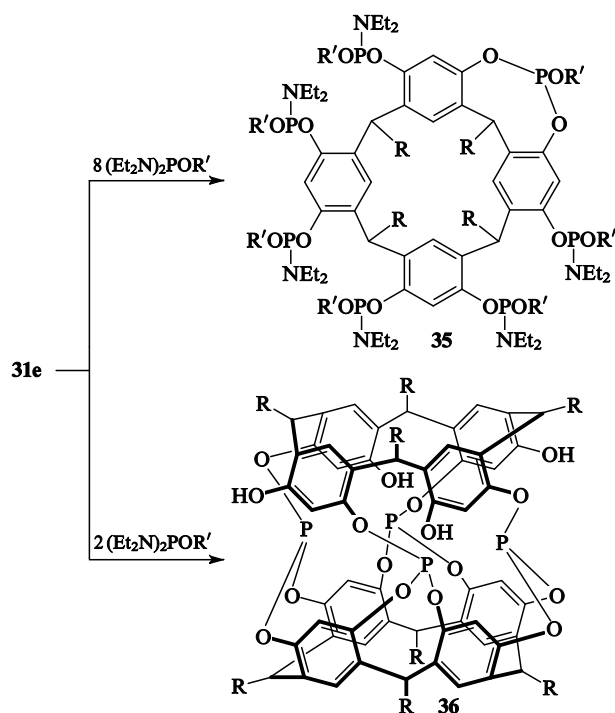
$R = \text{Ph}, \text{Me}$; $X = \text{NEt}_2, \text{OMe}$; $Y = \text{NEt}_2$.

When calixarenes **31d,e** were made to react with methyl and ethyl phosphorous diamides, the phosphates **33** were isolated from the reaction mixture instead of the expected macrocyclic phosphites **32**; the latter proved to be extremely unstable and were easily oxidised to phosphates by atmospheric oxygen. The macrocyclic phosphites **32** were detected only in the reactions of **31d,e** with heptyl and octyl phosphorous diamides.³⁹



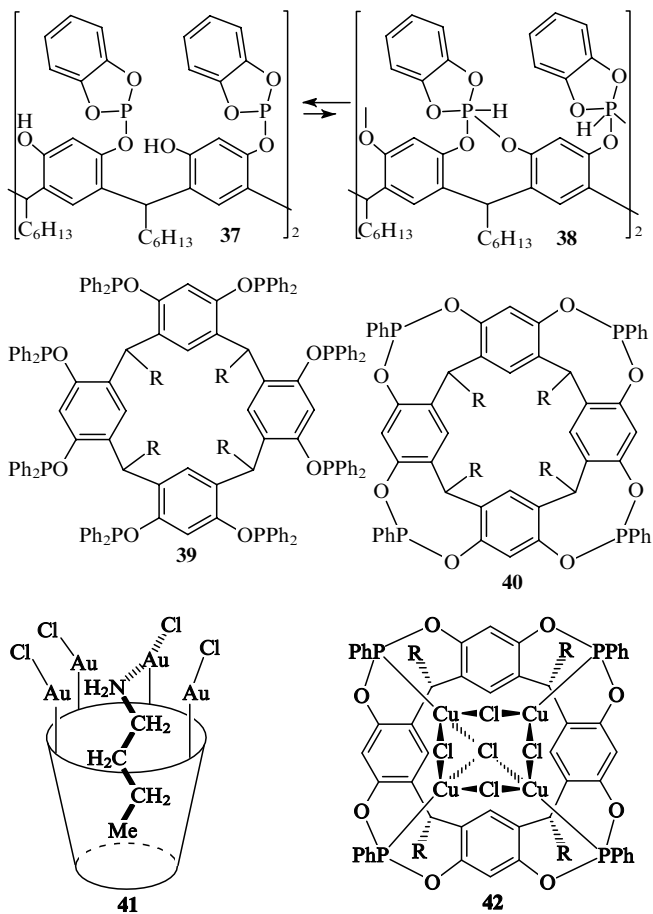
$R' = \text{Me, Et}$; $X = \text{OC}_7\text{H}_{15}, \text{OC}_8\text{H}_{17}$; $Y = \text{OMe, OEt}$.

Phosphorylation of the calixarene **31e** with (–)-menthyl tetraethylphosphorous diamide under mild conditions with different ratios of the reactants affords completely and partially phosphorylated optically active derivatives containing both cyclic phosphite groups and acyclic menthyl phosphorous amide fragments (for example, compound **35**). When the ratio of the reactants is 1 : 2 and the reaction conditions are more drastic the ‘ball’ structure **36** is formed.⁴⁰



$R = \text{C}_7\text{H}_{15}$, R' is menthyl.

The reaction of the calixarene **31d** with 2-chloro-1,3,2-benzodioxaphospholene at any ratio of the reactants gives phosphite **37**, occurring in an equilibrium with a slight amount of spiroposphorane **38**.⁴¹



$R = \text{CH}_2\text{CH}_2\text{Ph}$

Cavitands containing acyclic phosphinite (**39**) and cyclic phosphonite (**40**) fragments have been prepared by the reaction of the calixarene **31h** with chloro(diphenyl)phosphine and dichloro(phenyl)phosphine, respectively, in the presence of pyridine.⁴² The high complexation capacity of these calixarenes was confirmed by introducing them into reactions with Pt(II) and Au(I) salts. The structures of the resulting complexes (their composition is 1 : 4 or 1 : 8) depend on the nature of the metal (its coordination number). For the 1 : 4 complex, an unusual arrangement of the AuCl groups was established. Three of these groups are located at the upper rim of the calixresorcinolarene due to coordination to the phosphorus atom, while the fourth AuCl group resides in the macrocycle cavity; as a result, solvent molecules are arranged in the intermolecular space rather than inside the cavity. Only in the presence of amines, does the inclusion *endo*-complex **41** form. This property of the complex was used for extraction of alkali metal picrates.⁴²

An unusual μ_3 - and μ_4 -bridging position of halide anions has been established by X-ray diffraction analysis for inclusion complexes **42** and for the complexes $[\text{Py}][\mathbf{40} \cdot \text{Ag}_4(\mu\text{-Cl})_4 \cdot (\mu_4\text{-Cl})]$ and $[\text{Py}][\mathbf{40} \cdot \text{Cu}_4(\mu\text{-Cl})_4 \cdot (\mu_3\text{-Cl})]$, in which one of the Cl^- anions is located in the cavity formed by the four cationic centres.^{43,44} However, the bridging anion is only weakly fixed in the complex and can be easily replaced by other halide anions.

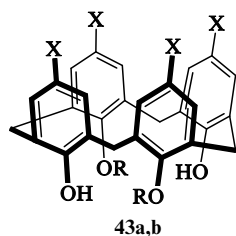
The use of phosphorus(III) halides for phosphorylation of calix[4]resorcinolarenes has been described.^{45,46} The reaction of the macrocyclic compound **31b** with excess PCl_3 affords cyclic phosphorochloridites, similar to compounds **32** ($X = \text{Cl}$), rather than octakis(phosphorodichloridites) **34** ($X = Y = \text{Cl}$).⁴⁵ The structure of the reaction products was confirmed by the data of IR

spectroscopy, mass spectrometry and elemental analysis. The halogen atom in these compounds can be readily replaced by a methyl or dimethylamino group upon the reaction with MeMgI or Me₃SiNMe₂, respectively. The latter reaction gives the cyclic phosphorous amide **32b**, which reacts with tetrachloro-*o*-benzoquinone or hexafluoroacetone yielding spiroposphorane structures containing four σ⁵λ⁵ phosphorus atoms.

The octakis(phosphorodifluoridite) **34** (X = Y = F) was formed in the reaction with PF₂Cl⁴⁶ only when the calix[4]resorcinolarene **31g** had been first treated with excess BuⁿLi. This product was relatively unstable and decomposed over a period of 24 h at –35 °C to give PF₃ and a mixture of various compounds containing P(=O)F(O) and P(=O)F₂ fragments.

III. O-Phosphorylation of calixarenes by P(V) compounds

Phosphorylation of the tetrahydroxy-derivative **1** with diethyl phosphorochloridate was carried out in the presence of sodium hydride,²² potassium carbonate in THF⁴⁷ or triethylamine in chloroform.^{48,49} In all cases, the reaction gave bisphosphate **43a**, which exists in a *cone* conformation.



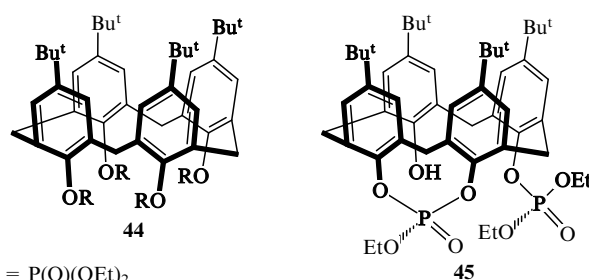
R = P(O)(OEt)₂, X = Bu^t (a), H (b).

Synthesis of the compound **43a** by the Atherton–Todd reaction (diethyl phosphite–triethylamine–tetrachloromethane, 0 °C) has been reported.^{50–53} The phosphorylation of 25,27-dihydroxy-26,28-dimethoxy-*p*-*tert*-butylcalix[4]arene with diethyl phosphorochloridate in the presence of NaH⁴⁷ gives bisphosphate in the 1,2-*alternate* conformation in which the methoxy groups are oppositely directed with respect to the main plane of the macrocycle.

A detailed study⁴⁹ of the reaction of the compound **1** with diethyl chlorophosphate in the presence of triethylamine in chloroform has shown that under these conditions, in addition to the previously described bisphosphate **43a**, occurring in a *cone* conformation, a 1,2-*alternate* with *anti*-orientation of the diethoxyphosphoryl groups with respect to the main plane of the macrocycle is also formed (its structure in the crystal was determined in another study⁵⁴). The content of this compound in the reaction mixture changes from 9% to 15% following an increase in the excess of triethylamine. Phosphorylation of unsubstituted calix[4]arene under the same conditions gives the bisphosphate **43b** exclusively in a *cone* conformation. Alkylation of the phenolic hydroxy groups in the phosphate **43a** with ethyl iodide in the presence of NaH (THF : DMF = 4 : 1) gives rise to 5,11,17,23-tetra-*tert*-butyl-25,27-diethoxy-26,28-bis(diethoxyphosphorylox-y)calix[4]arene in a *partial cone* conformation.⁴⁹

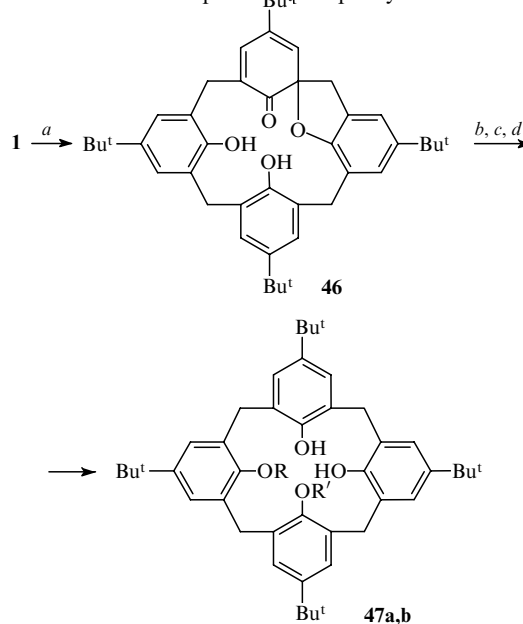
Phosphorylation of the calixarene **1** with excess diethyl phosphorochloridate⁵⁰ or diethyl phosphite⁵⁵ under phase transfer catalysis conditions (CCl₄–H₂O, 50% NaOH, tetrabutylammonium bromide) yields tetraphosphorylated derivative **44**.

When a less lipophilic catalyst (tetraethylammonium bromide) is used, the reaction affords a mixture of the tetrakis(phosphate) **44** in a *partial cone* conformation and bis(phosphate) **45**, which contains both cyclic and acyclic phosphate fragments.⁵⁶ Complex-forming properties of a number of phosphates based on calix[4]arene have been studied by extraction.⁵⁷ It was found that the introduction of these compounds in the organic phase markedly increases the extraction of lanthanide picrates; however, no pronounced selectivity was observed.



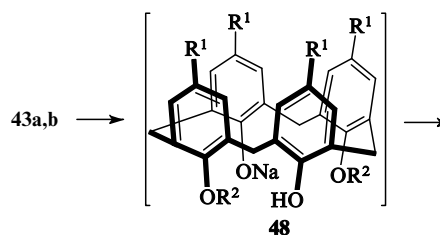
R = P(O)(OEt)₂

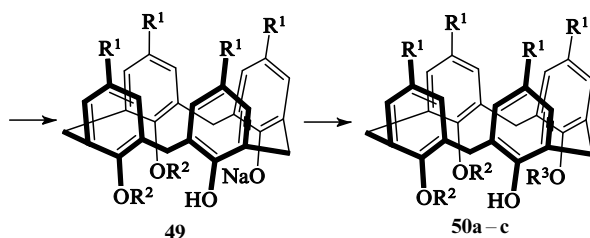
Mild oxidation of the compound **1** gives rise to spirodienone **46**, which can be used as the starting compound in the synthesis of mono- and 1,2-di-substituted calixarenes.^{58,59} In particular, treatment of this compound with lithium diisopropylamide (THF, –78 °C) followed by the reaction of the resulting mono- or dilithium salt with excess diisopropyl phosphorochloridate and subsequent reduction of the spirodienone fragment result in the formation of the correspondingly phosphorylated calixarenes **47**.



R = P(O)(OPri)₂, R' = H (a); R = R' = P(O)(OPri)₂ (b);
(a) Me₃PhN⁺Br₃[–], CH₂Cl₂, 0 °C; (b) LiNPr₂[–], THF, –78 °C;
(c) ClP(O)(OPri)₂; (d) EtOH, HBr.

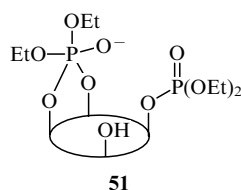
Synthesis of asymmetrically substituted phosphorylated calix[4]arenes **50** has been described by Markovskii *et al.*⁶⁰ The treatment of 1,3-bis(diethoxyphosphoryl)calix[4]arenes **43a,b** with sodium hydride in boiling benzene followed by interaction with electrophilic reagents, such as benzoyl chloride or methyl bromoacetate, affords asymmetrically substituted calix[4]arenes **50a–c** of the AABH type. The use of diethyl phosphorochloridate as an electrophilic reagent gives rise to triphosphorylated calixarenes **50c**.





$R^1 = \text{H or Bu}^t$, $R^2 = \text{P(O)(OEt)}_2$, $R^3 = \text{CH}_2\text{C(O)OMe}$ (**50a**), PhCO (**50b**), P(O)(OEt)_2 (**50c**).

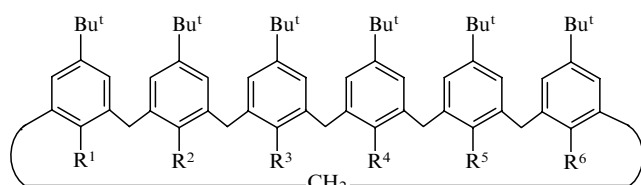
The key stage in the synthesis is the formation of the unstable monoanion of **48** and its *O,O*-phosphorotropic rearrangement to the 1,2-bis(diethoxyphosphoryl)calix[4]arene monoanion of **49**; the rearrangement occurs *via* phosphorane **51**, which was detected by ^{31}P NMR spectroscopy.



51

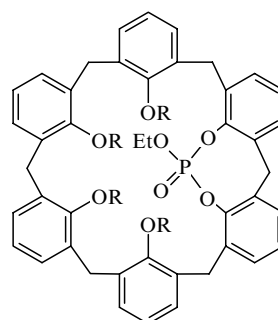
All these products exist in a *cone* conformation, while the asymmetrically substituted calix[4]arenes **50a,b** have C_1 symmetry and are formed as racemic mixtures, which is indicated by doubling ($\Delta\delta = 0.01$ ppm) of the phosphorus signals in the ^{31}P NMR spectra recorded in a chiral solvent.

O-Phosphorylation of calix[5]-, -[6]- and -[8]arenes is less studied. Data on selective phosphorylation are available only for calix[6]arene. Selective functionalisation of the hexahydroxy-derivative **26** by diethyl phosphorochloridate and *O,O*-diethyl phosphorothiochloridate has been performed and the conformational behavior of the products synthesised has been studied.^{61,62} In the case of diethyl phosphorochloridate, the reaction was carried out with various amounts of triethylamine in boiling chloroform. In all cases, the obtained product mixtures were analysed by HPLC and separated by column flash chromatography. This gave mono-, 1,3-bis-, 1,4-bis-, and 1,2,4-tris(phosphorylated) derivatives **52a-d**.



52a-l

$R^1 = \text{OP(O)(OEt)}_2$, $R^2 = R^3 = R^4 = R^5 = R^6 = \text{OH}$ (**a**);
 $R^1 = R^3 = \text{OP(O)(OEt)}_2$, $R^2 = R^4 = R^5 = R^6 = \text{OH}$ (**b**);
 $R^1 = R^4 = \text{OP(O)(OEt)}_2$, $R^2 = R^3 = R^5 = R^6 = \text{OH}$ (**c**);
 $R^1 = R^2 = R^4 = \text{OP(O)(OEt)}_2$, $R^3 = R^5 = R^6 = \text{OH}$ (**d**);
 $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = \text{OP(O)(OEt)}_2$ (**e**);
 $R^1 = R^4 = \text{OP(S)(OEt)}_2$, $R^2 = R^3 = R^5 = R^6 = \text{OH}$ (**f**);
 $R^1 = \text{OP(S)(OEt)}_2$, $R^2 = R^3 = R^4 = R^5 = R^6 = \text{OH}$ (**g**);
 $R^1 = R^3 = \text{OP(S)(OEt)}_2$, $R^2 = R^4 = R^5 = R^6 = \text{OH}$ (**h**);
 $R^1 = R^2 = R^3 = R^4 = R^5 = \text{OP(S)(OEt)}_2$, $R^6 = \text{OH}$ (**i**);
 $R^1 = R^3 = R^5 = \text{OMe}$, $R^2 = R^4 = R^6 = \text{OP(O)(OEt)}_2$ (**j**);
 $R^1 = R^3 = R^5 = \text{OMe}$, $R^2 = R^4 = R^6 = \text{OP(S)(OEt)}_2$ (**k**);
 $R^1 = R^2 = \text{OMe}$, $R^3 = R^4 = R^5 = R^6 = \text{OP(S)(OEt)}_2$ (**l**).

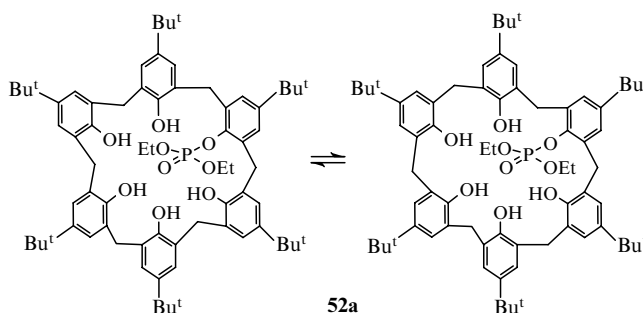


52m ($R = \text{P(O)(OEt)}_2$)

Depending on the reaction conditions, the optimum yields of these compounds vary from 28% to 56%. It is of interest that in another study,⁴⁸ 1,3,5-tris(phosphorylated) product was obtained in 60% yield under the same conditions.

The fully substituted derivative **52e** was synthesised in 20% yield under conditions of phase transfer catalysis in the CH_2Cl_2 –50% NaOH system in an excess of diethyl phosphorochloridate. The use of anhydrous solvent and solid alkali permitted the yield to be increased to 37%.⁶¹ Under the same conditions, pentakis(diisopropoxyphosphoryloxy)calix[5]arene²⁶ (in a *cone* conformation) and octakis(diethoxyphosphoryloxy)calix[8]arene⁶³ have been obtained. It was also noted⁶³ that phosphorylation of the compound **26** with diethyl phosphorochloridate can give not only the product **52e** but also the pentaphosphorylated derivative **52m** with one cyclic phosphate fragment. The use of sodium hydride as a base in a THF–DMF mixture (10:1) affords the compound **52e** as a *flattened 1,2,3-alternate* conformation in 75% yield.⁶⁴

When the calixarene **26** is made to react with a large excess of less reactive *O,O*-diethyl phosphorothiochloridate in the CH_2Cl_2 –50% aqueous NaOH system, the 1,4-bis(thiophosphorylated) product **52f** is formed selectively in 60%–70% yield. Variation of the conditions of phase transfer catalysis makes it possible to synthesise also mono-, 1,3-bis-, and pentakis-thiophosphorylated derivatives **52g-i**.⁶⁵ The phosphates **52j-l** were prepared by phosphorylation of partially methylated calix[6]arenes under similar conditions.⁶⁶ Study of the mono- (**52g**)⁶² and 1,4-bis(thiophosphorylated) (**52f**)⁶¹ products by X-ray diffraction analysis and ^1H NMR spectroscopy (solution in CDCl_3) showed that they exist in a *pinched cone* conformation (C_{2v} symmetry), in which the two opposite methylene bridges are directed towards the centre of the macrocycle. It is notable that 1,4-diphosphorylated compound **52c** exists in a *1,2,3-alternate* conformation. According to NMR spectroscopy, the macrocycle **52j** in CDCl_3 solutions exists as an equilibrium of two conformers, *cone* (C_{3v} symmetry) and *1,2,3-alternate* (C_s symmetry), the former conformation being 4 kJ mol⁻¹ more stable.⁶⁶ The researchers believe⁶⁶ that the *cone* conformation is stabilised due to the weak $\text{CH}-\pi$ interactions of the methyl groups, which, according to X-ray diffraction analysis, are directed inside the ring.

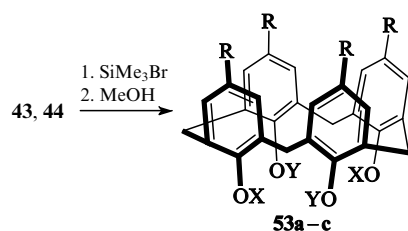


52a

Study of partially phosphorylated and thiophosphorylated *p*-*tert*-butylcalix[6]arenes, for example **52a**, by dynamic NMR has shown⁶² that these macrocycles participate in, at least, three dynamic processes: (a) interconversion of the macrocyclic ring; (b) redistribution of hydrogen bonds; (c) interconversion of two *pinched cone* conformations.

Monosubstituted derivatives proved to be conformationally more rigid than 1,3- and 1,4-disubstituted derivatives. This is due to the fact that the activation energy of conformation transitions depends on the number of hydrogen bonds, which can be formed by the hydroxy groups that remain free. The contributions of hydrogen bonding to $\Delta G^\ddagger$ are 45 and 31 kJ mol⁻¹ for the mono- and di-substituted derivatives, respectively.

The calix[4]arenes **53**, containing two or four dihydroxyphosphoryl groups on the 'lower' rim of the macrocycle, were prepared in high yields⁶⁷ from readily accessible bis- and tetrakis-diethoxyphosphoryl derivatives of calixarenes **43** and **44**.

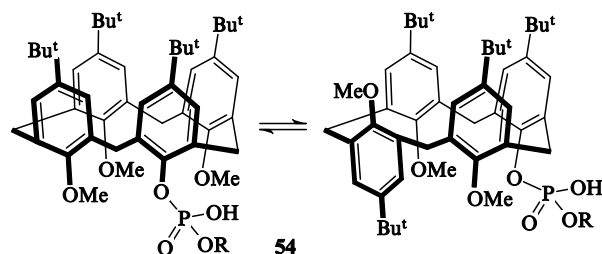


R = H, X = H, Y = (HO)₂PO (a);

R = Bu^t; X = H, Y = (HO)₂PO (b); X = Y = (HO)₂PO (c).

When these products are treated with excess bromotrimethylsilane in a solution in anhydrous chloroform, the corresponding silyl esters are prepared in quantitative yields. On treatment of these compounds with methanol, the labile P–O–Si bond ruptures; this gives the acids **53** as colorless crystalline compounds, readily soluble in polar organic solvents (alcohols, DMSO, DMF) and in aqueous solutions of alkali; they are stable in aqueous alcohols and in amine–alcohol mixtures for several days. The compounds **53a–c** are relatively strong acids [*p*K_a 2.85, 3.10 and 2.90 (aqueous methanol)]. They form 1 : 1 and 1 : 2 *exo*-complexes with *tert*-butylamine, α -phenylethylamine and ephedrine; the complexes exist in a solution in deuterated methanol as contact ion pairs.⁶⁷

In order to develop selective agents for the transfer of lithium cations through liquid membranes, the phosphates **54** were synthesised by the reaction of 25,26,27-trimethoxy-28-hydroxy-*p*-*tert*-butylcalix[4]arene with alkyl phosphorodichloridates followed by hydrolysis.⁶⁸ Spectral data indicate that the compounds **54a–c** occur in solution as mixtures of two conformers, a *cone* and a *partial cone*, the equilibrium being sensitive to the influence of the medium.

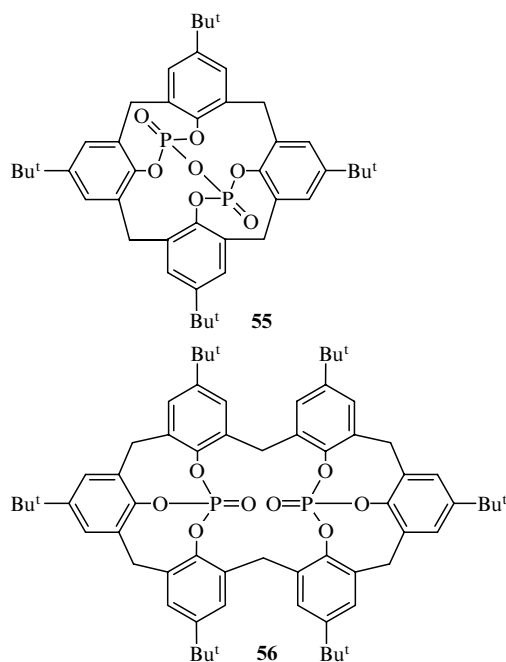


R = Me (a), Et (b), Prⁿ (c).

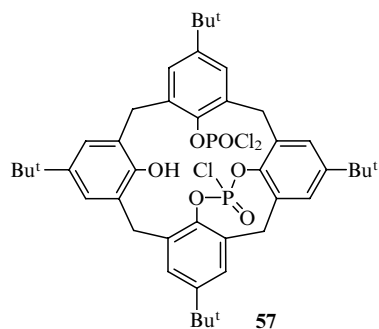
The fraction of the *cone* conformation in which all the four dipoles point in the same direction increases with increase in the solvent polarity. It is noteworthy that the complexation of the compounds **54** with Li⁺ and Na⁺ cations occurs more readily for

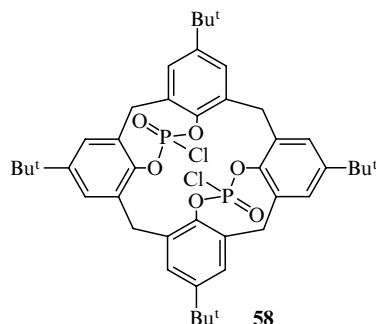
the *cone* conformation of the calixarenes; therefore, no macrocycles in the *partial cone* conformation were found in the complexes.

Pyrolysis *in vacuo* (230–240 °C) of mono-, bis-, and tetrakis-phosphates **43**, **44** and **47**, irrespective of the number of phosphorus-containing groups, gives the same product, pyrophosphate **55**, in which all the hydroxy groups are bound intramolecularly.^{26, 69} This means that the formation of the compound **55** involves stages of fragmentation and intermolecular migration of the phosphate groups. Study of the crystal structure of the pyrophosphate **55** showed that the two terminal oxygen atoms and the oxygen atom of the P–O–P bridge are directed away from the plane of the molecule. The conformation of the pyrophosphate can be defined as a *pinched* or *flattened cone*. Pyrolysis of a mixture of regioisomers of phosphorylated *p*-*tert*-butylcalix[6]arenes yields isomeric bridged bis(phosphates) **56**, which differ in the arrangement of the phosphoryl oxygen atoms (either *syn*- or *anti*-).

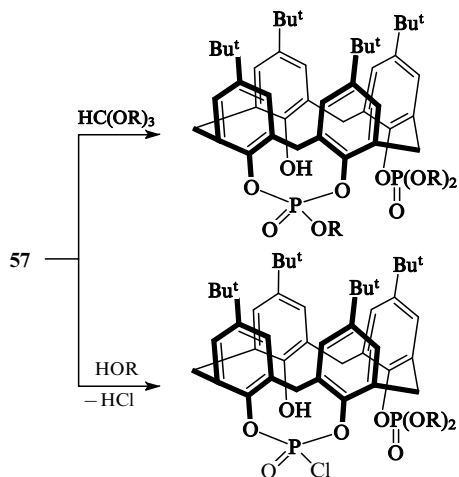


Yet another pathway to phosphorus-containing bridged macrocyclic structures is reaction of the compound **1** with phosphorus halides. Thus refluxing of **1** with POCl₃ in chloroform in the presence of Et₃N gives rise to the mono-bridged system **57**. At higher temperatures (xylene, 85 °C), the reaction affords structure **58** with two bridges, which might be a mixture of stereoisomers with different spatial arrangements of the P–Cl and P=O bonds.²³





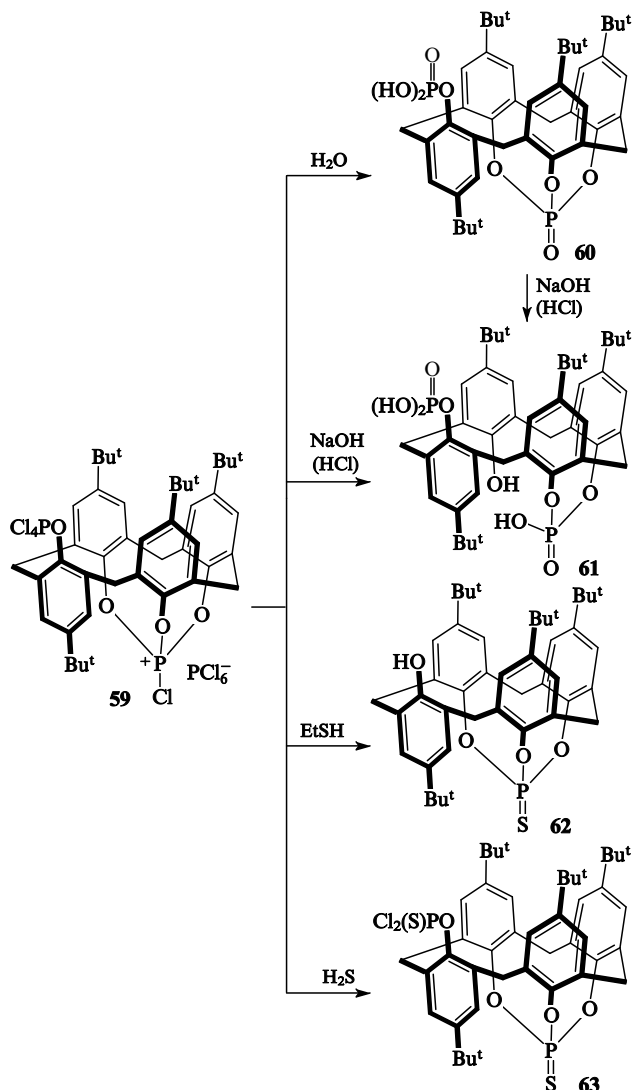
Interestingly, pyrolysis of the compound **57** also gives the pyrophosphate **55**. Glode *et al.*⁷⁰ have studied the reactivity of the compound **57** towards nucleophilic reagents such as water, alcohols and orthoformates. It was found that the halogen atoms can be successfully substituted by hydroxy or alkoxy groups to give the corresponding acids or esters; these reactions do not involve the P–O–C bonds.⁷⁰



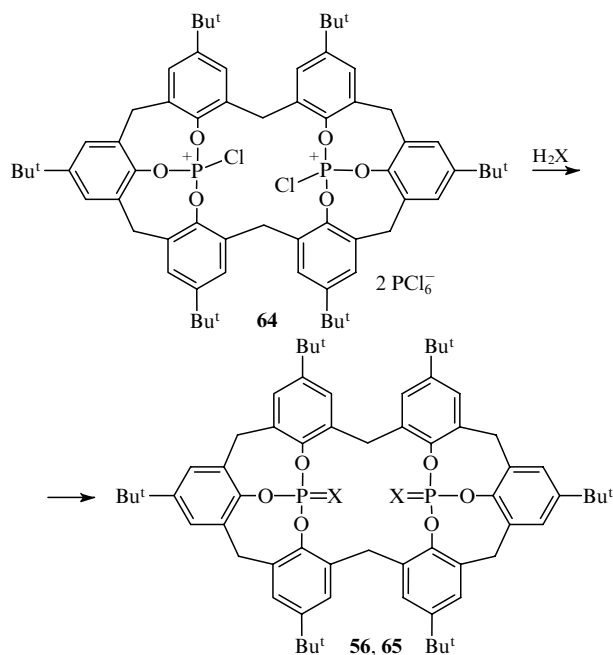
R = H, Me, Et.

When the calixarene **1** is treated with three equivalents of PCl_5 , the macrocyclic compound **59**, containing three phosphorus atoms, is formed.^{71,72} According to ^{31}P NMR spectroscopy, one of these atoms forms a phosphonium cation upon linking to the three phenolic groups, a second phosphorus atom forms the quasiphosphonium group OPCl_4 , while the third atom occurs as the PCl_6^- anion ($\delta_{\text{P}} = 8.1$, -66.0 and -296 ppm, respectively). The X-ray diffraction analysis of the compound **59** confirmed the presence of tetra-, penta- and hexa-coordinated phosphorus atoms. The macrocycle conformation is intermediate between a *partial cone* and *1,2-alternate*.⁷³ All the three phosphorus atoms in the compound **59** are reactive. On treatment with SbCl_5 , the PCl_6^- anion is replaced by SbCl_6^- ; reactions with nucleophiles occur as substitution at the P–Cl bond and, under more rigorous conditions, also at the P–O bond.

For example, the reaction of **59** with water gives phosphate **60** in which the P–O–C bonds remain intact. However, upon prolonged action of acids or alkali, the 1,2,3-linked phosphate is converted into 1,2-phosphate **61** as a result of hydrolysis of one P–O–C bond. The compounds **60** and **61** contain free hydroxy groups and can be easily converted into the corresponding esters on treatment with diazomethane or orthoformates. Reactions with sulfur-containing nucleophiles give phosphorothioates **62** and **63**, the character of binding in the lower rim of calix[4]arene remaining invariable; this points to high stability of phosphates and phosphorothioates bound to the 1,2,3-positions of the calixarene system. According to ^1H and ^{13}C NMR spectroscopy and X-ray diffraction analysis, the compounds **60–63** occur in a *partial cone* conformation.^{71,72,74,75}



The reaction of the calix[6]arene **26** with four equivalents of PCl_5 yields hexakis(chlorophosphate) **64**, which, like **59**, is capable of exchanging the PCl_6^- anion for the SbCl_6^- .⁷²



X = O (**56**), S (**65**).

The reactions with water and hydrogen sulfide afford the phosphate **56** and phosphothioate **65**. The phosphoryl oxygen and sulfur atoms point in the same direction in relation to the main plane of the macrocycle. This makes these compounds promising chelating agents for cations of many *d*- and *f*-elements.

The reaction of the compound **26** with ethyl phosphorodichloridate gives rise to cyclic mono- and bis-phosphates.⁷⁶ The reaction route depends on the nature of the base used. In the presence of CsF, monophosphate is formed, while the use of calcium hydride results in the formation of the diphosphorylated product.⁷⁶ The spatial structure of the macrocycles obtained was not determined.

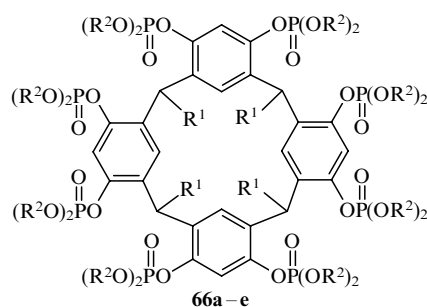
The calix[4]resorcinolares **31** are readily phosphorylated by traditional reagents, chlorides of acids of tetraordinated phosphorus and the (RO)₂PHO–CCl₄–Et₃N ternary system. The reactions of the octahydroxy-derivative **31** with excess diorganyl phosphorochloridates and triethylamine (20 °C, THF) afford octaphosphorylated cyclophanes **66**.^{77–79}

The reaction outcome depends on the nature of the radical in the diorganyl phosphorochloridate. Even when excess phosphorylating reagent is used, the reactions with diethyl and dipropyl phosphorochloridates give tetraphosphorylated products **67** together with octasubstituted derivatives. In the case where diisopropyl phosphorochloridate is employed, the reaction stops at the stage of formation of the tetraphosphorylated product, due to the steric hindrance during the process and the low solubility of the corresponding tetrasubstituted products, resulting in their removal from the reaction area.⁷⁹ The tetrakis(phosphates) **67** were obtained by using a large excess of the reagent (**31**: phosphorochloridate: triethylamine = 1:5:5) and by treating the compound **31** with the (RO)₂PHO–CCl₄–Et₃N ternary system (**31**: reagent = 1:10). It should be noted that in early studies,^{77,78} the structure with alternating positions of the phosphoryl groups along the macrocycle rim had been assigned to the tetrakis(phosphates) formed in these reactions; however, later it was found⁷⁹ that a structure of the type **67** in which the phosphoryl groups occupy the opposing positions is more probable. The tetrakis(phosphates) **67** were further modified. Thus hydrolysis of the phosphate groups in **67**, *via* the intermediate synthesis of the corresponding trimethylsilyl ester, gave tetrakis(dihydroxyphosphoryloxy)tetrahydroxycalix[4]resorcinolarene **67g**.⁸¹ Reaction of the free hydroxy groups in **67** with 4-chlorosulfonylbenzo-15-crown-5 in the presence of triethylamine gave the derivative **67h**.⁸²

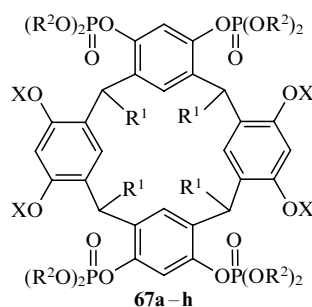
A study of the conformational behaviour of the tetrakis(phosphates) **67** by dynamic NMR spectroscopy has shown that at room temperature, fast pseudo-rotation of the *boat*–*boat* type occurs, which consists in the mutual transition of the two pairs of opposing benzene rings between the perpendicular and coplanar arrangements with respect to the main macrocycle plane.⁷⁹

Estimation of the complex-forming properties of the cyclophanes synthesized showed that they can form stable complexes both with some metal cations and with neutral aromatic molecules. The phosphoryl groups present in the molecule impart pronounced ionophoric properties to it. When the octakis(phosphate) **66d** is used as an ion transferring agent, the rate of transfer of alkali and alkaline earth metal picrates through a liquid membrane increases 1.3–9.0-fold compared to that attained with 15-crown-5; however, the transfer is almost nonselective.⁷⁹ The compound **67h** has demonstrated selectivity towards potassium cations.⁸² The octakis(phosphates) **66c,d**, owing to their lipophilic cavity, form crystalline ‘host–guest’ complexes with aromatic compounds, toluene and *m*-cresol.⁷⁹ Later,⁸⁰ the structures of several complexes of this type in solution and in the solid state were studied by X-ray diffraction analysis and NMR spectroscopy. The cyclophane **67g** forms ‘host–guest’ complexes with benzene, toluene, anisole, xylenes, phenol and 1-phenylalanine in aqueous solutions. The complexes result from inclusion

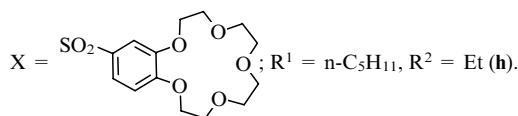
of a ‘guest’ molecule into the cavity formed by the preorganised pentyl radicals.⁸¹



R¹ = Me; R² = Et (**a**), Prⁿ (**b**), Ph (**c**), *p*-MeC₆H₄ (**d**);
R¹ = n-C₅H₁₁, R² = Ph (**e**).

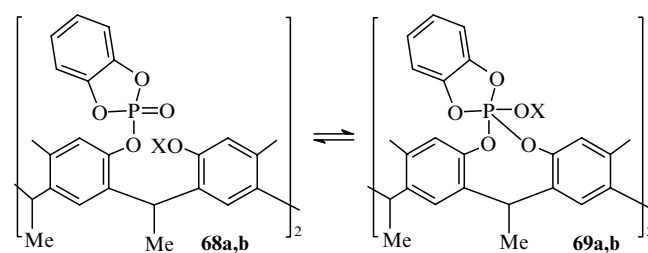


X = H, R¹ = Me; R² = Et (**a**), Prⁿ (**b**), Prⁱ (**c**), Buⁱ (**d**);
X = H, R¹ = n-C₅H₁₁; R² = Et (**e**), Prⁱ (**f**), H (**g**);



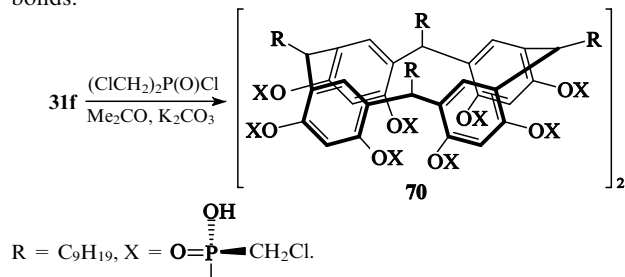
Tetrakis(phenylenephosphoryloxy)[1.4]metacyclophane **68a** was synthesised by the reaction of the octahydroxy-derivatives **31b** with four equivalents of *o*-phenylene phosphorochloridate and triethylamine.^{78,79}

Since the phosphorus atoms are located closely to the hydroxy groups of the neighbouring aromatic rings, intramolecular nucleophilic addition of the hydroxy groups to the P=O bonds occurs to give spirophosphorane structure **69a**. The driving force of this process is formation of the energetically more favourable penta-coordinated phosphorus atom in the dioxaphospholane ring. This reaction is reversible; the position of the equilibrium depends on the temperature and the nature of the solvent. On treatment with triethylamine, the **68a** ⇌ **69a** equilibrium shifts towards the more acidic form, **68a**. A similar equilibrium is observed for the **68b** ⇌ **69b** system. In pyridine, which is capable of binding to a pentacoordinated phosphorus atom,⁸³ the equilibrium shifts towards the spirocyclic tautomer **69b**.

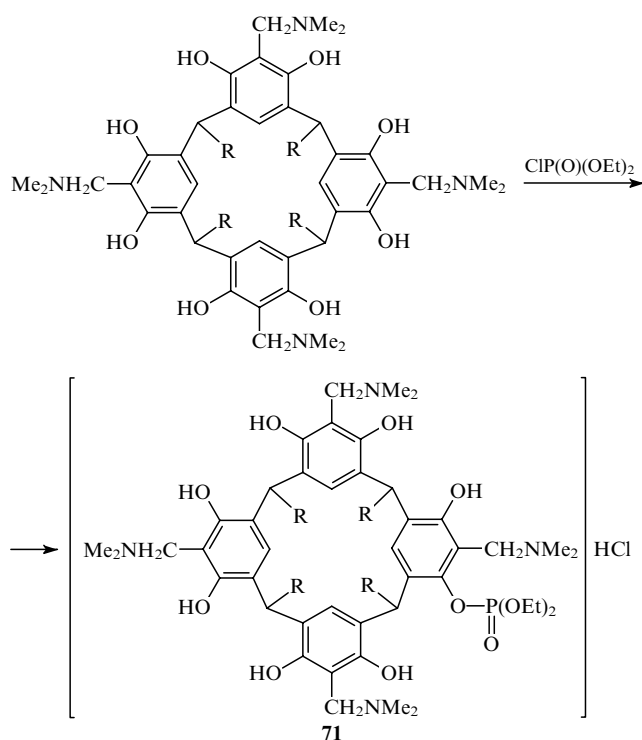


X = H (**a**), SiMe₃ (**b**).

When the compound **31f** ($R = C_9H_{19}$) was made to react with excess bis(chloromethyl)phosphinic chloride (acetone, K_2CO_3), instead of the expected bis(chloromethyl)phosphinic acid derivatives, octakis(chloromethylphosphonate) was isolated, due to the extremely easy rupture of one of the P–C bonds in the phosphinate. The product exists in solution as dimer **70** formed according to the ‘head-to-head’ pattern due to intermolecular hydrogen bonds.⁸⁴

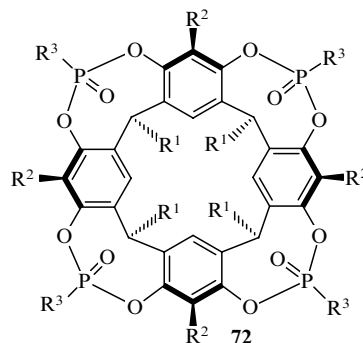


The first representatives of monophosphorylated cyclophanes **71** were prepared by refluxing in benzene of aminomethylated octahydroxy-derivatives with diethyl phosphorochloridate.⁸⁵



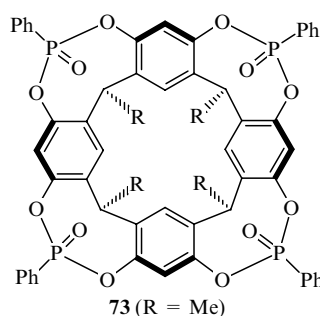
The use of organyl phosphorodichloridates or organylphosphonodichloridates for phosphorylation of the cyclophanes **31** has been reported.^{84, 86–88} The reaction with alkyl and aryl phosphorodichloridates in acetone in the presence of triethylamine results in the formation of diastereoisomeric cavitands **72**, which differ in the spatial arrangement of the P=O groups in the four phosphocine rings: *i* (the P=O group points to the centre of the upper rim) and *o* (the P=O group points outwards).^{86, 87} The reaction with ethyl phosphorodichloridate proceeds with a low yield (12%), owing to the competing intermolecular cross-linking of the calixarene fragments, resulting in the formation of polymers. The use of aryl phosphorodichloridates permits the yields of the target products to be increased to 50%–80%. The reaction gives all of the six possible stereoisomers, although three of them, *iiio*, *iioo* and *iooo*, proved to be more preferable (the proportion of each isomer was determined by HPLC). The proportions of the *iiii* (compound **72**) and *oooo* isomers in the reaction mixture are not

higher than 10%; in some cases, they do not form at all. It is quite natural that as the substituent R^3 becomes larger, the content of the *iiio* isomer increases, whereas the content of the *iooo* isomer correspondingly decreases. It is clear that the receptor capacity of the macrocyclic compounds obtained depends on the spatial arrangement of the phosphoryl groups. The *iiii* and *iiio* isomers are the most promising complex-forming agents. Thus the *iiio* isomer forms a complex with cyclohexylammonium ($K_a = 1370$ litre mol^{−1}) as a result of three-point hydrogen binding, whereas the *iioo* and *iooo* isomers do not form complexes of this type.



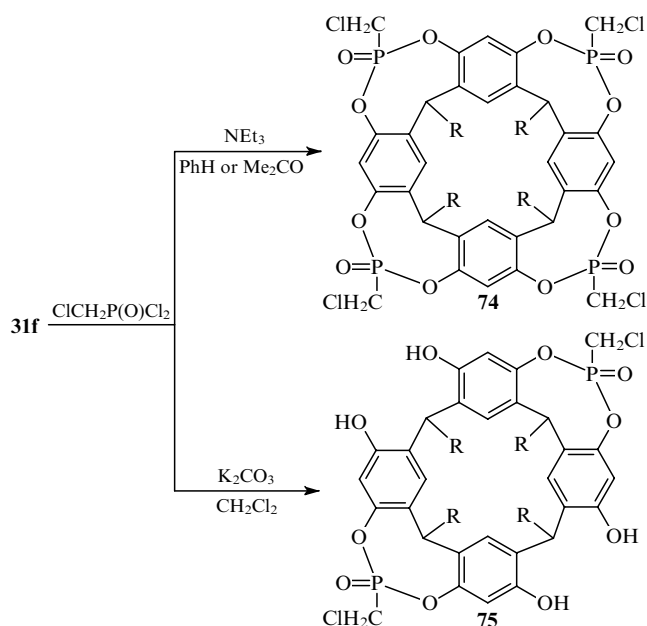
$R^1 = Ph, Alk; R^2 = H, Br; R^3 = OEt, OAr$.

It has been reported⁸⁸ that the *iiii* stereoisomer of compound **73** is formed as the major product in the reaction of the octahydroxy-derivative **31a** with phenylphosphonic dichloride. The publication does not present the conditions of the synthesis. The product was identified as having the *iiii* configuration based on its C_{4v} symmetry (although the *oooo* isomer has the same symmetry). The strong complexing properties of the reaction product served as additional evidence for its *iiii* configuration. The compound **73** forms stoichiometric complexes with alkali metal and alkylammonium cations, characterised by association constants of 10^8 – 10^{10} litre mol^{−1}; the composition of the complexes is 1 : 1 (K^+ , Rb^+ , Cs^+ , NH_4^+ , $MeNH_3^+$, $BuNH_3^+$) or 1 : 2 (Li^+ , Na^+).



The reaction of the long-chain calix[4]resorcinolarene **31f** with chloromethylphosphonic dichloride in the presence of triethylamine gives completely phosphorylated product **74**; when potassium carbonate is used as the base, partially phosphorylated product **75** is formed.⁸⁴

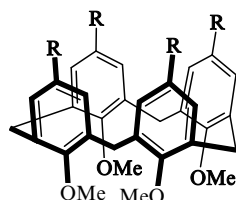
The use of $POCl_3$ (in the presence of pyridine as the base) for introduction of phosphate groups has been reported.⁸⁹ In relation to *C*-undecylcalix[4]resorcinolarene, it was shown that at various ratios of the reactants (ranging from 1 : 1 to 1 : 39), complex mixtures of cyclic and acyclic phosphates with different numbers of phosphate fragments (from 1 to 6.3) are formed. Complete phosphorylation was not attained even with a large excess of $POCl_3$. These compounds exhibit surfactant properties and form stable complexes with UO_2^{2+} .



IV. Phosphorylation of the aromatic rings in calixarenes

Phosphorylation of the aromatic rings in calixarenes gives rise to a new type of receptors in which, unlike *O*-phosphorylated derivatives, the molecular cavity of the cyclophane can also be involved in the molecular binding of a substrate. The presence of organophosphorus compounds in the upper rim of the macrocycle permits the receptor to interact both with polar or ionic groups of a substrate and with non-polar fragments, the latter being included in the molecular cavity of the cavitand. Thus, multi-point 'host-guest' binding is attained, which is known to increase sharply the efficiency and selectivity of complex formation.^{90,91} Moreover, P–C bonds are thermally and hydrolytically more stable than P–O bonds, which are formed upon phosphorylation of the lower rim of calix[*n*]arenes.

The first representative of this type of cyclophanes, tetrakis(diphenylphosphino)calixarene **76**, was synthesised by successive reactions of the tetramethyl ether of *p*-tetrabromo-calix[4]arene **76a** with butyllithium and chloro(diphenyl)phosphine.⁹² Nevertheless, the Arbuzov reaction catalysed by nickel(II) salts is now the simplest and the most efficient method for direct phosphorylation of the upper rim of calix[4]arenes.⁹³

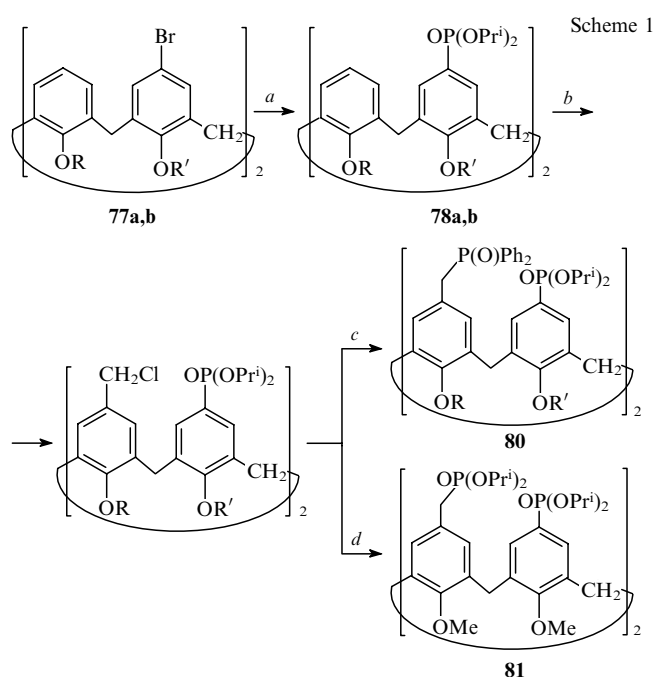


76a–d

R = Br (**a**), PPh₂ (**b**), P(O)(OPr^{*i*})₂ (**c**), P(O)Ph₂ (**d**).

The reaction of the compound **76a** with triisopropyl phosphite or isopropyl diphenylphosphinite gives the corresponding tetraphosphorylated calix[4]arenes **76c,d** in high (75%–80%) yields.

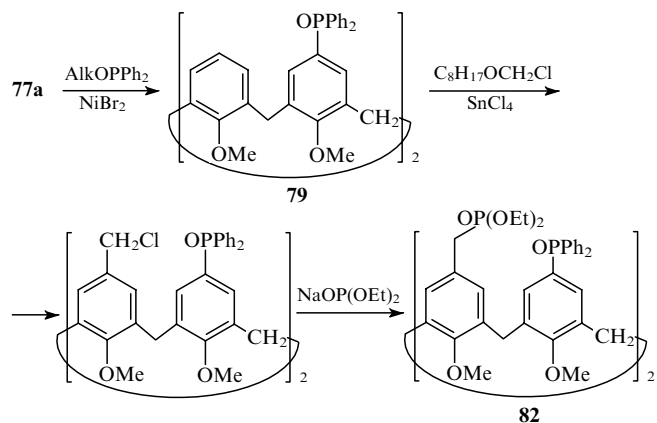
The same approach was used in another study⁹⁴ in order to prepare bis- and ABAB-tetrakis-phosphorylated derivatives. The reactions of *O*-alkylated dibromides **77a,b** with triisopropyl phosphite or alkyl diphenylphosphinite in the presence of NiBr₂ gave bisphosphonates **78a,b** and bis(phosphine oxide) **79** (Scheme 1). Treatment of the compounds **78** and **79** with octyl chloromethyl ether in the presence of SnCl₄ resulted in the introduction of CH₂Cl groups into the free *p*-positions of the



R = R' = Me (**a**); R = Me, R' = C₁₂H₂₅ (**b**).

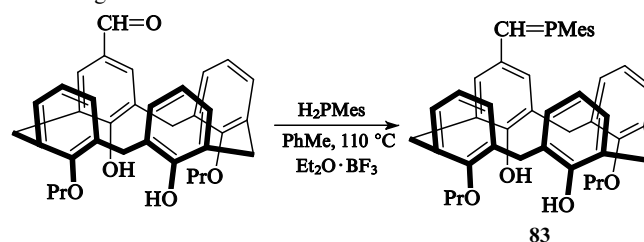
(a) P(OPr^{*i*})₃, NiBr₂; (b) C₈H₁₇OCH₂Cl, SnCl₄; (c) AlkOPPh₂;

(d) P(OPr^{*i*})₃, R = R' = Me.



aromatic rings. It is of interest that in the case of the methyl ethers **78a** and **79**, the chloromethyl derivatives are formed in high yields (60%–70%); when the dodecyl ether **77b** is used, the yield decreases to 26%. It has been reported that the size of the alkyl radical has a considerable influence on the kinetics of phosphorylation of calix[4]resorcinolarenes.^{95,96} This was explained by assuming formation of different types of aggregates in the solution. The subsequent substitution of the chlorine atom by phosphorus-containing nucleophiles gave rise to ABAB-tetrakis-phosphorylated cyclophanes **80–82**.

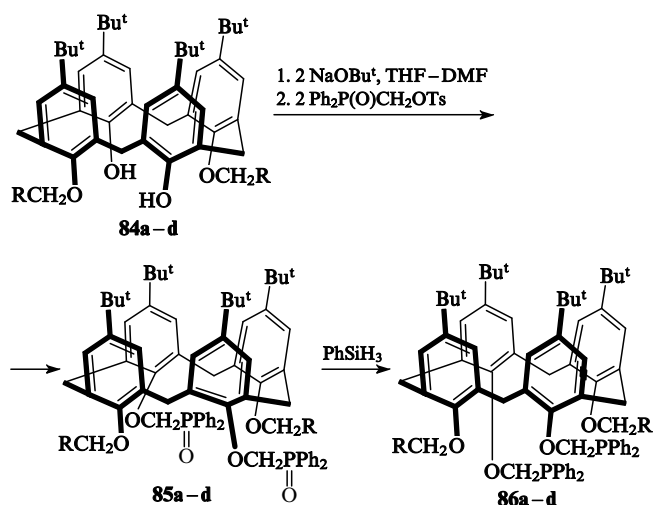
The first representative of calixarenes containing a low-coordinate phosphorus atom, phosphinylidenemethylcalixarene **83**, was synthesised as a mixture of stable *Z*- and *E*-stereoisomers capable of forming complexes with transition metals, by the following reaction:⁹⁷



V. Introduction of phosphorus-containing fragments *via* a chain of atoms (spacer)

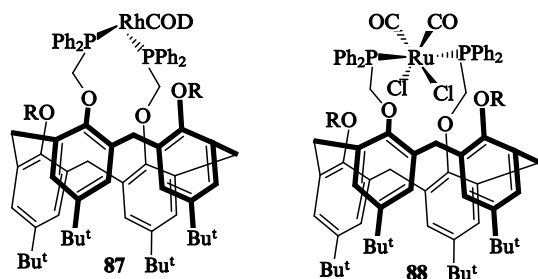
A vigorously developing route of the functionalisation of calix[4]-arenes aimed at producing more efficient and selective complex-forming agents is introduction of organophosphorus groups in which phosphorus atoms are not attached directly to the lower or upper rim of the macrocycle but are linked to the calixarene platform *via* a chain of other atoms (spacer). This approach makes it possible to extend substantially the synthetic potential in the construction of new macrocyclic receptors.

Deprotonation of 1,3-bis(ethoxycarbonylmethyl) calix[4]-arene derivative **84a** with sodium *tert*-butoxide and subsequent alkylation of the resulting dianion with $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{OTs}$ gives rise to bis(phosphine oxide) cyclophane **85a** in a *cone* conformation.⁹⁸



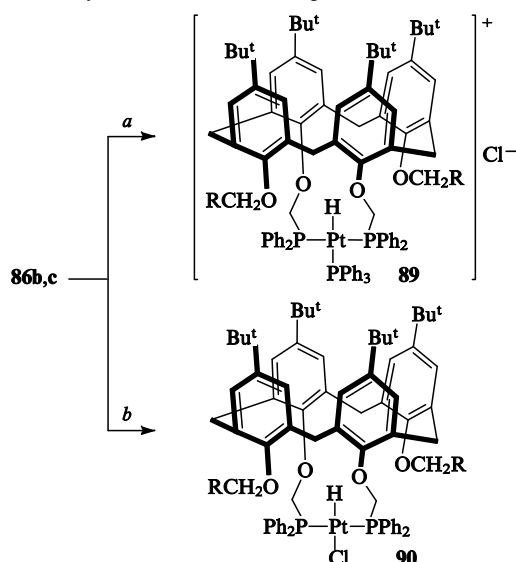
$\text{R} = \text{C}(\text{O})\text{OEt} \text{ (a)}, \text{C}(\text{O})\text{NEt}_2 \text{ (b)}, \text{CH}_2\text{OMe} \text{ (c)}, \text{C}(\text{O})\text{NHCH}(\text{Me})\text{Ph} \text{ (d)}.$

When potassium *tert*-butoxide is used as the base in this reaction, the product **85a** is formed in a *partial cone* conformation. The crucial influence of the nature of the cation on the stereochemical outcome of the reaction was explained by the difference in the energy of binding of potassium and sodium cations to the intermediate diphenoxide. The harder sodium cation interacts more strongly with phenoxide anions and thus it fixes the *cone* conformation of the calixarene platform. When the compounds **85** are refluxed with phenylsilane in toluene, the phosphine oxide group is quantitatively reduced to give the corresponding bis(phosphine) macrocycles **86**; according to X-ray diffraction and ^1H and ^{13}C NMR data, this product also occurs in a *cone* conformation.⁹⁸ The compounds **86** can act as both *cis*- and *trans*-chelating ligands. *cis*-Complexes are formed upon the reactions of the calixarene **86a** with $\text{PtCl}_2(\text{PhCN})_2$ and $[\text{Rh}(\text{COD})\text{Cl}]_2$ (**87**) in the presence of AgBF_4 . The reaction of the compound **86a** with RuCl_3 and CO in boiling 2-ethoxyethanol affords the complex **88** with *trans*-P,P stereochemistry in a quantitative yield.⁹⁸



$\text{R} = \text{CH}_2\text{CO}_2\text{Et}$; COD is cycloocta-1,5-diene.

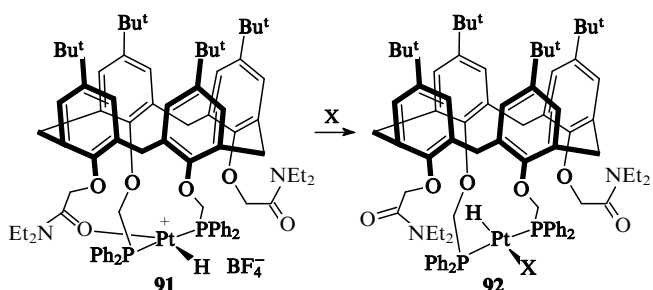
This method was used to prepare a series of metal-containing calixarenes^{99–104} able to participate in catalytic processes. Based on the bis(phosphine) cyclophanes **86**, a number of new Pt(II), Pd(II), Rh(I) and Ru(II) complexes were prepared. The reaction of the compound **86c** with the platinum(II) bis(triphenylphosphine) complex in boiling THF is accompanied by displacement of a PPh_3 molecule and the chloride anion from the metal coordination sphere and yields the cationic complex **89**.



$\text{R} = \text{C}(\text{O})\text{NEt}_2 \text{ (86b, 90)}, \text{CH}_2\text{OMe} \text{ (86c, 89)}$;
(a) $(\text{Ph}_3\text{P})_2\text{PtHCl}$, THF; (b) $(\text{Ph}_3\text{P})_2\text{PtHCl}$, CH_2Cl_2 .

The replacement of the ester side groups by amide groups, which interact more strongly with cations, crucially changes the reaction route. In this case, both triphenylphosphine ligands are replaced and neutral hydrido complex **90** is formed. Apparently, this outcome is due to the participation of two amide groups in the interaction with Pt(II); this accelerates the formation of intermediate species with pentacoordinated platinum and facilitates the ligand substitution.^{101–103}

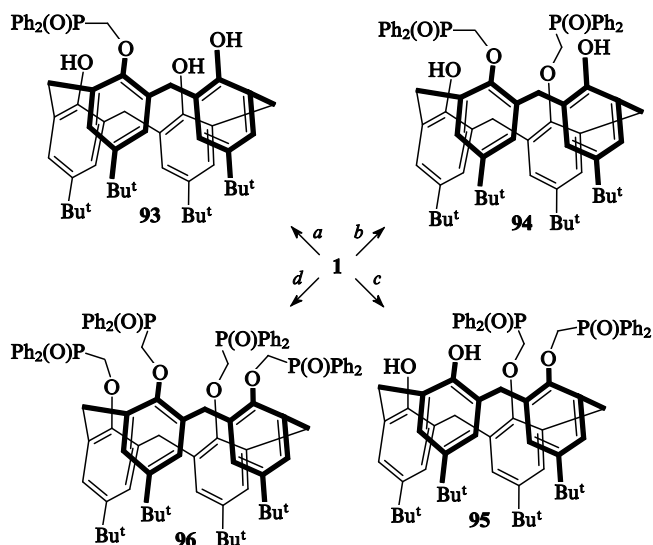
The structure of the complex **90** was studied. Two-dimensional (ROESY) NMR spectra and X-ray diffraction data attest convincingly that the hydride ion, responsible for the resonance signal at $\delta = -15.04$ ppm ($J_{\text{H-Pt}} = 1150$ Hz, $J_{\text{P-H}} = 15$ Hz), points to the centre of the calixarene cavity.^{101, 103} The stereochemistry of the Pt–H bond can be changed by involving the amide groups in complex formation. Thus the reaction of the complex **90** with silver tetrafluoroborate yields hydrido complex **91** in which the Pt–H bond is directed outwards.^{102, 103}



X is a donor.

In this environment, the hydride becomes much more reactive and can participate in various reactions. It is of interest that addition of a strong donor to the complex **91** results in displacement of the amide group from the coordination sphere yielding complex **92**, in which hydrogen is again directed inwards. This reaction makes it possible to change the reactivity of the hydride ion and creates conditions for the synthesis of bimetal hydrido complexes upon reactions with bidentate donors.¹⁰³

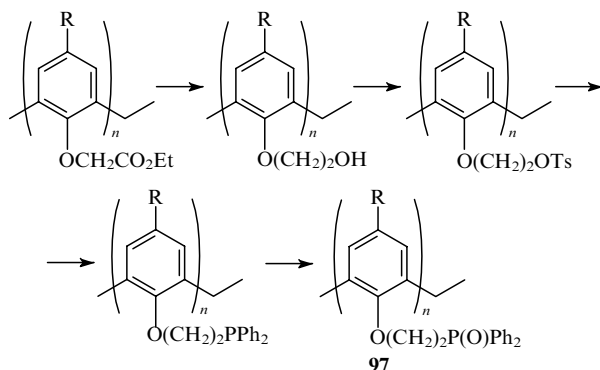
Selective introduction of one, two or four $\text{CH}_2\text{P}(\text{O})\text{Ph}_2$ substituents into the lower rim of *tert*-butylcalix[4]arene **1** was attained by using NaH and an appropriate alkylating reagent.^{105, 106}



- (a) 3 equiv. NaH, 2.2 equiv. $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{I}$, THF, 50%;
 (b) 5 equiv. NaH, 2.5 equiv. $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{I}$, PhMe, 80%;
 (c) 2.5 equiv. NaH, 2.2 equiv. $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{OTs}$, THF–DMF, 25%;
 (d) 6 equiv. NaH, 4.2 equiv. $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{OTs}$, THF–DMF, 70%.

When iodomethyl(diphenyl)phosphine oxide is employed as the alkylating reagent, the reaction gives, depending on the temperature and the amount of NaH used, either mono- (**93**) or 1,3-bis-(phosphine oxide) **94**. The reaction with more reactive hydroxymethyl(diphenyl)phosphine oxide tosylate allows the synthesis of the corresponding 1,2-di- (**95**) and tetra-substituted (**96**) derivatives. According to NMR and X-ray diffraction analysis, the cyclophanes **93**–**96** occur in a *cone* conformation; they are widely used as complexing reagents and membrane transferring agents for various metal cations.^{107–109} The reduction of the compound **96** with phenylsilane gives a tetrakis(phosphine) ligand capable of forming polynuclear complexes.^{105, 110}

A new series of polyfunctional phosphine oxide derivatives of calix[4]-, -[6]- and -[8]arenes **97**, containing $(\text{CH}_2)_2\text{P}(\text{O})\text{Ph}_2$ fragments, have been modelled and synthesised for the extraction and complexation of actinide and lanthanide ions.¹¹¹ The synthetic strategy is presented in the scheme.



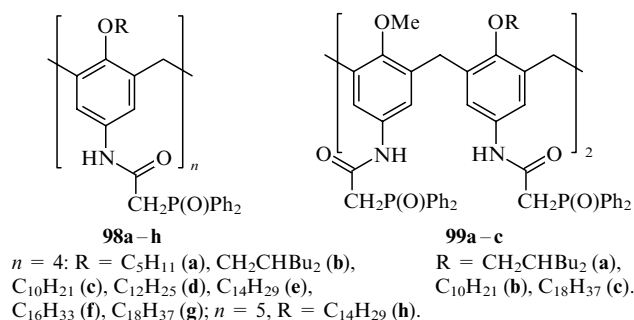
R = Bu^t, H; n = 4, 6, 8.

The properties of these compounds as extractants have been studied.^{112–115}

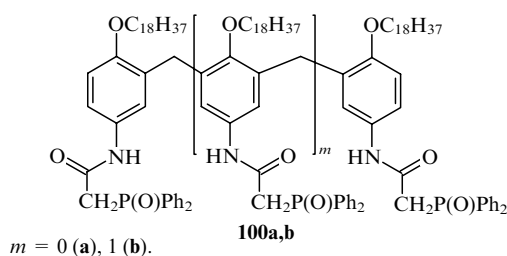
The further development of the methods for functionalisation of calixarenes followed the path of introduction of groups containing both an organophosphorus fragment and another binding site into the upper or lower rim of the macrocycle. Cavitands with the carbamoylmethylphosphine oxide

$[\text{NHC}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Ph}_2]$ ^{116–118} and α -aminophosphonate $[\text{NHC}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OR})_2]$ ¹¹⁹ groups have now been obtained.

It has been shown¹¹⁶ that the extraction properties of the traditional extractant for actinides, (*N,N*-diisopropylcarbamoylmethyl)octylphenylphosphine oxide (CMPO), can be markedly improved by grafting four or five carbamoylphosphine oxide groups to the upper rim of calix[4]- or -[5]arenes **98** and **99**.

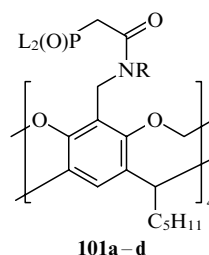


It is worth noting that the extraction capacity of the specially synthesised¹¹⁶ linear analogues of receptors **98** and **99** — the dimer and the trimer **100a,b** — was equal to that of the initial CMPO.



These results demonstrate the synergistic effect of combining carbamoylphosphine oxide fragments with the calixarene platform within the same molecule. The compounds **98** and **99** were prepared by aminolysis of *p*-nitrophenyl diphenylphosphorylacetate with *O*-tetra- or *O*-pentaalkyl ethers of *p*-aminocalix[4]- or -[5]arenes. The calixarenes **98** occur in a *cone* conformation, whereas **99** can be a mixture of *cone*, *partial cone* and *1,3-alternate*, because for mixed ethers with two methoxy groups, inversion of the macrocycle is possible.

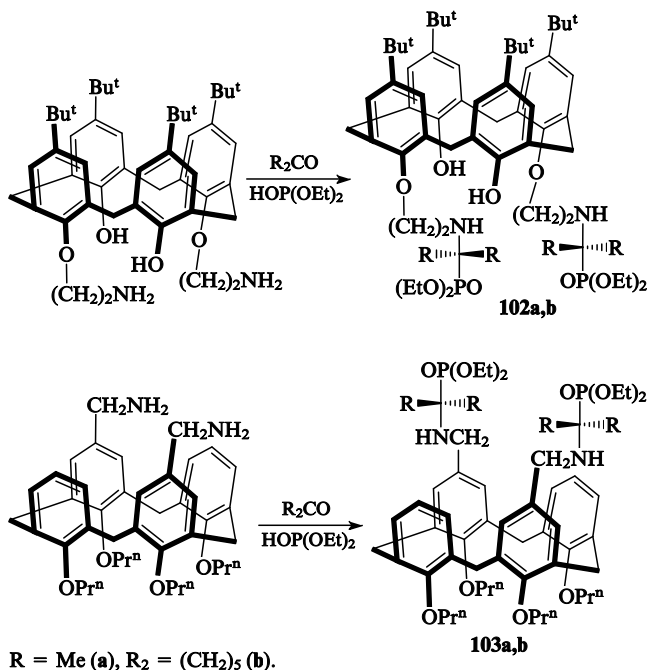
Several studies have been devoted to the introduction of carbamoylmethylphosphonate fragments into the calix[4]resorcinolarenes **31** and to the extraction properties of the products towards a number of metal cations.^{117, 118} Mono-, 1,2-bis-, 1,3-bis-, tris- and tetrakis(carbamoylmethyl)phosphonates and -phosphine oxides **101** were synthesised starting from tetrakis(bromo-methyl)calix[4]resorcinolarene. The conditions for partial functionalisation were created at the stage of formation of the aminomethyl derivatives. The amino group was introduced *via* phthalimide derivatives, by their hydrazinolysis. The transition to the cyclophanes **101** was accomplished either by acylation of the amines with chloroacetyl chloride followed by Arbuzov introduction of the phosphorus-containing fragment or by aminolysis of *p*-nitrophenyl diphenylphosphorylacetate.



R = H: L = Ph (**a**), OEt (**b**); R = Prⁿ: L = Ph (**c**), OEt (**d**).

Study of the extraction of Na^+ , Cs^+ , Sr^{2+} , UO_2^{2+} , Fe^{3+} and Eu^{3+} with the compounds **101** showed that Na^+ and Cs^+ are not extracted, while the degree of extraction of Sr^{2+} reaches 85%. The cavitands containing three or four carbamoylmethylphosphine oxide groups were found to be the most efficient extractants. As the number of these groups decreases, the efficiency of extraction and its selectivity with respect to Eu^{3+} decrease. Interestingly, 1,2-disubstituted cavitands are more efficient than the 1,3-isomers.

Calixarenes **102** and **103**, which contain α -amino phosphonate fragments in the lower and upper rims of the macrocycle, have been constructed as receptors and membrane transferring agents for α -amino acids occurring in the zwitter-ionic form.¹¹⁹



These compounds were synthesised by the Kabachnik – Fields reaction from the corresponding 1,3-bis(aminoalkyl)-derivatives, diethyl phosphite and a carbonyl compound (yields 50% – 65%). The calixarenes **102** and **103** occur in a *cone* conformation.

It should be noted that transfer of highly hydrophilic amino acid zwitter-ions through lipophilic organic membranes is a difficult task due to the very high energy of hydration of these species. Therefore, the receptor should interact efficiently with as many active sites in the substrate as possible. As applied to α -amino acids, this can be interaction with the carboxylate and ammonium groups and with the side chain, which normally does not contain any polar or charged substituents. The presence of α -amino phosphonate fragments, containing both proton-donor (NH bond) and proton-acceptor (P=O bond and the lone electron pairs of nitrogen) groups together with the calixarene molecular cavity in the receptor molecule ensures efficient transport of α -amino and α -hydroxy acids.^{120, 121} The cavitands **102** and **103** exhibited high selectivity of transfer of α -amino acids, the compounds **102** being more efficient towards histidine, and **103**, towards *d,l*-phenylalanine.

A water-soluble receptor for the uranyl ion UO_2^{2+} was synthesised by introducing six phosphonic acid fragments $[\text{CH}_2\text{P}(\text{O})(\text{OH})_2]$ into the calix[6]arene upper rim. This was done by the Arbuzov reaction of the corresponding chloromethyl derivatives with triethyl phosphite and subsequent hydrolysis.^{122, 123}

This review surveys the main routes of functionalisation of calix[4]resorcinolarenes and calix[*n*]arenes by organophosphorus compounds of various types and clearly demonstrates the great potential and the prospects for the use of these macrocycles for complex formation and molecular recognition (extraction, mem-

brane transfer) of both charged and neutral substrates and for the assembly of novel supramolecular systems.

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

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

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

Synthesis and properties of β,β -bisfunctionalised ketene N,N -acetals

V A Makarov, V G Granik

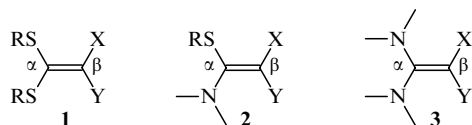
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Abstract. Data on the synthesis of β,β -disubstituted ketene N,N -acetals as well as their physicochemical properties and reactions with electrophilic and nucleophilic reagents are generalised. Special attention is paid to the synthesis of various heterocyclic compounds based on these compounds. The bibliography includes 182 references.

I. Introduction

Ketene S,S -, S,N - and N,N -acetals[†] **1–3** draw the chemists' attention due to their high reactivity and the prospects of their broad and versatile synthetic utilisation, in particular, for the synthesis of heterocyclic compounds.



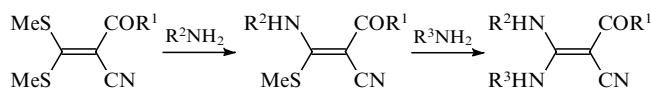
Compounds **1** have been considered in comprehensive reviews.^{1–4} These reviews cover the properties and transformations of N,S -acetals **2** to a considerably smaller extent. Ketene N,N -acetals **3** have been discussed there rather incompletely.

The results of the use of ketene N,N -acetals for the synthesis of heterocyclic compounds are generalised in the review;⁵ however, it mostly discusses monosubstituted ketene N,N -acetals **3** ($Y = H$). On the other hand, a considerable number of studies have been devoted to the synthesis and transformations of disubstituted ketenes **3** in which X and Y are functional, mostly electron-acceptor substituents. The present review considers the methods for the synthesis of ketene N,N -acetals, their physicochemical and chemical properties and prospects of their use in the synthesis of various heterocyclic systems.

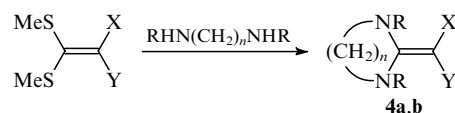
II. Synthesis of disubstituted ketene N,N -acetals

1. Synthesis based on ketene S,S - and N,S -acetals and ketene dihalides

The majority of publications concerning the synthesis of ketene N,N -acetals **3** deal with the reactions of substituted ketene S,S - (**1**) or N,S -acetals (**2**) with amines.^{6–39} It is well known that the alkyl(aryl, hetaryl)thio group (SR) is a 'good leaving group', and its replacement by an amine-containing fragment is usually not problematic. However, replacement of one alkylthio group in ketene S,S -acetals **1** by the amino group results in a considerable decrease in the reactivity of the other SR-substituent due to the strong electron-donor effect of the amino group. Thus, it is possible to obtain asymmetrical N,N -acetals **3** in several stages from N,S -acetals **2**. A typical example of such a sequential synthesis of ketene N,N -acetals is presented in Ref. 29.



In some cases, ketene S,S -acetals were made to react with ethylenediamines.^{8, 10, 12, 13, 17, 23, 24, 28, 30, 33–36, 39} This resulted in 2-methyleneimidazoline derivatives **4a**.¹⁰ If substituted propane-1,3-diamines are used instead of ethylenediamine derivatives,^{12, 28, 33} hydrogenated pyrimidine derivatives **4b** are formed.



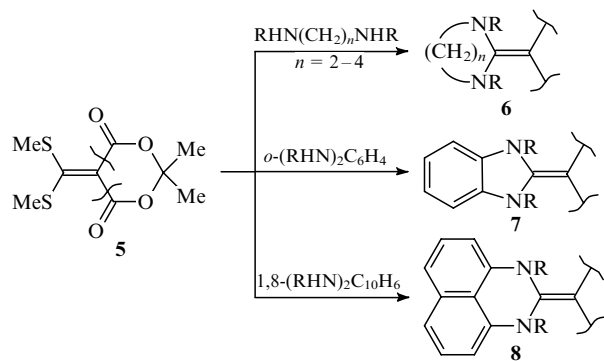
$X = COR', CO_2R', CN, Ar; Y = COR', CO_2R', CN; n = 2$ (**a**), 3 (**b**).

Reactions of cyclic ketene S,S -acetal **5** with various diamines, including *o*-phenylenediamine derivatives (see also Refs 14, 17, 19, 24, 30, and 34) and 1,8-diaminonaphthalene, have been studied.²⁸ It was found that the rate of formation of cyclic systems **6–8** depends on the nature of the diamine. The reaction of ketene S,S -acetal **5** with butane-1,4-diamine derivatives ($n = 4$) or aromatic amines occurs much more slowly than that with ethane(-propane)diamines ($n = 2, 3$).

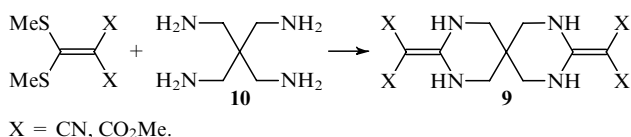
V A Makarov, V G Granik Russian Research Centre 'Research Institute of Organic Intermediaries and Dyes', ul. Bol'shaya Sadovaya 1/4, 103787 Moscow, Russian Federation.
Fax (7-095) 254 12 00. Tel. (7-095) 254 97 24 (V A Makarov), (7-095) 254 94 65 (V G Granik)

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Uspekhi Khimii **67** (11) 1013–1031 (1998); translated by S S Veselyi

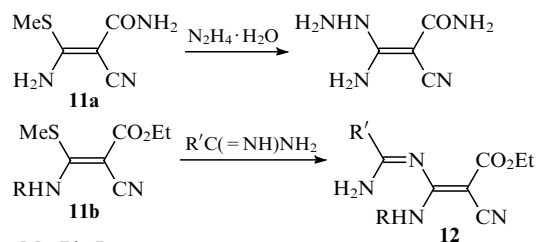
[†] Other names for these compounds, such as ketene amins, highly polarised or 'push-pull' enamines, and enediamines are also widely used in the literature.



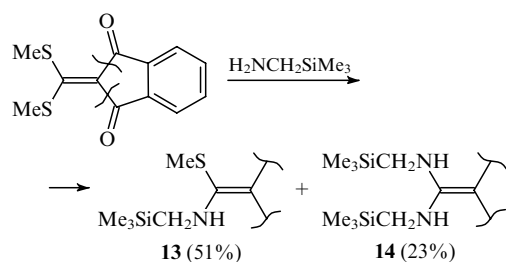
The reaction of *S,S*-acetals **1** or *S,N*-acetals **2** with various compounds containing the unsubstituted amino group opens up no less wide prospects for the synthesis of diverse derivatives of ketene *N,N*-acetals. For example, spiro compounds **9** incorporating two enediamine fragments have been synthesised from ketene *S,S*-acetals and the tetramine **10**.⁴⁰



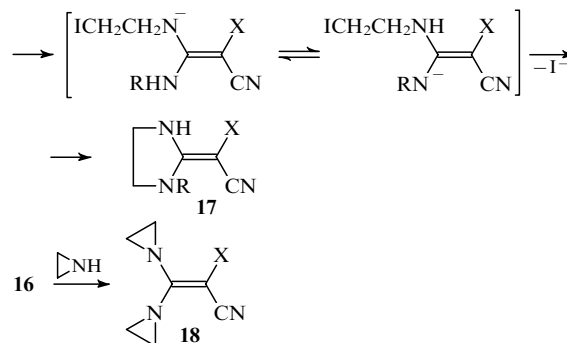
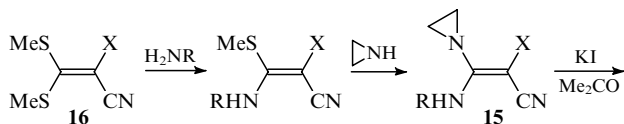
The reaction of *S,N*-acetal **11a** with hydrazine afforded 3-amino-2-cyano-3-hydrazinoacrylamide.²² Reactions of substituted acetals **11b** with various amidines and guanidines result in the corresponding 'push-pull' enamidines **12**.^{20, 21}



2-Bis(methylthio)methylenindane-1,3-dione reacts with trimethylsilylmethylamine on refluxing in methanol to give a mixture of mono- and disubstituted products **13** and **14**.³²

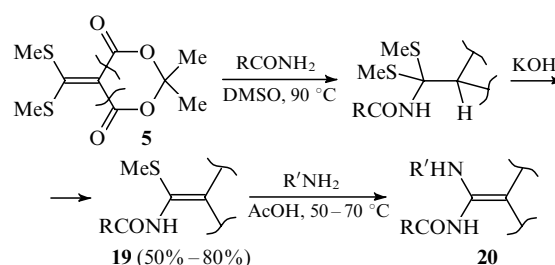


Monoaziridino-*R*-amino derivatives of ketene *N,N*-acetals **15** are formed upon successive introduction of, first, monosubstituted amines and then ethyleneimine in the reaction with ketene *S,S*-acetals **16**. The action of the iodide ion on compounds **15** results in ketene acetals of the imidazolidine series **17**.¹⁸ Direct reaction of ethyleneimine with compounds **16** gives bisaziridino derivatives of ketene *N,N*-acetals **18**.¹⁸

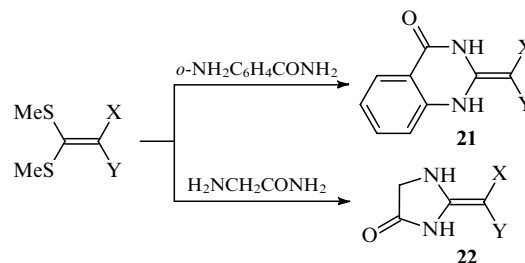


X = ArCO, HetCO.

Ketene *S,S*-acetals **5** can react even with such weakly basic compounds as carboxamides. This reaction gives *N*-acyl derivatives of ketene *S,N*-acetals **19** as the final products. The latter readily give *N*-acylketene *N,N*-acetals **20** on treatment with primary amines.²⁹

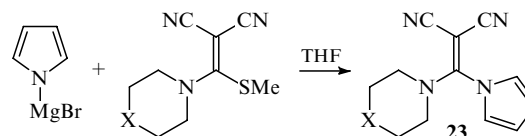


Reaction of ketene *S,S*-acetals with anthranilamide³⁷ or glycylamide¹⁶ results in the corresponding pyrimidinone (**21**) or imidazolidone (**22**) derivatives.



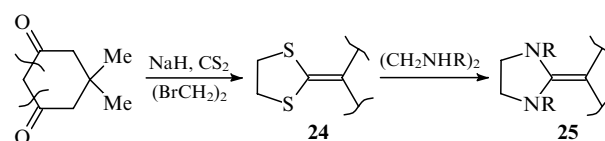
X, Y = CN, CO₂Et.

The reaction of ketene *N,S*-acetals with pyrrolyl-1-magnesium bromide readily gives ketene *N,N*-acetals **23** containing the pyrrole ring as one of the amine moieties.³¹



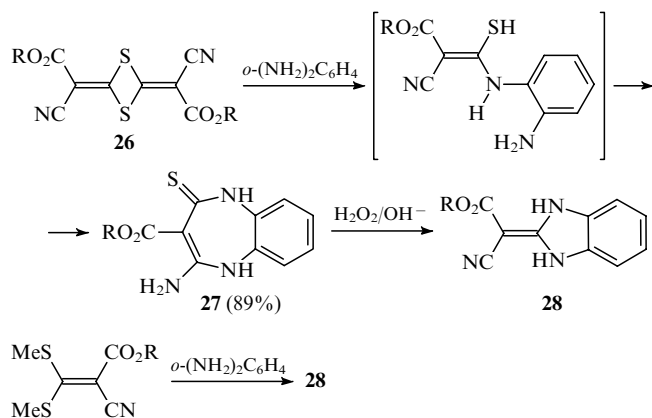
X = CH₂, O.

It should be noted that ketene *S,S*-acetals in which the sulfur atoms are incorporated in the cyclic systems can also be converted to ketene *N,N*-acetals. For example, 1,3-dithiolane **24** reacts with *N,N'*-substituted ethylenediamines to give imidazolidine derivatives **25**.⁸

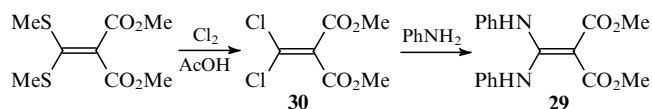


R = Ar, ArAlk.

The reaction of substituted 1,3-dithietanes **26** with *o*-phenylenediamine results in benzodiazepine derivatives **27**, which are oxidised in alkaline medium to give ketene *N,N*-acetals of the benzoimidazole series **28**. These compounds have also been obtained by independent synthesis from alkyl 2,2-bismethylthiomethylenecyanoacetate and *o*-phenylenediamine.¹⁹



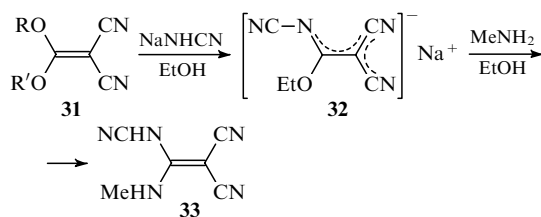
Chlorination of ketene *S,S*-acetals in acetic acid readily gives ketene dichlorides, which represent convenient starting compounds for subsequent synthesis of ketene *N,N*-acetals. For example, acetal **29** was obtained by the reaction of the appropriate dichloride **30** with aniline.⁴¹



Similar reactions are also known for other ketene dichlorides, *viz.*, 2-dichloromethyleneindane-1,3-dione⁴² and 2-dichloromethylene-4,5-dichlorocyclopent-4-ene-1,3-dione,⁴³ as well as for some ketene dibromides⁴⁴ and ketene diiodides.⁴⁵

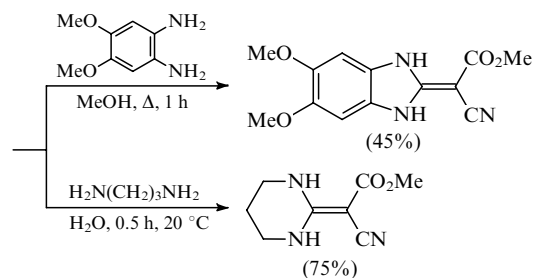
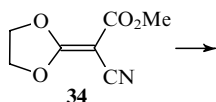
2. Synthesis based on ketene *O,O*- and *O,N*-acetals and related compounds

Ketene *O,O*-acetals and related compounds are promising starting reagents for the synthesis of ketene *N,N*-acetals. For example, bisalkoxymethylenemalonodinitriles **31** react with sodium cyanamide under mild conditions with formation of the sodium salt **32**, which gives *N*-cyanoketene *N,N*-acetal **33** on heating with methylamine.⁴⁶ Dimethoxymethylenemalonodinitrile **31** ($\text{R} = \text{R}' = \text{Me}$) reacts similarly with ammonia and ethylenediamine.⁴⁷

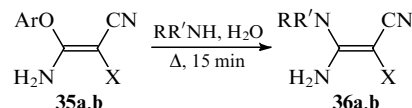


$\text{R} = \text{R}' = \text{Et}$; $\text{R}, \text{R}' = (\text{CH}_2)_2$.

The reaction of the 1,3-dioxolane derivative **34** with various diamines results in cyclic ketene *N,N*-acetals, while the reaction of compound **34** with aromatic diamines requires more drastic conditions than that with aliphatic ones.⁴⁸



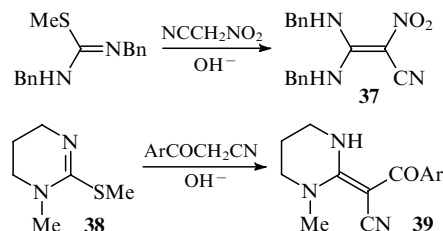
Amino(aryloxy)methylenemalonodinitrile (**35a**) and ethyl amino(aryloxy)methylenecyanoacetate (**35b**) react with amines to give the corresponding enediamine derivatives **36a,b**.⁴⁹



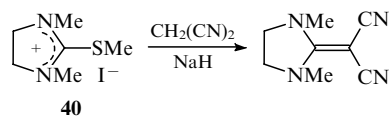
$\text{X} = \text{CN}$ (**a**), CO_2Et (**b**).

3. Synthesis based on thiourea derivatives

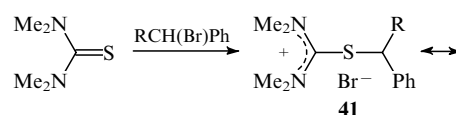
It is well known that ketene *S,S*- and *S,N*-acetals react with amines rather smoothly, since the alkylthio group is a 'good leaving group' (see Section 1). Yet another group of reactions based on the replacement of the RS group, *viz.*, the reactions of compounds containing the reactive methylene group with *S*-alkylisothioureas, also result in the corresponding 'push-pull' enediamines. For instance, treatment of *N,N'*-dibenzyl-*S*-methylisothiourea with nitroacetone in alkaline medium gave a small yield ($\sim 20\%$) of β -nitro- β -cyanoenediamine **37**.⁵⁰ Cyclic thiourea derivatives react similarly.^{51–57} For example, the reaction of compound **38** with arylacetone results in cyclic acetals **39**.

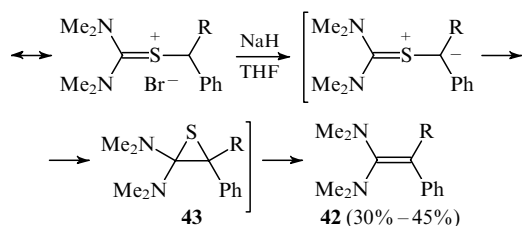


Isothiuronium salts also react with compounds containing the reactive methylene group in the presence of sodium hydride.⁵⁸ For example, the reaction of salt **40** with malonodinitrile results in the corresponding symmetric enediamine.



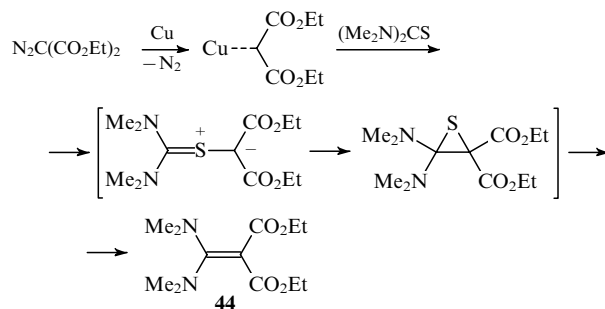
Not only *S*-methyl derivatives of isothiuronium salts, but also compounds with more complex *S*-substituents can serve as starting compounds in the synthesis of ketene *N,N*-acetals.⁵⁹ Treatment of salts **41** containing an electron-acceptor group at the sulfur atom with sodium hydride in tetrahydrofuran gives enediamines **42** in moderate yields. It is believed⁵⁹ that this reaction gives intermediate ylides, which then undergo cyclisation to thiiranes **43**. Elimination of the sulfur atom from the thiirane ring results in compounds **42**.



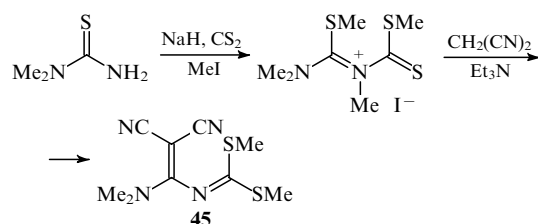


R = CO₂R', Bz.

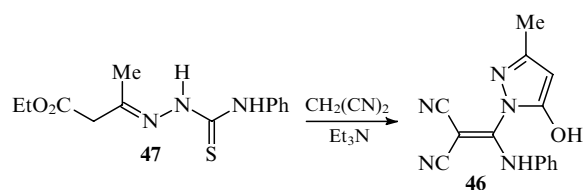
In the same study,⁵⁹ a method is proposed for the synthesis of ketene *N,N*-acetal **44** with the use of diethyl diazomalonate and tetramethylthiourea as the starting compounds.



An interesting method for the synthesis of enediamine **45** is described in Ref 60.



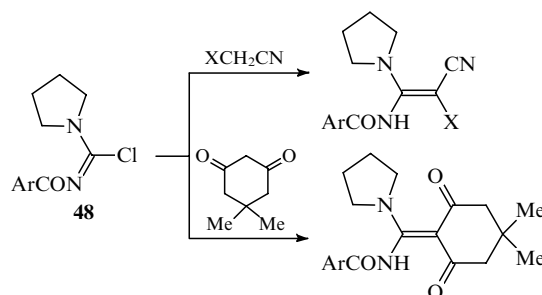
It was reported⁶¹ that ketene *N,N*-acetals can also be obtained from thiourea derivatives without preliminary S-alkylation. For example, enediamine **46** is obtained by condensation of compound **47** with malonodinitrile.



It is evident from the scheme shown above that the formation of the enamine moiety is accompanied by the pyrazole ring closure.

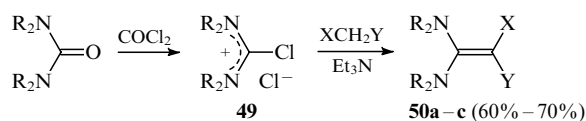
4. Synthesis based on 'activated' amides and ureas

It is known that 'activated amides', *i.e.*, amide acetals, imidates, imidoil chlorides and related compounds, are rather promising starting reagents for the formation of various enamine systems. Enediamines, including highly polarised ones, are obtained by the condensation of 'activated amides' with compounds having a reactive methylene group.⁶²⁻⁶⁴ For example, imidoil chloride **48** reacts readily with such compounds as ethyl cyanoacetate, malonodinitrile and dimedone in dimethyl sulfoxide in the presence of sodium hydride to give substituted ketene *N,N*-acetals.⁶⁵



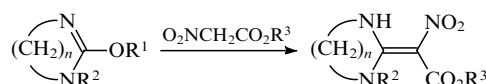
X = CN, CO₂Et.

Chloroamidines **49** obtained by the action of phosgene on tetraalkylurea are converted to 'push-pull' enamines **50a-c** in the reaction with ethyl malonate and ethyl cyanoacetate or malonodinitrile.⁶⁶



X = Y = CN (**a**), CO₂Et (**b**); X = CN, Y = CO₂Et (**c**).

Derivatives of cyclic ureas, particularly imidates, also react readily with compounds that incorporate a reactive methylene unit.⁶⁷

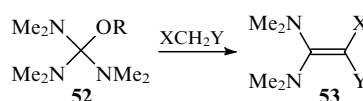


The urea acetals **51** can undergo condensation with ethyl cyanoacetate or malonodinitrile to afford ketene *N,N*-acetals **50a,c**.^{68, 69}

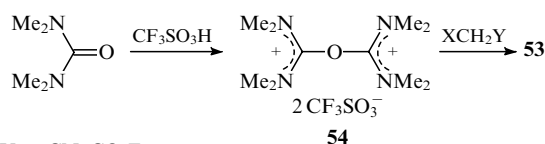


X = CN, CO₂Et.

Orthoamidoesters **52** also enter into similar reactions to give aminals **53**.^{70, 71} It should be noted that compounds **52** are much more reactive than urea acetals **51**.

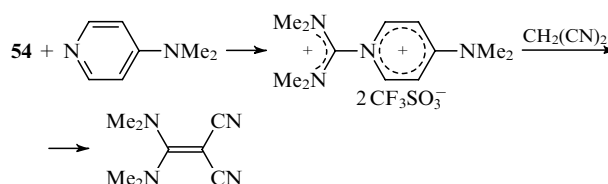


The bisamidinium salt **54** obtained by the reaction of an urea derivative with trifluoromethanesulfonic acid was also used for the synthesis of 'push-pull' enediamines **53**.⁷²

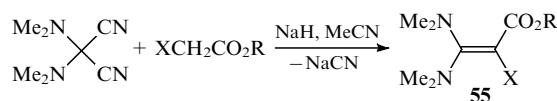


X, Y = CN, CO₂Et.

A modified procedure has been reported,⁷³ in which salt **54** was initially treated with 4-dimethylaminopyridine, and its condensation with malonodinitrile was carried out only thereafter.



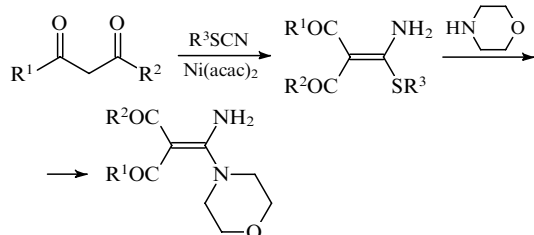
Bis(dialkylamino)malononitriles, like urea acetals, can undergo condensation with compounds containing the reactive methylene unit. For example, the reaction of bis(dimethyl-amino)malonodinitrile with alkyl malonate or acetoacetate in the presence of sodium hydride in acetonitrile gives enediamines **55**.⁷⁴



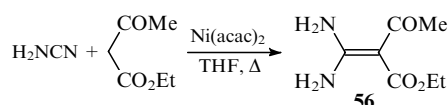
X = CO₂R', COMe.

5. Synthesis based on various *S*-, *N*- and *C*-cyano derivatives

A number of studies deal with the synthesis of enediamines under consideration by addition of the cyano group to the reactive methylene unit. For example, the reaction of organic thiocyanates with β -diketones in the presence of nickel acetylacetonate gives ketene *S,N*-acetals, which can react with amines (in particular with morpholine) to afford ketene *N,N*-acetals in high yields.⁷⁵

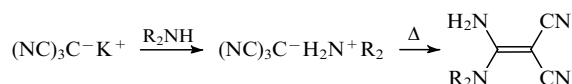


Cyanamide and its derivatives react in a similar way.^{76–80} For example, the reaction of cyanamide with ethyl acetoacetate in the presence of nickel acetylacetonate results in the amina **56**.

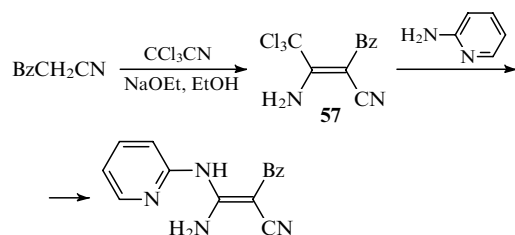


Cyanamide reacts similarly with β -dicarbonyl compounds in the presence of SnCl₄.⁸¹

Another way for the synthesis of ketene *N,N*-acetals is based on the reaction of tricyanomethane (cyanoforn) and related compounds with amines.^{82, 83}



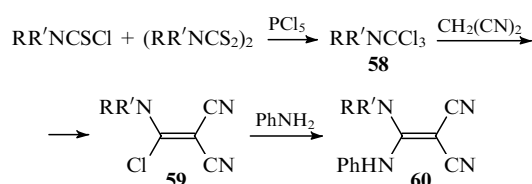
Trichloroacetonitrile proved to be a convenient starting reagent in the synthesis of the target enamines. Its condensation with CH₂-acids initially gives (α -trichloromethyl)enamines, in which the CCl₃ group is readily replaced by the amino group with the formation of enediamines.^{84–86} The reaction of trichloroacetonitrile with benzoylacetonitrile followed by the reaction of the resulting compound **57** with 2-aminopyridine can be presented as an example.⁸⁶



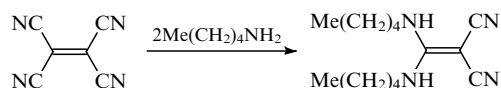
Similar replacement of the CCl₃ and CF₃ groups in enamines by the amino groups with the formation vicinal ethylenediamine derivatives has been reported.^{87, 88}

Reactions of trichloromethyldialkylamines **58** with compounds containing reactive methylene groups also result in ketene *N,N*-acetals.⁸⁹ For example, compounds **58** react with malonodi-

nitrile to give chloroenamines **59**. The latter react with aniline to afford enediamines **60**.

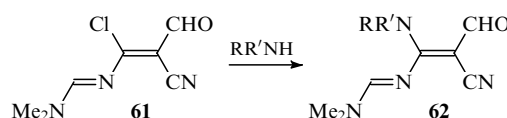


Finally, the reaction of tetracyanoethylene with primary amines (*e.g.*, pentylamine) readily yields symmetrical enediamines. Secondary amines can also be used in this reaction.^{90, 91}



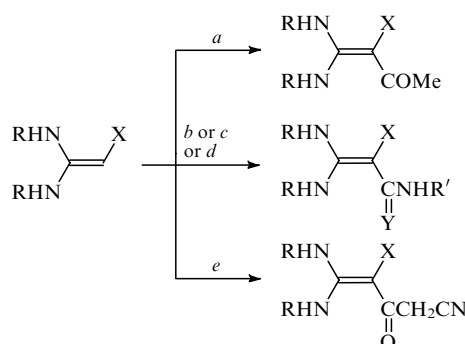
6. Synthesis based on enamine derivatives

α -Chloroenamines⁹² and α -chloroenamides⁹³ react with amines to give ketene *N,N*-acetals. For example, the reaction of chloroenamidine **61** with a secondary amine results in the product **62**.⁹³



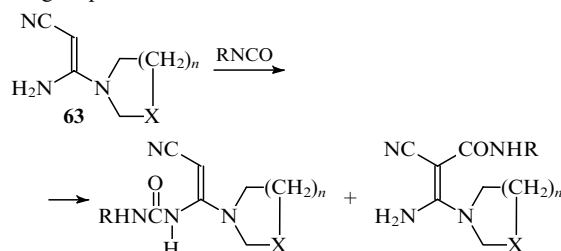
A wide range of β,β -disubstituted ketene *N,N*-acetals have been synthesised by C-acylation of β -monosubstituted α,α -diaminoethylenes.^{94–99} Cyanoacetic acid in the presence of Ac₂O,⁹⁴ acetic anhydride,⁹⁵ isocyanates, isothiocyanates,^{96, 97} and benzoyl-isothiocyanate were used as acylating agents.^{98, 99}

Scheme 1



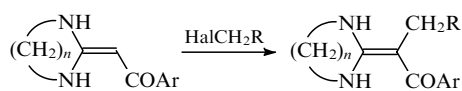
- (a) Ac₂O, R–R = (CH₂)₂, X = CO₂Et;
(b) R'NCY, R' = Bz, R–R = (CH₂)₃, X = CSAr, Y = S;
(c) R'NCY, R' = Bz, X = NO₂, Y = S;
(d) R'NCY, R' = Ph, X = CN, Y = O, S;
(e) NCCH₂CO₂H, Ac₂O, X = NO₂.

It has been shown⁹⁷ that acylation of enamines **63** with isocyanates occurs not only at the β -carbon atom but also at the amino group.



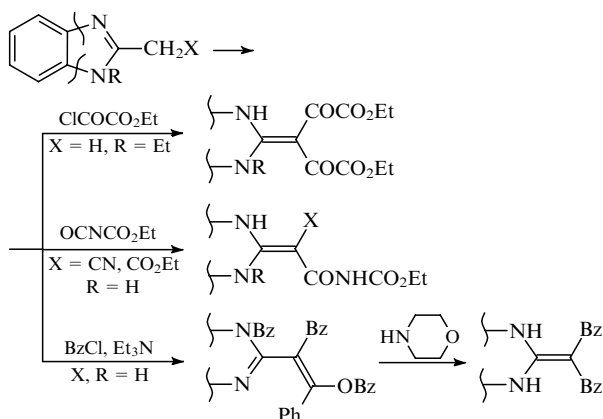
X = CH₂, n = 1, 2; X = O, n = 2.

β -Alkylation of β -monosubstituted ketene aminaals with compounds containing reactive halogen has also been reported.¹⁰⁰

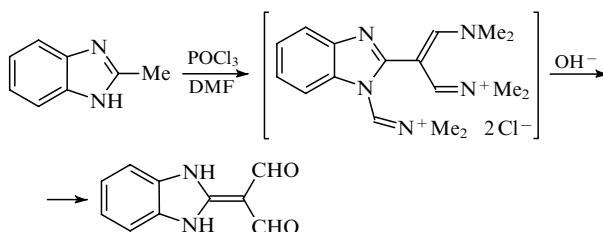


R = CO₂Et, Ph; Hal = Cl, Br.

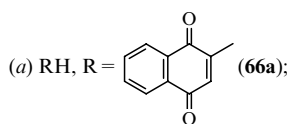
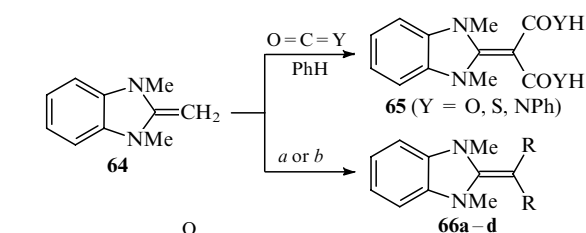
A series of ketene aminals have been synthesised by acylation of derivatives of 2-methylimidazoline,¹⁰¹ 2-alkylbenzimidazoles^{102–104} and 2-methyltetrahydropyrimidines.¹⁰⁵ Examples of such syntheses based on 2-alkylbenzimidazoles are shown in the scheme below.



2-Methylbenzimidazole also undergoes bisformylation according to Vilsmeier in the presence of phosphorus oxychloride.¹⁰⁶



The reaction of 1,3-dimethyl-2-methylenebenzimidazoline (**64**) with compounds of general formula O=C=Y, where Y = O, S, NPh,¹⁰⁷ or with 1,4-naphthoquinone¹⁰⁸ results in ketene *N,N*-acetals **65** or **66a**, respectively. Acylation of compound **64** with acyl halides or related halogen-containing compounds in triethylamine gives the enediamines **66b–d**.¹⁰⁸

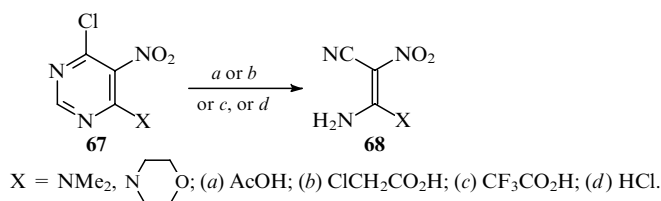


(b) RCl, Et₃N, R = MeCO (**66b**), Bz (**66c**), MeSO₂ (**66d**).

7. Synthesis based on pyrimidine derivatives

One of the most peculiar preparative methods for the synthesis of 'push-pull' enamines is that starting from pyrimidines with a strong electron-acceptor substituent at position 5 of the pyrimidine ring. In 1967, it was found¹⁰⁹ that the action of organic or mineral acids on such pyrimidines results in easy opening of their ring. For example, the reaction of substituted pyrimidine **67** with acetic, chloroacetic, trifluoroacetic or hydrochloric acids results in

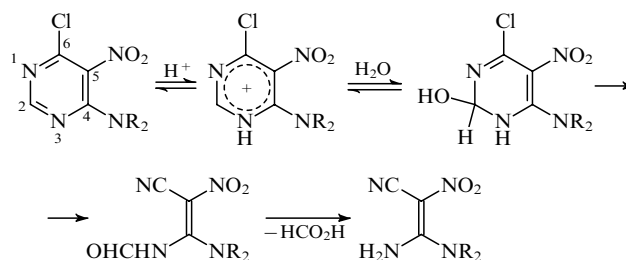
the opening of the pyrimidine ring and formation of the enediamine **68**.



It was established¹⁰⁹ that if X is a tertiary amino group, the yields of enediamines **68** range from 50% to 95%. If X is a secondary amino group, the yields of compounds **68** are much lower. For example, if X = NHMe, the yield of the product is 18%, and if X = NH₂, it becomes impossible to obtain the corresponding enamine at all. In the latter case, the halogen at the pyrimidine ring is replaced by the hydroxy group.

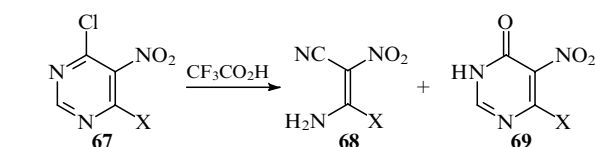
The following mechanism of the pyrimidine ring opening has been proposed (Scheme 2).¹¹⁰ First, the nitrogen atom of the starting pyrimidine is protonated. The resulting pyrimidinium cation adds a molecule of water at position 2. Then elimination of the substituent from position 6 occurs with simultaneous opening of the pyrimidine ring at N(1)–C(2) bond. Subsequent *N*-deformylation of the resulting nitrile finally results in the enamine.

Scheme 2



The effect of the extent of substitution of the amino group in 4-amino-6-chloro-5-nitropyrimidines on the processes that occur on their heating in acetic or trifluoroacetic acids has been studied in detail.¹¹¹ This confirmed the conclusions¹⁰⁹ that ketene aminals **68** are formed in good yields if a tertiary amino group is present at position 4.

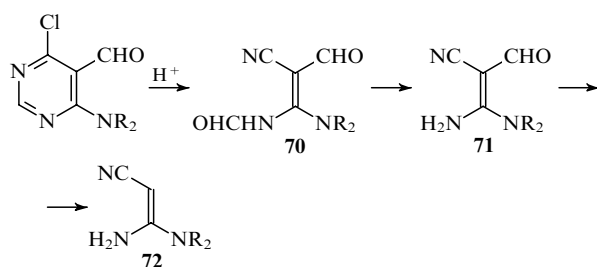
The action of trifluoroacetic acid on pyrimidine derivatives containing a primary or secondary amino group at position 4 was monitored by ¹H NMR spectroscopy.¹¹²



X	NHMe	NHEt	NHPr ⁱ	NHBut ⁱ	NH ₂
Yield of compound 68 (%)	47	20	21	25	30
Yield of compound 69 (%)	53	80	79	75	70

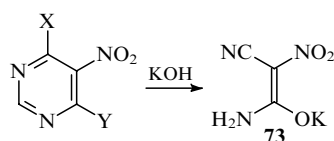
The formation of 'push-pull' enamines of the type **68** is also observed upon ring opening of 5-formyl-, 5-cyano- and 5-carboxypyrimidines.^{112,113} However, compounds of this type tend to form pyrimidones **69** to a greater extent than nitropyrimidines.

The mechanism of the pyrimidine ring opening shown in Scheme 2 has been confirmed.¹¹² The authors managed to isolate and identify the *N*-formyl derivative **70**. It was also found that prolonged heating of 5-formylpyrimidines in an acidic medium results in compounds **70**, then 3,3-diamino-2-formylacrylonitrile derivatives **71** are formed, and finally their C-deformylation occurs to give cyanoenediamines **72**.¹¹²



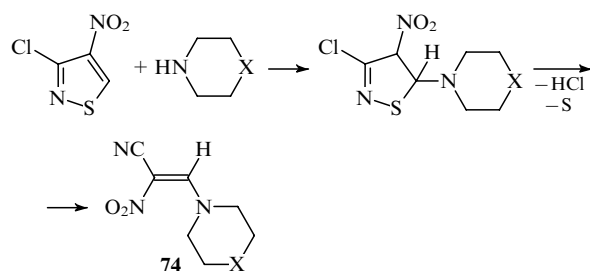
It was shown¹¹⁴ that treatment of 4-amino-6-chloro-5-formylpyrimidines with an alkali also results in ketene *N,N*-acetals.

It is of note that heating of 4-chloro- or 4-methoxy-5-nitro-6-X-pyrimidines in an alkaline medium made it possible to obtain potassium cyanonitroacetamide **73**.¹¹⁵



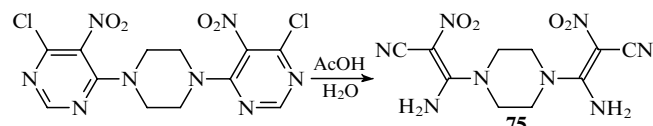
X = SC(S)NEt₂, Y = OMe; X = Y = Cl.

Ring opening of 4,6-dichloro-5-nitropyrimidine can be achieved on heating with secondary amines. However, treatment of chloronitroisothiazole with piperidine or morpholine gives β -cyano- β -nitroenamines **74** rather than enediamines.¹¹⁶

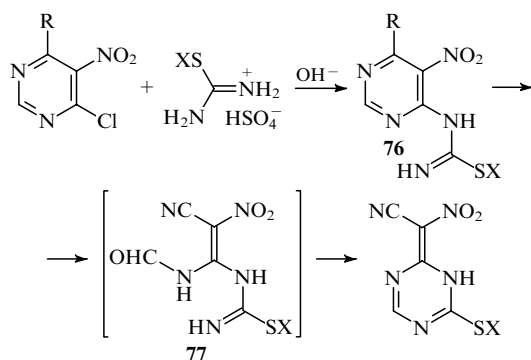


X = CH₂, O.

The bisketene aminal **75** was obtained according to the following scheme:¹¹⁷



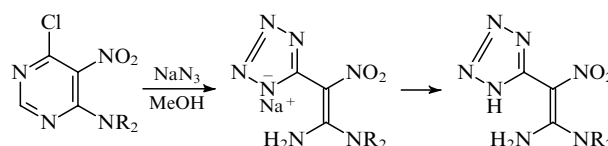
The reaction of 4-chloro-5-nitro-6-R-pyrimidines with *S*-alkyl(aryl)isothiuronium salts on heating in an alkaline medium results in substituted pyrimidines **76**. Subsequently, the products **76** were converted to 'push-pull' enamines **77**, which then underwent cyclisation into substituted *sym*-triazines.¹¹⁸



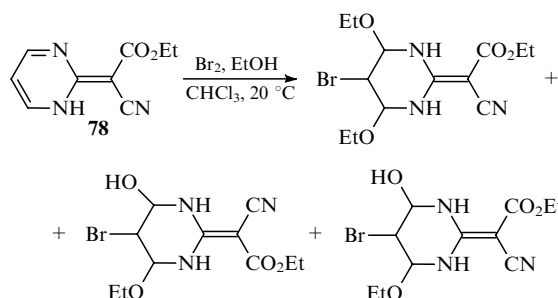
R = Cl, OMe; X = Alk, Ar.

It has recently been shown¹¹⁹ that 4-arylamino-6-chloro-5-nitropyrimidines are transformed to enediamines **68** on boiling in dilute HCl to give considerable amounts of the corresponding 4-arylamino-5-nitropyrimidin-6-ones **69**.

A peculiar method for the synthesis of nitroenediamines containing a tetrazole moiety at the β -position is based on the reaction of 4-amino-6-chloro-5-nitropyrimidine derivatives with sodium azide.¹²⁰

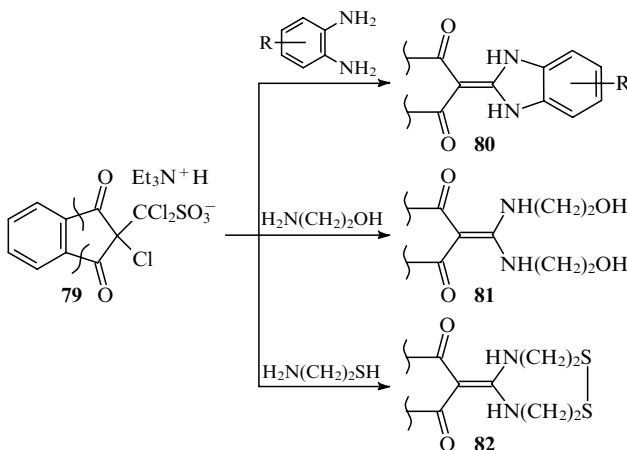


Bromination of methylenedihydropyrimidine **78** gives a mixture of cyclic enamines.¹²¹

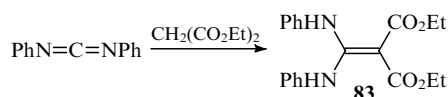


8. Miscellaneous methods for the synthesis of ketene aminals

The reaction of triethylammonium (2-chloro-1,3-dioxindan-2-yl)dichloromethanesulfonate (**79**) with various amines results in ketene *N,N*-acetals **80–82**.¹²²

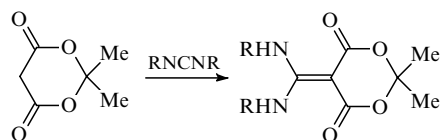


In certain studies, carbodiimides have been used for the synthesis of ketene aminals. This reaction was first described in 1899 with the synthesis of enediamine **83** from *N,N'*-diphenylcarbodiimide and diethyl malonate as an example.¹²³

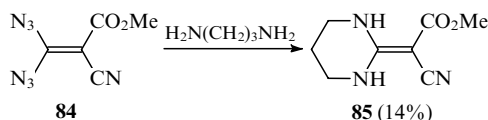


Compound **83** can also be obtained by the reaction of *N,N'*-diphenylthiourea with sodium diethyl malonate.¹²⁴

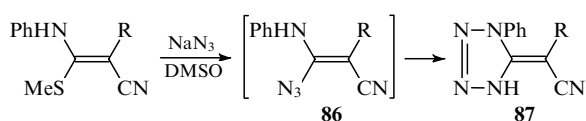
Dicyclohexylcarbodiimide and other carbodiimides react with Meldrum's acid to give the corresponding enediamines.^{125, 126}



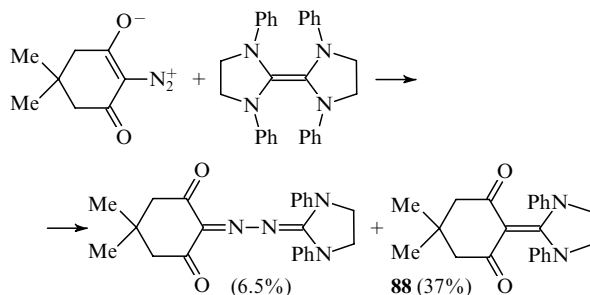
Vinyl azides have also been used as the starting compounds in the synthesis of ketene N,N -acetals.^{127,128} For example, the reaction of vinyl diazide **84** with diaminopropane gave a small yield of cyclic product **85**.



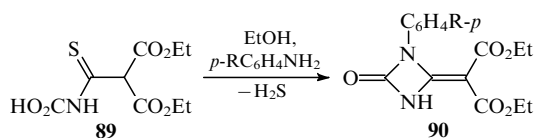
The reaction of ketene N,S -acetals with sodium azide probably gives vinyl azides **86** as intermediates, which are then converted into heterocyclic ketene aminals **87**.¹²⁹



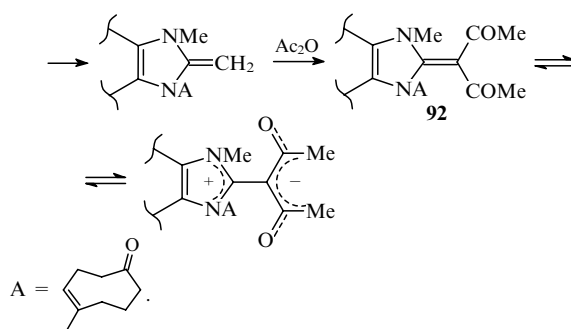
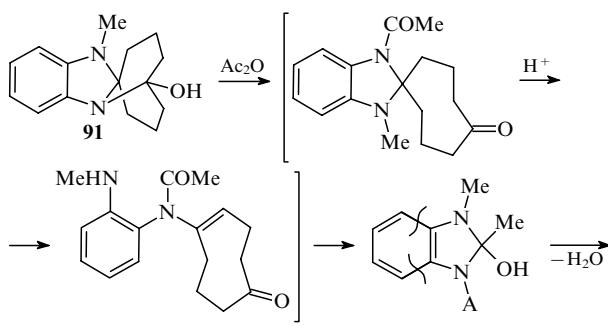
The reaction of 2-diazo-1,3-diketones with tetraaminoethylene derivatives results mainly in enediamino diketones **88**.¹³⁰



The synthesis of four-membered heterocyclic compounds, viz., diazetidine derivatives incorporating the enediamine moiety, has been reported.¹³¹ For example, condensation of N -(thioacyl)-carbamic acid derivative **89** with *para*-substituted anilines yields cyclic products **90**.



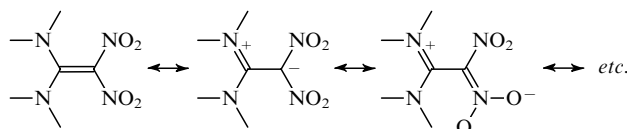
Heating of 1-hydroxy-5-methyl-1,2,3,4,4a,5-hexahydro-1,4a-propanopyrido[1,2-*a*]benzimidazole (**91**) with acetic anhydride in toluene results eventually in ketene aminal of the benzimidazole series **92**.¹³² This process is believed¹³² to occur according to the following scheme:



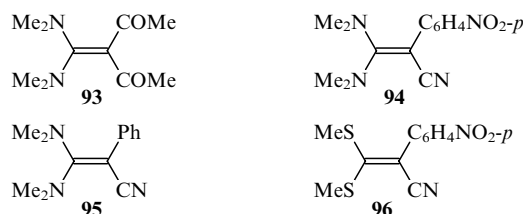
III. Properties of ketene N,N -acetals

1. Physicochemical parameters

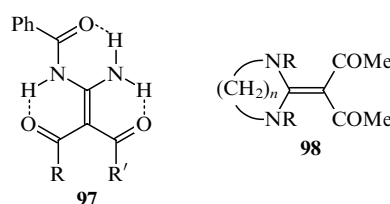
The major characteristics of ketene N,N -acetals is the direct polar conjugation of two α -amino groups with β,β -electron-acceptor substituents. Naturally, this conjugation affects the spectral and other physicochemical properties of ketene N,N -acetals. For example, according to X-ray diffraction data, abrupt elongation of the $\text{C}=\text{C}$ bond in β,β -dinitroenediamines is observed, while the $\text{N}-\text{C}$ bonds are much shortened. This can be rationalised as the superposition of the following resonance structures:



The lengths of the $\text{C}=\text{C}$ bonds in β,β -dinitroenediamines lie within 1.451–1.474 Å, those of the $\text{N}-\text{C}$ bonds lie within 1.315–1.316 Å and those of the $\text{C}-\text{NO}_2$ bonds lie within 1.399–1.494 Å.⁴⁵ It is known¹³³ that the barrier to *cis-trans*-isomerisation in β,β -diacyl N,N -acetals **93** ('rotation' around the carbon-carbon double bond) is extremely low and is $\Delta G^\ddagger < 8 \text{ kcal mol}^{-1}$ (to compare with enamines, see Refs 134–136).

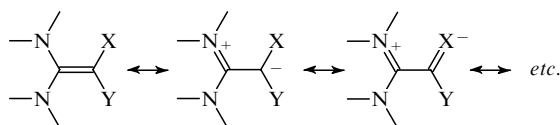


If weaker electron-acceptor substituents are present in the molecule (for example, in compounds **94** and **95**), the rotation barrier increases to 15 and 21 kcal mol^{-1} , respectively.¹⁰ The same trend is observed if the electron-donor effect of the α -substituents decreases. For example, for ketene S,S -acetal **96**, $\Delta G^\ddagger > 25 \text{ kcal mol}^{-1}$. It is essential that in the cases where the formation of intramolecular hydrogen bonds in diacyl ketene aminals is possible, *cis-trans*-isomerisation is slowed down considerably. For example, the ^1H NMR spectrum of compound **97** (in CDCl_3) contains a double set of signals corresponding to the *E*- and *Z*-isomers, whereas one series of signals is observed in a solvent that favours the scission of intramolecular hydrogen bonds ($\text{DMSO}-d_6$).^{8,77,78}

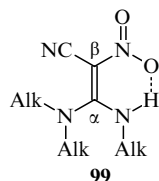


In cyclic enediamines **98**, the rotation barriers are also very low and are ~ 12 – 13 kcal mol $^{-1}$ (see Refs 137, 138). It is of note that replacement of the C=O group in the β -substituent by the C=S group increases the $\Delta G^\ddagger$ to ~ 30 kcal mol $^{-1}$. This effect is related to the stabilisation of the ground state and destabilisation of the transition state.¹³⁹

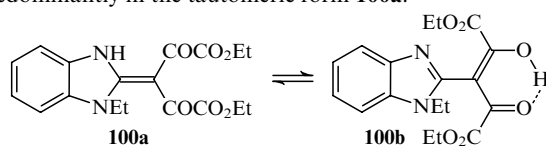
IR spectra of 'push-pull' enediamines containing the carbonyl group are their important characteristics, the absorption bands of the CO groups are observed in the region below 1650 cm $^{-1}$. This indicates strong conjugation of the carbonyl groups with the electron-donor, substituted α -amino groups.^{59, 77, 126, 140, 141} ^{13}C NMR spectra of this type of compounds are also rather characteristic.^{28, 78, 142} For example, the signal for the C $_\beta$ atom in N -benzoylenediamino diketones **97** is in the region $\delta \sim 87$ – 100 ppm, while the signal for the C $_\alpha$ atom is at $\delta \sim 161$ – 163 ppm. These chemical shifts indicate that the electron pairs of the nitrogen atoms participate in the 'enamine conjugation'.



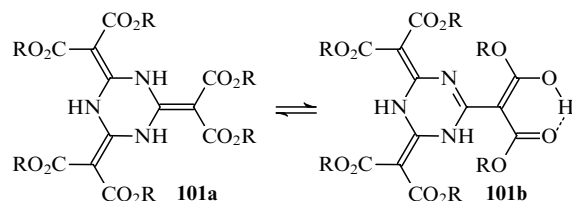
A detailed study of ^1H and ^{13}C NMR spectra carried out for nitrocyanoenediamines **99**¹⁴³ showed that the stereochemistry of these compounds is determined by the possibility of formation of intramolecular hydrogen bonds between the amino group and the nitro group.



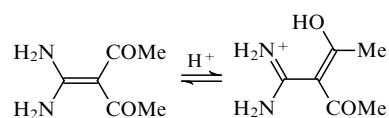
^{13}C NMR spectra of compounds **99** are also characterised by an upfield shift of signals for the C $_\beta$ atom ($\delta \sim 90$ – 103 ppm), while the signals for the C $_\alpha$ atoms are in the region $\delta 157$ – 170 ppm. Specific conformation features of cyclic 'push-pull' ethylenes with sterically hindered electron-donor and electron-acceptor groups were studied.^{144, 145} It was shown that the electron-donor and electron-acceptor fragments in these compounds are turned relative to the central carbon-carbon double bond. The tautomerism in ketene aminals and related compounds was studied.^{102, 146, 147} It was shown that compound **100** exists predominantly in the tautomeric form **100a**.



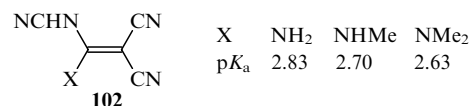
The position of tautomeric equilibrium depends on the solvent. For example, the equilibrium **101a** $\rightleftharpoons$ **101b** in CHCl_3 , dioxane, methanol and water is shifted towards the enamine **101a**, whereas in DMSO and DMF it is shifted towards the enol **101b**. In acetonitrile, a mixture of tautomers **101a,b** is formed.¹⁴⁶



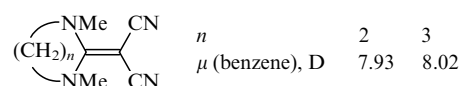
It was shown⁷⁹ that diacyl ketene aminals represent bases and are protonated on the oxygen atom.



However, if the amino group has a strong electron-acceptor substituent, these compounds are strong organic acids. For example, the ionisation constants ($\text{p}K_\text{a}$) of N -cyano- β,β -dicyano-ketene aminals **102** in water are ~ 2.6 – 2.8 , *i.e.*, they are even stronger acids than formic acid ($\text{p}K_\text{a}$ 3.75)

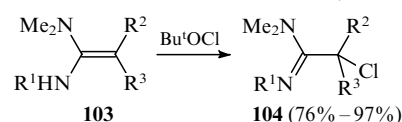


Finally, the pronounced effect of direct polar conjugation in 'push-pull' enamines is also characterised by their high dipole moments.⁵⁸ For example, the dipole moments of imidazoline or pyrimidine derivatives of ketene N,N -acetals are ~ 8 D, while it is only 6.5 D for such a strongly polarised compound as N -phenyl-sydnone.¹⁴⁸



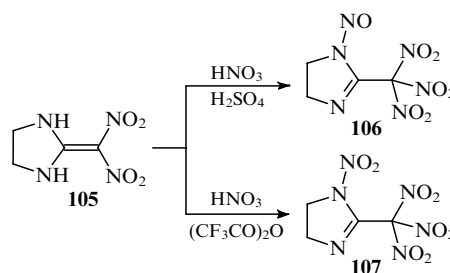
2. Reactions of β,β -disubstituted ketene N,N -acetals with electrophilic and nucleophilic reagents

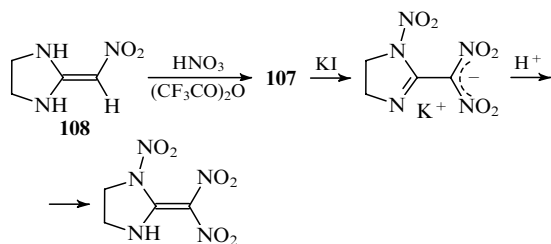
The presence of two α,α -amino groups in ketene aminals increases the nucleophilicity of the C $_\beta$ -position considerably, and hence increases the possibility of attack on this position by electrophilic reagents. For example, it is known¹⁴⁹ that the reaction of ketene aminals **103** with *tert*-butyl hypochlorite smoothly gives the corresponding chloroamidines **104** in high yields despite the presence of two substituents at the C $_\beta$ -atom.



$\text{R}^1 = \text{Ph, Me, Pr}^i$; $\text{R}^2, \text{R}^3 = \text{CN, CO}_2\text{Et}$.

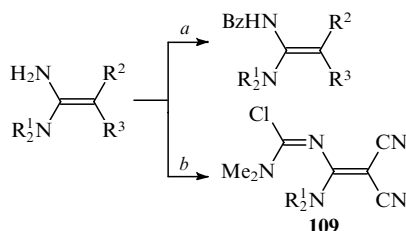
Nitration of 'push-pull' enediamines under various conditions has been studied.¹⁵⁰ It was found that the use of a mixture of nitric and sulfuric acids resulted in C $_\beta$ -nitration and N -nitrosation, while in a mixture of HNO_3 and trifluoroacetic anhydride, C $_\beta$ - and N -nitration occurred. In the latter case, the order of nitration steps on the C $_\beta$ and N atoms has not been determined. Nitration of the ketene alinal **105** under various conditions results in products **106** and **107**.¹⁵⁰ It is essential that compound **107** is also formed upon nitration of β -monosubstituted 'push-pull' enediamine **108** with an HNO_3 –trifluoroacetic anhydride mixture.





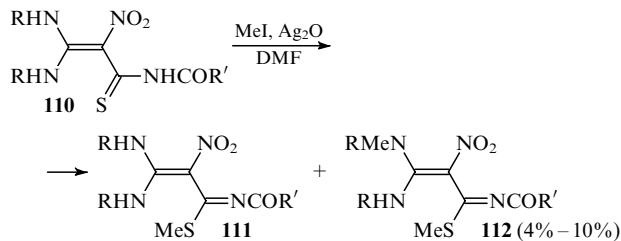
A method for reductive elimination of one NO₂ group from the C_β atom in compound **107** upon treatment with potassium iodide has been described.¹⁵¹

The reaction of β,β-disubstituted ketene *N,N*-acetals with acyl halides results in *N*-acylation products.⁸⁸ If dimethyltrichloromethylamine is used as the acylating reagent, the reaction occurs at the nitrogen atom to give the derivative **109** containing the chloroformamidine moiety.

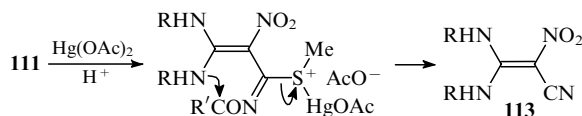


(a) BzCl, R¹ = H, R², R³ = CN, CO₂R⁴;
(b) CCl₃NMe₂, R¹ = Me, R² = R³ = CN.

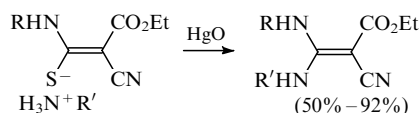
Alkylation of ketene amins is an important reaction that characterises enamines and deserves separate discussion. For example, the alkylation of thioamides **110** with methyl iodide occurs mostly on the sulfur atom. In addition to *S*-methyl derivatives **111**, *N,S*-dimethyl derivatives **112** are formed.¹⁵²



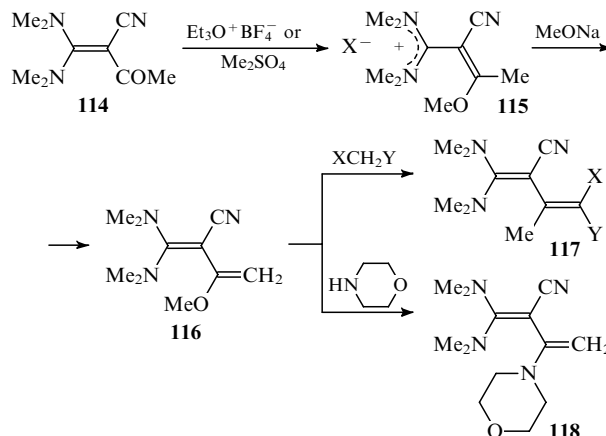
Oxidation of amins **111** with mercuric acetate in acidic medium results in enediamines **113**.¹⁵²



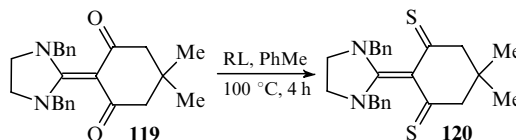
It should be noted that the oxidation of the ammonium salts of cyano(ethoxycarbonyl)thiocarbamoylmethanes with mercury(II) oxide readily gives ketene amins.¹⁵³



Enediamino ketone **114** undergoes alkylation with triethyloxonium tetrafluoroborate or dimethyl sulfate on the oxygen atom to give the corresponding complex **115**, which, in turn, can react with alkoxide anions to produce alkoxydienediamine **116**. Compound **116** is a convenient starting reagent for the synthesis of various dienamines, e.g., dienediamine **117** or dienetriamine **118**.⁷⁰

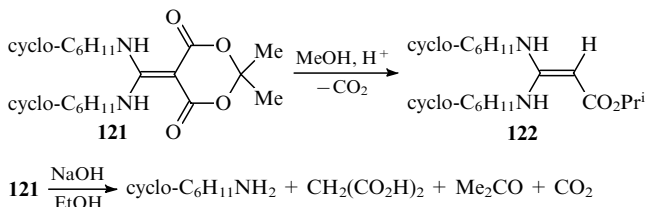


Yet another reaction of ketene amins with electrophilic reagents worthy of note is that of enediamino diketones with the Lawesson reagent (LR). For example, enediamino diketone **119** can be converted to the corresponding enediamino dithione **120**.⁸

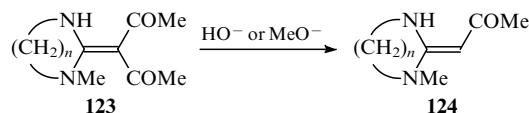


LR = $p\text{-MeOC}_6\text{H}_4\text{P}(=\text{S})_2\text{P}(=\text{S})_2\text{C}_6\text{H}_4\text{OMe-}p$.

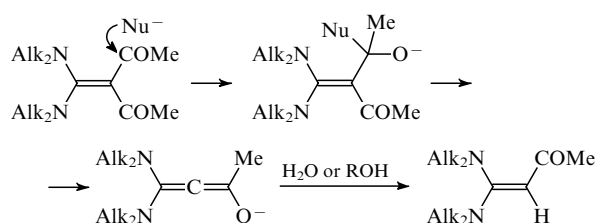
A series of reactions of ketene amins with nucleophilic reagents has been described.¹²⁵ For example, acid hydrolysis of a Meldrum's acid derivative **121** resulting in the β-monosubstituted derivative **122** is worth mentioning. The same authors described degradation of compound **121** upon treatment with ethanolic alkali.



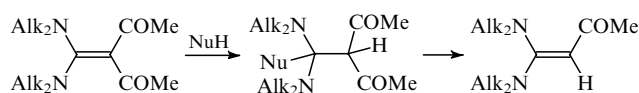
Monodeacylation of enediamino diketones has been described.¹² For example, the action of the hydroxy or methoxide anion on diketones **123** results in ketones **124**.



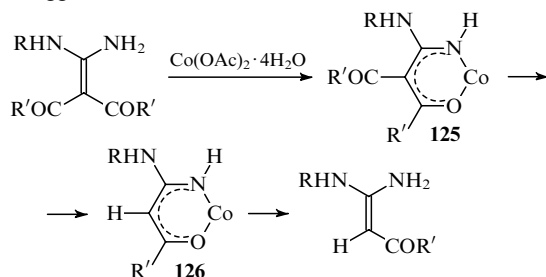
A possible version of the mechanism of this process includes the addition of the nucleophile at the carbonyl group.¹²



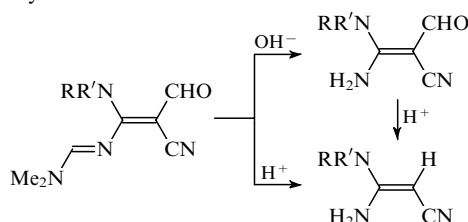
A version involving the attack of the nucleophile on the α-position may not be ruled out, either.



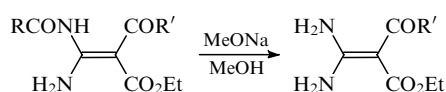
Recently,¹⁵⁴ an important method for C-deacylation of enediamino diketones upon treatment with cobalt acetate with intermediate formation of chelate complexes **125** and **126** has been suggested.



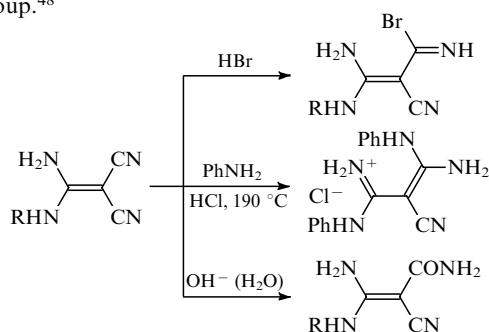
Elimination of the β -formyl group in acidic medium has been described⁹³ for ketene aminals incorporating the formamidine moiety.



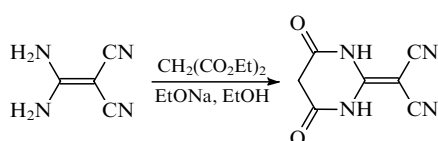
N-Acylketene *N,N*-acetals readily undergo N-deacylation on treatment with sodium methoxide in methanol.⁸⁰



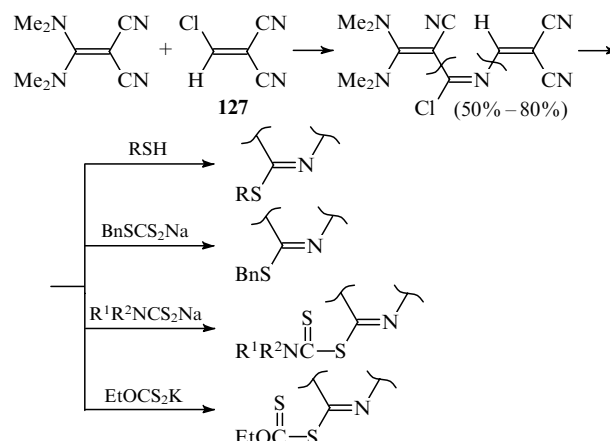
The transformation of β -substituents in 'push-pull' enamines under the action of nucleophilic reagents has been reported.^{47, 48, 92} For example, treatment with hydrobromic acid gives bromoimines,⁹² and heating with aniline hydrochloride results in salts of ketene aminals. Treatment with alkali converts the cyano group in 'push-pull' enamines into the carbamoyl group.⁴⁸



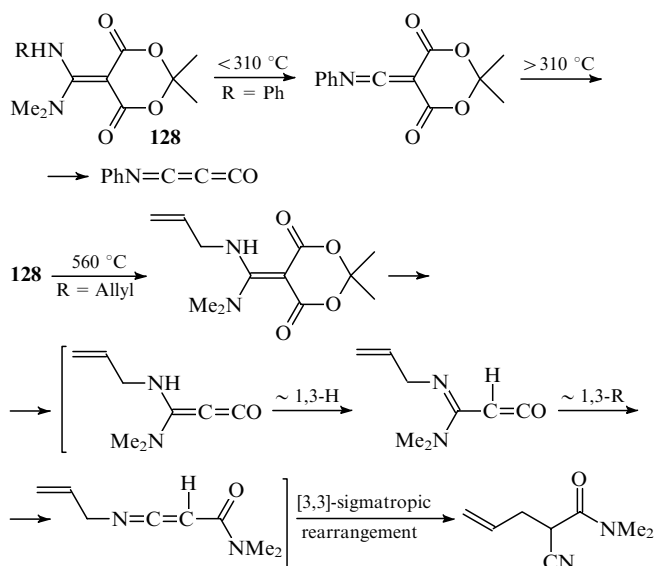
If a ketene amina contains two unsubstituted amino groups, it can react with diethyl malonate to give a cyclic diacylketene amina.⁴⁷



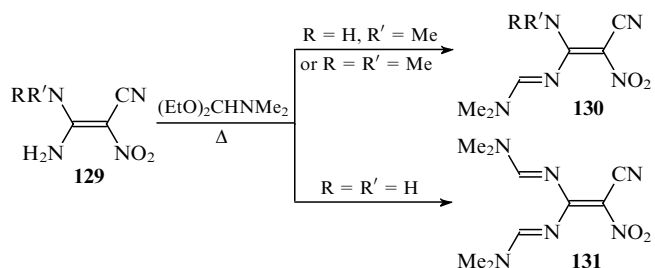
Diverse transformations of the cyano group in dicyanodiaminoethylene **127** have been discovered in a study of its reaction with chloromethylenemalononitrile.¹⁵⁵



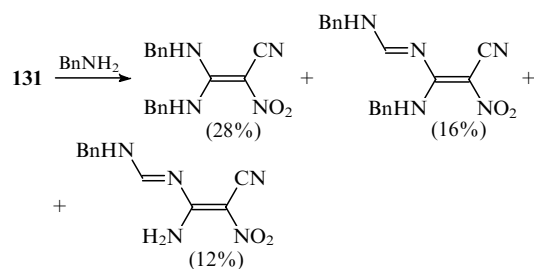
In addition, one should note such a reaction involving ketene *N,N*-acetals as thermolysis of compounds **128** based on Meldrum's acid.^{9, 25} The result of this process depends on the reaction temperature and the nature of the *N*-substituent.



It has been found recently¹¹⁹ that the 'push-pull' enamines **129** with at least one nonsubstituted amino group readily react with amidacetals to give the corresponding amidines **130** and **131** and the reaction rate depends on the extent of substitution of the other amino group ($\text{NH}_2 > \text{NHMe} > \text{NMe}_2$).

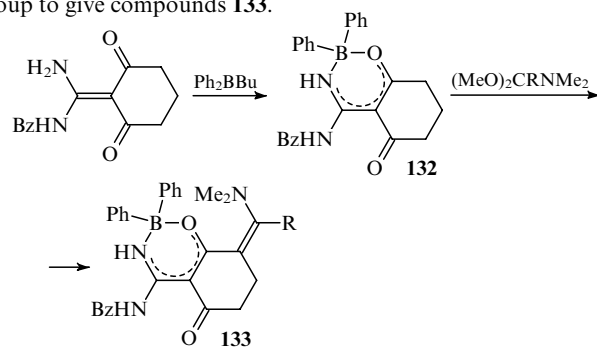


Transamination was studied using enamide **131** as an example. It is known¹⁵⁶ that enamides undergo transamination more readily than the corresponding enamines. However, it was found that compound **131** reacts in a non-standard way due to the additional α -amino-containing fragment, and replacement of enamide fragments is accompanied by the reaction on the *meso*-carbon atom of the amidine group.¹¹⁹



A very important property of ketene *N,N*-acetals is their ability to form chelate complexes with metals^{115, 157–160} and boron compounds.^{161–166} This enabled the development of a new direction of heterocyclic synthesis that opens a route to diverse azaheterocyclic compounds (see below). We consider here only some of the unusual properties of chelate complexes, which provide the possibility to perform processes non-characteristic of the starting ligands.

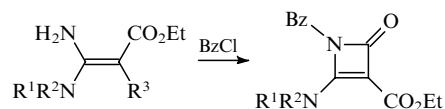
It is known^{167, 168} that enamines incorporating a primary amino group react with amide and lactam acetals primarily on the NH_2 group. If boron chelates are used, an opportunity appears to perform reactions on the active methylene group without involving the amino group. For example, it has been shown^{161–162, 165} that the chelate **132** reacts with dimethylformamide and dimethylacetamide acetals selectively on the CH_2 group to give compounds **133**.



3. Synthesis of heterocyclic compounds based on ketene *N,N*-acetals

a. Four-membered heterocycles

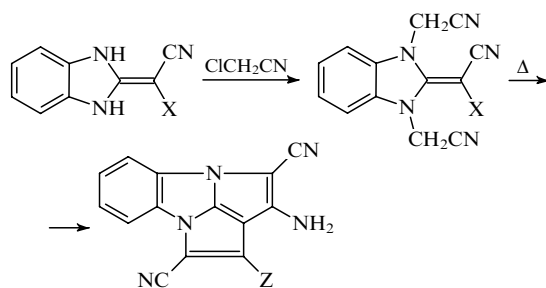
Benzoylation of ketene amins results in azetine derivatives.⁸⁸



The formation of diazetidine derivatives¹³¹ has been discussed above (see Section II.8).

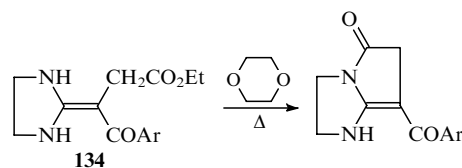
b. Five-membered heterocycles

The closure of pyrrole rings according to the Thorpe–Ziegler and/or Dieckmann reaction starting from ketene *N,N*-acetals of the benzimidazole series has been described.¹⁴



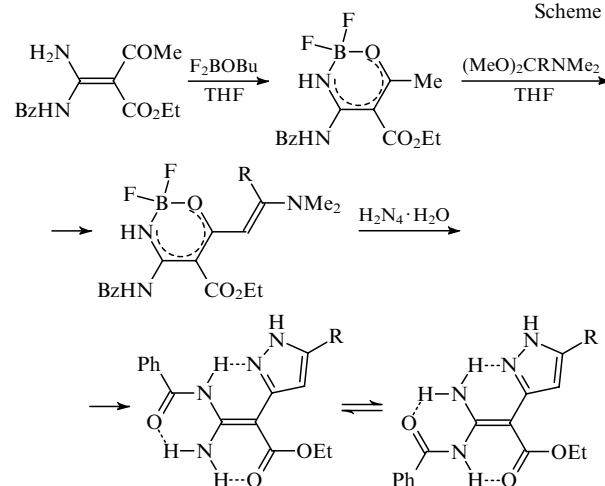
$\text{X} = \text{CN}, \text{CO}_2\text{Et}; \text{Z} = \text{NH}_2, \text{OH}$.

The pyrrole ring could also be obtained by cyclisation of amins **134** on refluxing in dioxane.¹⁰⁰

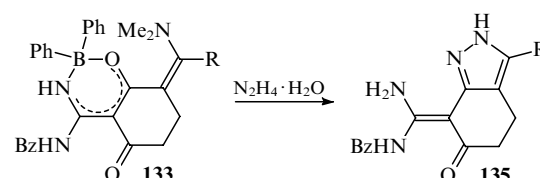


Synthesis of pyrazole derivatives occupies an important place in the chemistry of ‘push-pull’ enamines. For example, the strategy of chelate synthesis considered above was also found to be very efficient for the synthesis of various substituted pyrazole-containing systems.^{162, 165} An example of this kind of synthesis is shown in the Scheme 3.

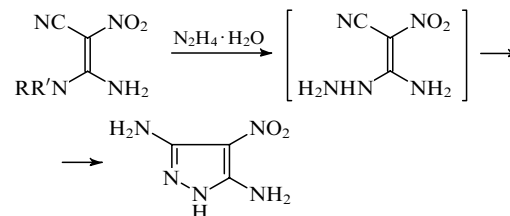
Scheme 3



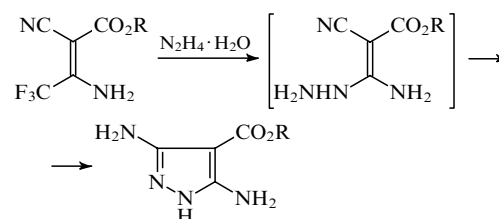
Similar synthesis of indazole derivatives **135** from the chelate **133** and hydrazine hydrate has been described.¹⁶⁵



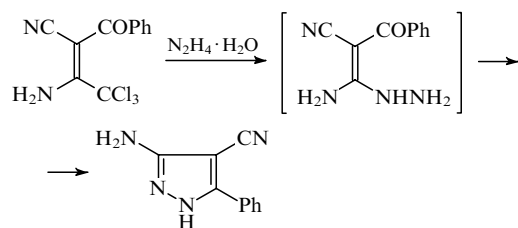
A wide range of substituted pyrazoles have been obtained by transamination of the dialkylamino group in ketene amins with hydrazine hydrate followed by cyclisation on the cyano group.^{50, 84, 113, 143, 169, 170} For example, 3,5-diamino-4-pyrazole has been obtained this way.



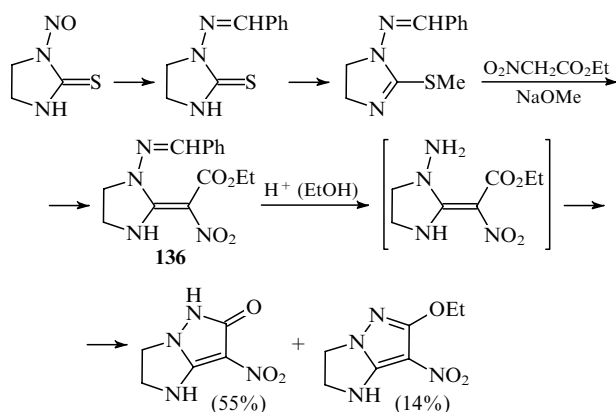
Similarly, the hydrazino group can replace the good leaving group, *viz.*, CHAl_3 .⁸⁷ For example, this method was used to obtain alkyl 3,5-diaminopyrazole-4-carboxylates.



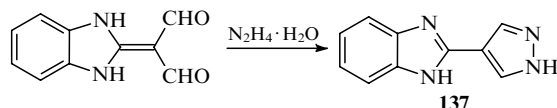
Cyclisation can involve not only cyano groups but also other functional groups.^{85, 86}



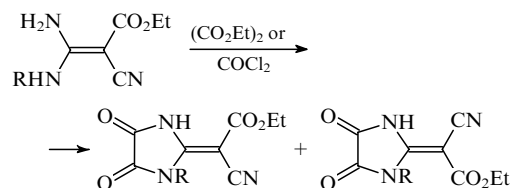
N-Aminoketene amins obtained in a different way can also be used as starting compounds in the synthesis of fused pyrazoles.⁵² An example of such a synthesis based on compound **136** is shown in the scheme:



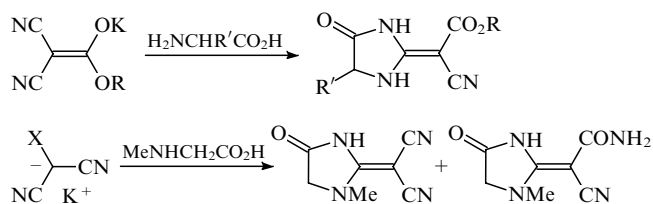
The synthesis of pyrazolylbenzimidazole **137** is based on the reaction of *gem*-formyl groups of the starting benzimidazole with hydrazine hydrate.¹⁰⁶



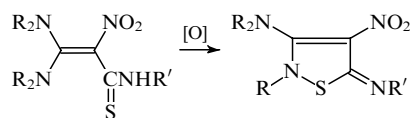
Several studies^{171, 172} dealt with the synthesis of imidazole derivatives from 'push-pull' enamines (see also Ref. 18). For example, the reaction of ethyl diaminomethylenecyanoacetate with phosgene or diethyl oxalate results in imidazolidinediones.¹⁷¹



Imidazoles are formed from salts of alkyl dicyanoacetate or tricyanomethane and amino acids,¹⁷² ketene amins being the intermediate products.

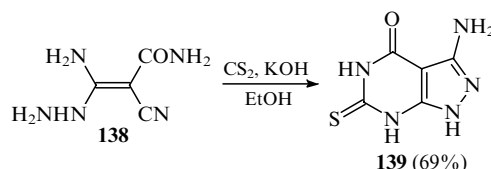


Substituted isothiazoles were synthesised by the oxidation of the appropriate enediaminothioamides.^{26, 98}



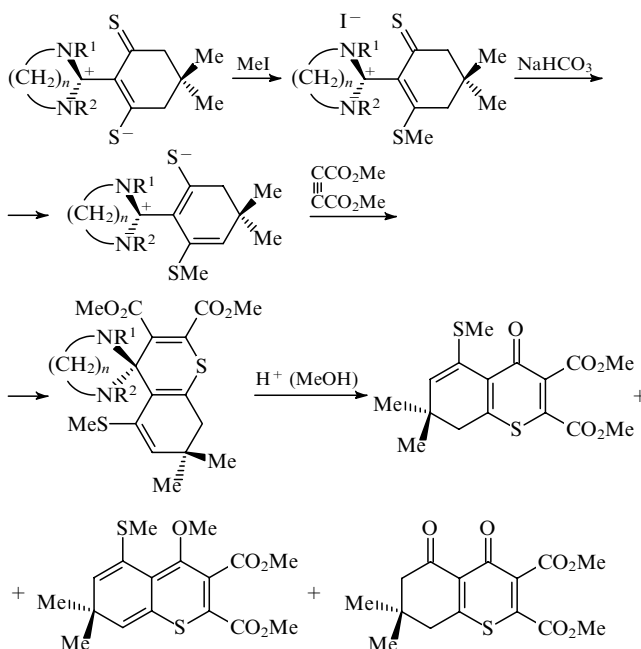
The synthesis of tetrazoles from ketene amins has already been discussed above (see Section II.8).¹²⁹

Finally, the reaction of hydrazinoenamine **138** with carbon disulfide results in the closure of both the pyrazole and pyrimidine rings to give a purine isoster, viz., pyrazolo[3,4-*d*]pyrimidine **139**.²²

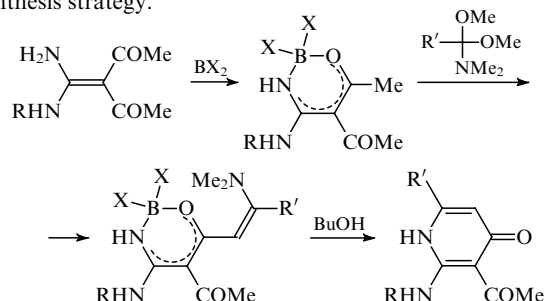


c. Synthesis of six-membered heterocycles

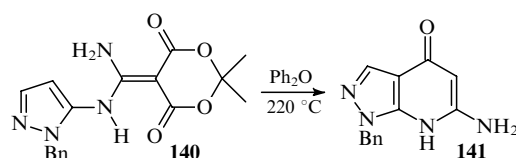
Thiapyran derivatives were obtained according to the following scheme.¹⁴⁵



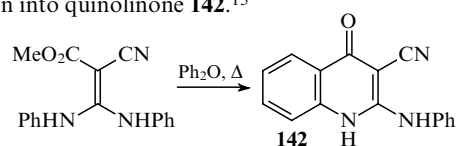
A few studies^{166, 173} deal with the synthesis of substituted pyridines based on ketene amins with the use of the chelate synthesis strategy.



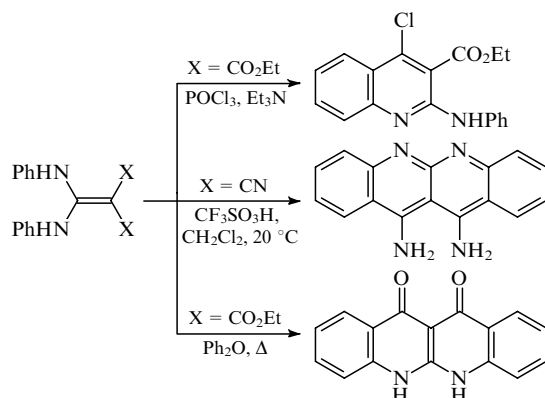
Recyclisation of pyrazolylketene acetal **140** at high temperature results in pyrazolo[3,4-*b*]pyridone **141**.⁷



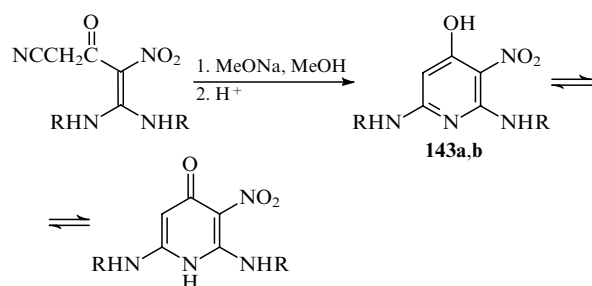
Methyl bisanilinomethylene cyanoacetate undergoes cyclisation into quinolinone **142**.¹⁵



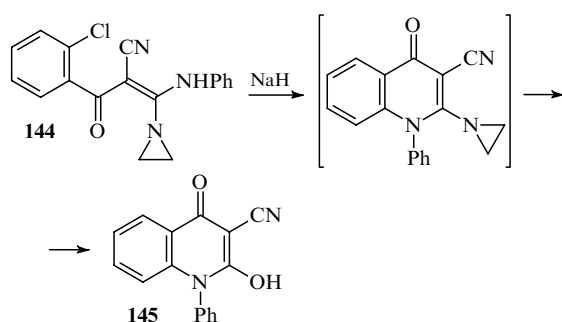
Similar cyclisations have been described in Refs 128 and 140.



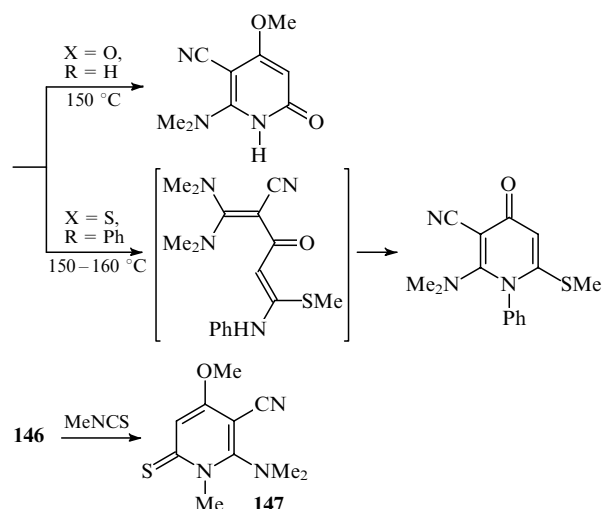
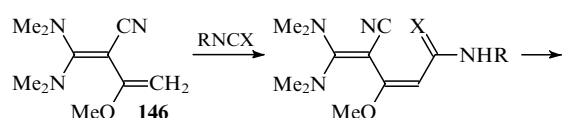
Intramolecular cyclisation of substituted β -cyanoacetyl- β -nitroketene *N,N*-acetals results in 4-pyridone derivatives **143a,b**.⁹⁴ It is of note that the hydroxypyridine tautomeric form predominates for pyridone **143a** ($R = H$), whereas the pyridone form predominates for pyridone **143b** ($R = Me$).



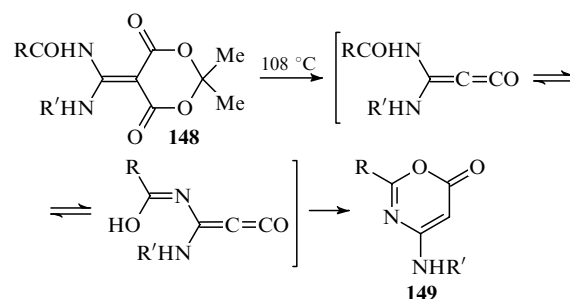
Intramolecular cyclisation of ketene *N,N*-acetal **144** upon treatment with sodium hydride to give benzopyridone **145** has been reported.¹⁸



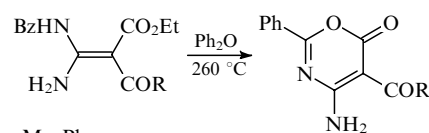
Finally, the synthesis of various pyridones based on alkoxy-dienediamine vinylogues **146** and **147** should be noted.⁷⁰



Thermolysis of *N*-acylaminals **148** results in substituted oxazin-6-ones **149**.²⁹



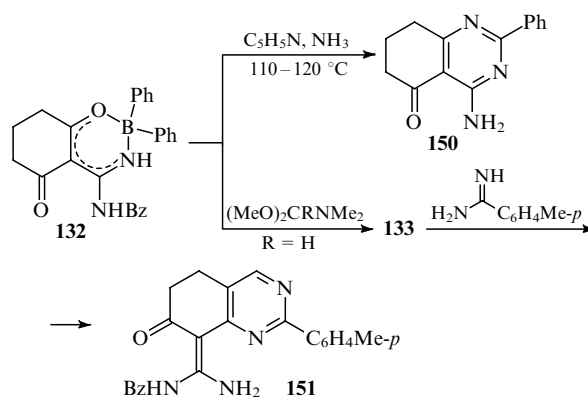
Another method for the synthesis of substituted 1,3-oxazin-6-ones has also been reported.¹⁷⁴



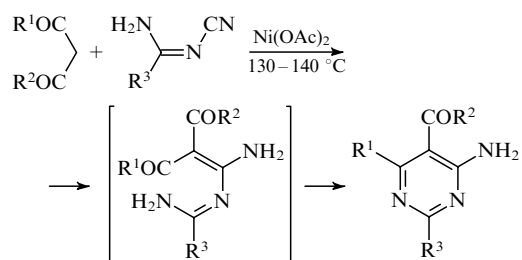
$R = Me, Ph$.

The majority of studies devoted to the synthesis of heterocyclic compounds from ketene amins deal with the synthesis of pyrimidine derivatives. In this case, chelate synthesis is also an important approach to their synthesis.

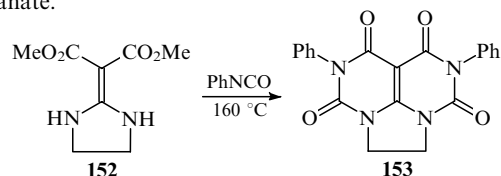
The use of boron chelates **132** has enabled the synthesis of substituted pyrimidines **150** and **151**.^{161, 163, 164}



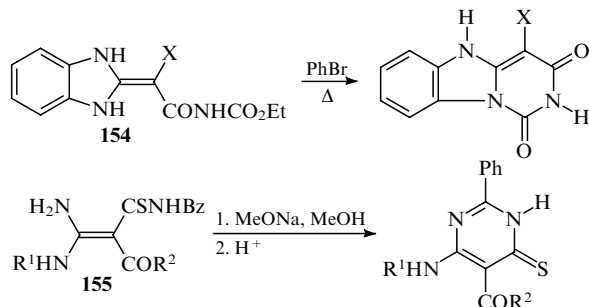
The condensation of β -diketones with *N*-cyanoamidines ($R^3 = Me, Ph$) or dicyanoguanidine ($R^3 = NH_2$) in the presence of nickel acetate, which is required for the formation of reactive chelates, occurs through intermediate derivatives of ketene *N,N*-acetals with their subsequent cyclisation into substituted 2,4-diaminopyrimidines.^{160, 175}



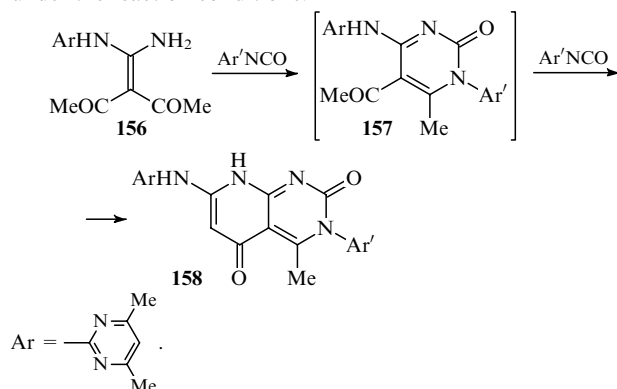
Enediaminodicarbonyl compounds react with isocyanates to give pyrimidines.^{176,177} For example, cyclic aminal **152** was converted into pyrimidinone **153** by treatment with phenyl isocyanate.



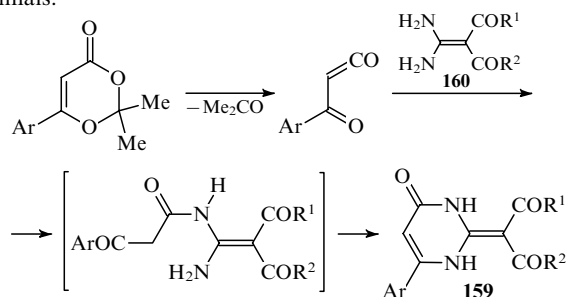
Ketene aminals with the *N*-ethoxycarbonylcarbamoyl substituent¹⁰³ (**154**) or with the *N*-benzoylthiocarbamoyl substituent¹⁷⁸ (**155**) at the β -position undergo cyclisation into pyrimidine derivatives on heating or under conditions of basic catalysis.



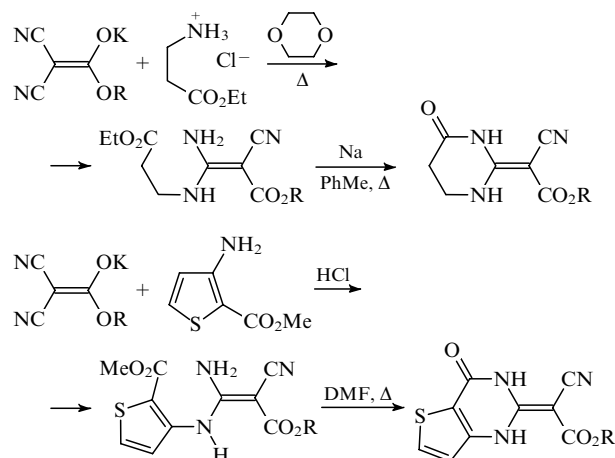
Enediamino diketones **156** react with aryl isocyanates giving intermediate 4-arylamino-5-acetylpyrimidin-2-one derivatives **157**, which are converted into pyrido[2,3-*d*]pyrimidines **158** under the reaction conditions.¹⁷⁹



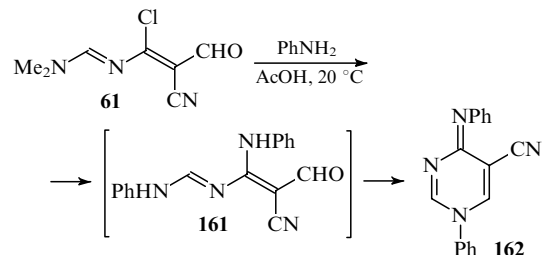
Pyrimidine derivatives **159** have been obtained as products of the reaction of 6-aryl-2,2-dimethyl-1,3-dioxin-4-ones with ketene aminals.^{180,181}



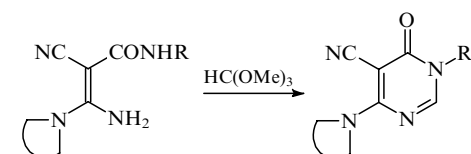
The ethoxycarbonyldicyanomethane salt **160** reacts with methyl 3-aminothiophene-2-carboxylate and amino acid esters to give ketene *N,N*-acetals which can undergo cyclisation into pyrimidine and thieno[3,2-*d*]pyrimidine derivatives.¹⁴²



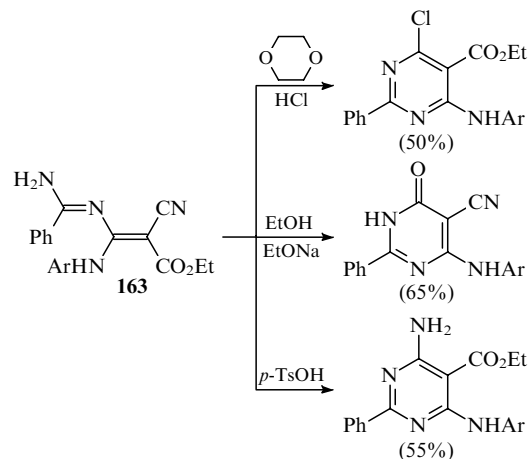
Compound **61** reacts with aniline in acetic acid to give the intermediate ketene aminal **161**, which then undergoes cyclisation into pyrimidinone imine **162**.⁹³



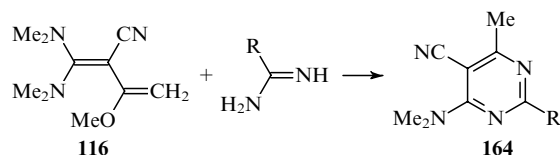
α,α -Diamino- β -carbamoyl- β -cyanoethylene derivatives are transformed on heating with methyl orthoformate to give substituted 4-amino-5-cyanopyrimidin-6-ones.⁹⁷



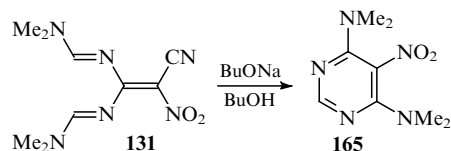
Cyclisation of 'push-pull' enaminoamidines **163** under various conditions results in moderate yields of 6-amino-2-phenylpyrimidine derivatives.²⁰



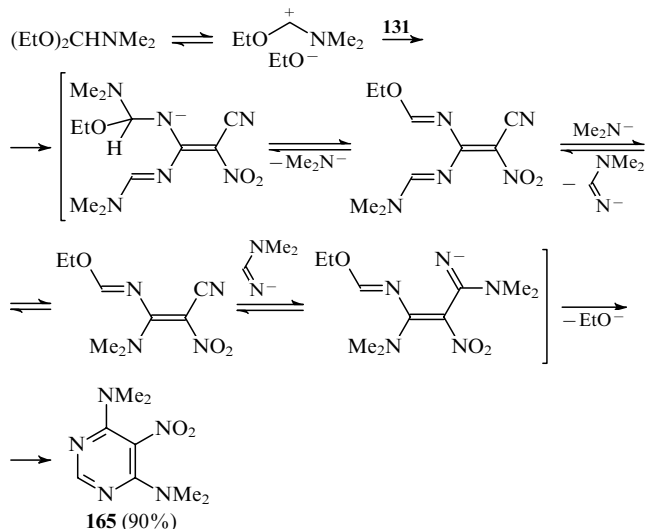
Alkoxydienediamines are also convenient starting compounds for pyrimidine synthesis.⁷⁰ For example, diamine **116** reacts with amidines to give substituted pyrimidines **164**.



Finally, let us mention an unusual synthesis of 4,6-bis(dimethylamino)-5-nitropyrimidine **165** from diamidine **131**.¹⁸²

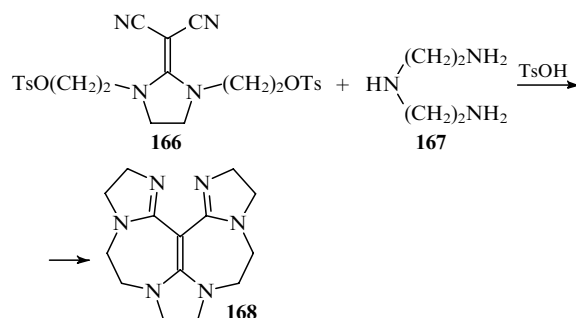


Compound **165** is also formed upon treatment of diamidine **131** with DMF diethyl acetal. The following scheme of this non-trivial transformation was suggested:¹⁸²



d. Seven-membered heterocycles

Simultaneous closure of five- and seven-membered heterocycles in the reaction of amination **166** with triamine **167** to give compound **168** has been reported in a study¹³ dealing with the synthesis of diazepine derivatives from ketene amination.



A different approach¹⁹ to the synthesis of benzodiazepines has been considered in Section II.1.

IV. Conclusion

To sum up the data presented in this review, it can be stated that a fruitful direction based on the use of β,β -bifunctionally substituted ketene N,N -acetals in organic synthesis has been created by now. The preparative availability of these compounds and their high reactivity form considerable prospects for their application in

the synthesis of diverse organic and especially heterocyclic systems that are of interest both in theoretical and practical aspects.

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Catalytic synthesis of isoalkanes and aromatic hydrocarbons from CO and H₂

A L Lapidus, A Yu Krylova

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Abstract. Characteristic features of the synthesis of isoalkanes and arenes from CO and H₂ in the presence of oxide, metallic and zeolite-containing catalysts are considered. Primary attention is paid to cobalt–zeolite systems. The bibliography includes 96 references.

I. Introduction

Nowadays, petroleum is the main source of hydrocarbons. However, since petroleum resources are limited, development of methods for production of hydrocarbons from coal, natural gas, oil shales, plant biomass, *etc.* becomes a topical task. One of these methods is the Fischer–Tropsch synthesis, which includes three stages: (1) production of synthesis gas (a mixture of hydrogen and carbon monoxide) by gasification of solid raw materials (coal, peat, biomass, *etc.*) or reforming of natural gas; (2) synthesis of hydrocarbons from synthesis gas; (3) upgrading (hydrocracking, hydroisomerisation) of the resulting mixture giving commercial products. The term ‘Fischer–Tropsch synthesis’ is often used in the literature to denote only the second stage of the process, that is, production of a mixture of liquid and solid hydrocarbons from synthesis gas. It is in this sense that we use this term in this review.

The synthesis of hydrocarbons from carbon monoxide and hydrogen in the presence of Group VIII transition metals is a widely employed polymerisation reaction on heterogeneous catalysts. This process yields mostly alkenes and alkanes the yields and composition of which depend on the nature of the catalyst and the reaction conditions.

In some countries, iron and cobalt catalysts are used in industrial syntheses of hydrocarbons from non-petroleum raw materials. At present, catalysts of this type are preferred because they are highly selective in relation to the formation of paraffins the proportion of which in the synthesis products usually exceeds 90%.

Cobalt catalysts are traditionally used to produce linear alkanes. These products can be separated to give petrol (C₅–C₁₀) and diesel (C₁₁–C₁₈) fractions of liquid hydrocarbons and a wax fraction (synthetic ceresin C₁₉₊).

Mixtures of liquid hydrocarbons are mostly needed to produce components of engine fuels, detergents, solvents and some medicines and perfumes. At present, production of fuels is the predominant field of application of the Fischer–Tropsch products.

The hydrocarbon mixtures synthesised from CO and H₂ are not finished liquid fuels. However, the main characteristics of the diesel fraction obtained on Co catalysts conform to those required of diesel fuels (for example, its cetane number is greater than 50). In contrast, the substantial amount of linear alkanes (70% or more) present in the petrol fraction considerably reduces the possibility of using it directly in internal combustion engines.

Figure 1 presents the plots for the octane numbers of individual hydrocarbons of various homologous series.¹ It can be seen

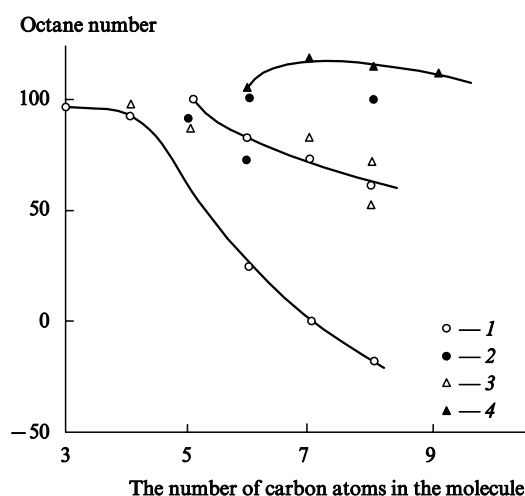


Figure 1. Octane numbers of individual hydrocarbons of various homologous series.

(1) saturated hydrocarbons (paraffins and naphthenes); (2) isoparaffins; (3) olefins; (4) aromatic hydrocarbons.

A L Lapidus, A Yu Krylova N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel (7-095) 135 69 93 (A L Lapidus)

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that aromatic compounds possess the highest octane numbers and that the octane numbers of isoalkanes are markedly higher than those of the corresponding linear alkanes (especially when the number of carbon atoms in the molecule is large). Thus, isoparaffins, aromatic compounds and cycloalkanes, which are formed in relatively small amounts in the Fischer–Tropsch synthesis in the presence of traditional Co catalysts, are the desirable components of high-octane petrols. These compounds can be produced from linear alkanes by isomerisation, cyclisation and cracking; aromatics can also be obtained by dehydrogenation.

At present, it is considered expedient to use branched alkanes for increasing the octane numbers of petrols, because these substances give less harmful exhausts into the atmosphere upon transformations in internal combustion engines than do aromatic hydrocarbons, which are also used to improve the quality of petrol. A fairly promising method is direct production of hydrocarbon mixtures with increased contents of isoalkanes from synthesis gas. This can be accomplished using oxide and metal-containing catalysts.

II. Oxide catalysts

Let us consider synthesis of branched hydrocarbons from CO and H₂ in the presence of oxide catalysts.¹ For example, the process catalysed by TiO₂, ZrO₂ or CeO₂ (375–475 °C, 30–60 MPa) gives isobutane as the major product, its yield being 20–50 g m⁻³ of synthesis gas.[†]

The synthesis of branched hydrocarbons from CO and H₂ in the presence of oxide catalysts includes apparently the following stages: formation of methanol and dimethyl ether, hydrocarbon chain growth, dehydration of higher alcohols and hydrogenation of alkenes to give isoalkanes.^{2,3}

In the presence of mixed oxide catalysts such as TiO₂–Al₂O₃, ThO₂–ZnO and ZnO–Al₂O₃ at 400–450 °C and 2.5 MPa, synthesis gas is converted into hydrocarbons in a yield of 105 g m⁻³ at a degree of CO conversion of 70%–80%. Liquid hydrocarbons (C₅₊) account for about 57 g m⁻³ of the products formed.³ At temperatures above 450 °C, gaseous hydrocarbons are mainly produced (up to 50–70 g m⁻³ of isobutane), whereas below 375 °C alcohols are formed as the major products. In addition to isoparaffins, the reaction products contain unsaturated aliphatic hydrocarbons (more than 90% of which are branched), and small amounts of aromatic hydrocarbons and naphthenes.

To produce high-quality petrols from CO and H₂, catalysts consisting of aluminium, tungsten, zirconium, uranium and lanthanide oxides with ZnO, Cr₂O₃ and CuO present as additives have been developed. These catalysts are active at > 10 MPa and at temperatures above 350 °C.⁴ A two-stage process for production of olefins and high-octane petrol from synthesis gas in the presence of iron and oxide catalysts has also been proposed.⁵ The first stage is carried out over the Fe₃O₄ (96.8%)–Al₂O₃ (2.4%)–K₂O (0.8%) catalyst at 310 °C and at 1–3 MPa and affords a mixture of alkenes in a yield of 171 g m⁻³. In the second stage catalysed by ThO₂, the remaining CO and H₂ are converted at 400–450 °C and 28–30 MPa into petrol (yield 137 g m⁻³).

The process of selective production of branched hydrocarbons from CO and H₂ on oxide catalysts has not yet found practical application, because it usually requires relatively drastic conditions. In addition, most often, the yield of the main products of this synthesis in the presence of oxide catalysts is rather low. Therefore, hybrid or bifunctional metal-containing catalysts, which are active under milder conditions, are considered to be more promising for the synthesis of branched hydrocarbons.

[†] The activity of catalysts in the Fischer–Tropsch synthesis is usually estimated based on the yield of hydrocarbons produced from 1 m³ of synthesis gas under normal (or standard) conditions (s.t.p.). The maximum theoretical yield of hydrocarbons amounts to 208.5 g m⁻³ (s.t.p.).

These catalytic systems combine the properties of hydrogenating catalysts (to convert CO and H₂ into hydrocarbons) and catalysts for hydrocarbon transformations (in particular, isomerisation).

It is known^{6–9} that hydrocarbons can undergo various transformations in the presence of solid acids. Mixed oxides (for example, amorphous aluminosilicate) and zeolites belong to this class of catalysts. Deposition of metal salts onto solid acids or introduction of reducible cations into zeolites by ion exchange gives (after reduction of the metal cations) bifunctional catalysts, which combine the properties of metallic and acidic contacts.

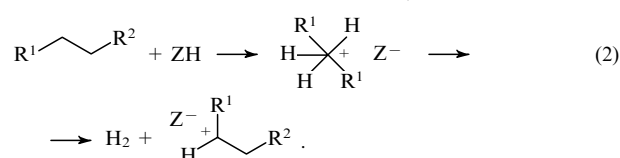
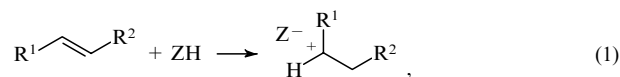
Hydrocarbons or intermediates formed from CO and H₂ with participation of the metallic component of the catalyst can undergo secondary transformations on the oxide (acid) surface. The majority of these transformations resemble homogeneous catalytic reactions occurring in the presence of strong acids. Therefore, it is usually assumed that the mechanisms of these processes are similar.

III. Transformations of hydrocarbons on acidic catalysts

In reactions occurring on solid acidic catalysts (as well as in homogeneous acid-catalysed reactions), carbocations play an important role. These species are generated on bifunctional catalysts upon proton transfer from a Brønsted acid site to an alkene formed on the metallic phase.

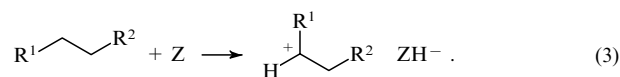
Carbocations can be classified into carbenium and carbonium ions. Carbenium ions contain a positively charged carbon atom coordinated to three alkyl groups or three hydrogen atoms (R₃C⁺). Carbonium ions are based on a pentacoordinated positively charged carbon atom surrounded by the same substituents, at least one of them being hydrogen (R₄C⁺H).

The formation of carbocations on solid acids Z (in particular, on zeolites) includes the following reactions:⁹



According to reaction (1), a zeolite proton reacts with an alkene to give a carbenium ion. Reaction (2) describes protonation of alkanes resulting in a carbonium ion. The latter is then converted into a smaller carbenium ion upon elimination of an alkane molecule or molecular hydrogen. Both reactions occur on Brønsted acid sites. It should be noted that process (1) occurs more rapidly and at lower temperatures than process (2).

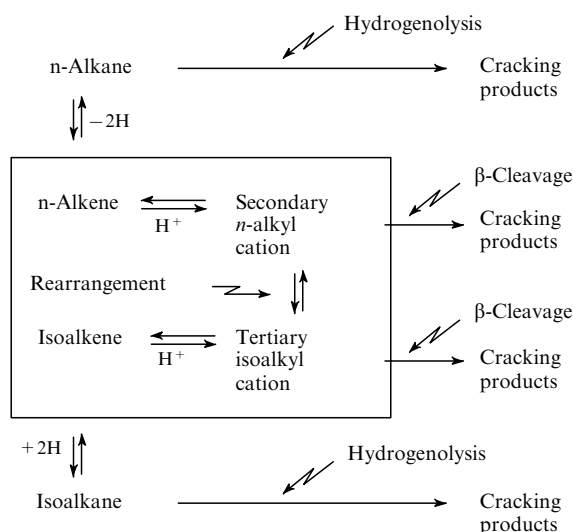
Transformations with hydride ion transfer can also occur on Lewis acid sites.



The formation of carbenium ions on bifunctional metal-containing catalysts occurs mostly by reaction (1), *i.e.* these ions result from the transfer of a proton from a Brønsted acid site to an alkene formed on the metallic phase. The proton transfer is terminated as a result of fast hydrogenation of unsaturated fragments on metal particles. The presence of a metal permits the reaction temperature to be decreased by ~100 °C.⁹ Simultaneously, isomerisation and cracking of isomerised hydrocarbons occur on acid sites. The rearrangements and cleavage of alkylcarbenium ions are the rate-determining steps.

In bifunctional catalysts, a metal ensures the occurrence of hydrogenation–dehydrogenation reactions, whereas the role of a solid acid (zeolite or a mixed oxide) consists in the formation of

carbocations on acid sites. These cations undergo isomerisation and destruction and then they are desorbed, mostly as alkenes. The latter are converted into alkanes upon hydrogenation on the metal component of the catalyst. The classical transformation chart can be represented as follows:



In accordance with this scheme, carbenium ions result from protonation of alkenes. These ions can rearrange and be desorbed as isomers, or they can be cracked (β -cleavage). Thus, cracking and isomerisation are competing processes. In the general case, isomerisation of alkanes with high molecular masses occurs at lower temperatures than hydrocracking.⁹

Alkylcarbenium ions can participate in the following transformations:⁹ intramolecular hydride shift, skeletal isomerisation, intermolecular transfer of a hydride ion from a carbenium ion to a substrate molecule to give a new carbenium ion and an alkene (this is normally the slowest step occurring on the strongest acid sites of the catalyst),¹⁰ alkylation by alkenes resulting in the formation of longer alkylcarbenium ions, β -cleavage yielding shorter alkylcarbenium ions and alkene fragments and deprotonation (chain termination). All alkylcarbenium ions formed from both neutral molecules and various intermediates can enter into the above reactions.

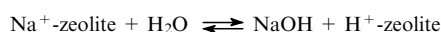
In the presence of bifunctional catalysts, lower alkanes participate in more complex processes, namely, dehydrogenation and oligomerisation of 'internal alkenes' (those with an internal double bond) followed by cracking of the oligomers.¹¹

IV. Zeolite-containing catalysts

In recent years, studies have been started on bifunctional catalysts that combine the properties of traditional Fischer–Tropsch catalysts (redox function) and selective zeolite catalysts (acid–base function). Both types of catalytic sites are involved in consecutive and parallel transformations.¹² Alkenes formed from CO and H₂ on the metal-containing component of the catalyst are converted on the zeolite into aromatic and branched aliphatic hydrocarbons, while alkanes are cracked, which increases the petrol fraction.

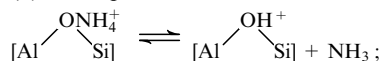
The catalytic sites for acid–base reactions are hydroxy groups of the zeolites or water molecules dissociated in the cation field.¹³ The zeolite hydroxy groups can result from the following processes:

(a) hydrolysis

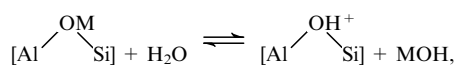


(since the sodium form of a zeolite is the salt of a weak acid and a strong base, this equilibrium is shifted to the right, and aqueous suspensions of zeolites are normally alkaline);

(b) decomposition of the ammonium form of a zeolite



(c) heterolytic dissociation of water molecules in the field of a polyvalent cation and the zeolite framework atoms



where M is metal.

The aluminium atom has a vacant *p* orbital; occupation of this orbital results in withdrawal of the electron density from oxygen in the [Al–O(H)–Si] group and thus in polarisation of the O–H bond. Thus, the OH group in the [SiOH] fragment, which exhibits weakly acidic properties when incorporated in silica gel, behaves as a strong Brønsted acid site in the presence of aluminium atoms.

Bifunctional catalysts are usually prepared on the basis of HZSM-5 zeolite. This choice is due to the following reasons:⁸ the average size of the zeolite pores is 5.5 Å, which facilitates selective formation of molecules containing less than 10 carbon atoms, *i.e.* hydrocarbons of the petrol fraction; the strong acid sites of HZSM-5 are responsible for oligomerisation, cracking and aromatisation; this zeolite is stable against coking, because the presence of medium-size pores prevents the formation of coke precursors; the zeolite is stable under hydrothermal conditions and resistant against dealumination, which is possible under the Fischer–Tropsch synthesis conditions because this reaction yields a substantial amount of water.

The high selectivity of zeolites of the HZSM-5 type towards the formation and subsequent transformations of light hydrocarbons is determined by their structure. In the pores containing strong acid sites, organic molecules are adsorbed according to the 'tail-to-tail' pattern.¹⁴ In the majority of cases, only alkenes and/or carbonium ions containing five or fewer carbon atoms are able to participate in reactions occurring in zeolite channels with a size of ~ 9 Å; therefore, the oligomers formed in these reactions contain not more than 10 carbon atoms. In addition, HZSM-5 zeolites 'control the movement of molecules': the reactants enter the zeolite structure through sinusoidal channels, whereas the products are removed through linear channels. As this takes place, alkenes, which slowly diffuse through the pores, are transformed into branched alkanes. The absence of back diffusion is a crucial factor determining the use of HZSM-5 zeolites in catalytic transformations.

The use of HZSM-5 and other high-silica zeolites as supports for the catalysts for the synthesis of hydrocarbons from CO and H₂ has been started quite recently.^{15–17} To increase the content of aromatic hydrocarbons or isoalkanes in the synthesis products, two types of catalysts are usually employed, namely, hybrid systems comprising an oxide catalyst for methanol synthesis and a zeolite (for example, Zn/HZSM-5 and Zn–Cr/HZSM-6)¹⁶ and also bifunctional systems based on metallic catalysts of the Fischer–Tropsch synthesis and zeolites. Both types of catalysts have advantages and drawbacks. Systems of the former type permit selective and highly efficient synthesis of mixtures of aromatic hydrocarbons; however, they are insufficiently stable (the period between catalyst regenerations varies from one to several months). Systems of the latter type are characterised by a lower productivity but they are suitable for the synthesis of both aromatic hydrocarbons and branched paraffins.

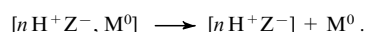
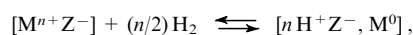
V. Synthesis of aromatic hydrocarbons and isoalkanes on zeolite-containing catalysts

Zeolite-containing catalysts based on Group VIII transition metals are usually prepared by co-precipitation or ion exchange followed by activation with hydrogen. The transition metal cations occur initially within the zeolite structure and on its surface and can be reduced almost completely.¹³ In the general

case, the degree of reduction depends on the method of cation activation with hydrogen, the nature of these cations and the reactivity of their oxygen environment in the zeolite. In addition, it depends on the degree of dispersion of the initial compound containing the transition element and on the diffusion processes in the zeolite during reduction.

The Co–O bond of an isolated cobalt species in a zeolite framework is ionic.¹⁸ The reduction of cations in the coordination sphere of these zeolites occurs at temperatures above 450 °C,¹⁹ cation-exchange zeolites behaving as ordinary salt systems.

The mechanism of reduction of transition metal cations in zeolites differs from the mechanism of reduction of the corresponding metal oxides.²⁰ The latter is irreversible, the hydrogen that has reacted being removed as water. On the contrary, in zeolites, the protons are retained by the framework where they form hydroxy groups.



Cations located in different crystallographic positions have different electrostatic environments and, therefore, different reducibilities.²¹ The reducibility depends also on the silicon to aluminium ratio in the zeolite framework,²² *i.e.* on the Si–O bond length, the residual charge on the framework, and the effective charge on the cation itself.

The character of localisation of cations and their reducibility depend appreciably on the catalyst pretreatment conditions. In particular, dehydration leads to the destruction of aqua complexes of transition metal cations; the cations migrate to positions with higher degrees of coordination unsaturation, which decreases their reducibility.²³

After reduction, transition metals can occur in zeolite-containing catalysts as separate atoms, clusters or crystallites with a size of ≥ 100 Å located on the external surface of the zeolite.¹³ It should be noted that decationised zeolites contain large amounts of strong proton-releasing and electron-withdrawing sites. Thus, the use of a zeolite support makes it possible to prepare catalytic systems differing in the degree of metal dispersion and in the strength of its interaction with the surface.

The activity of the most widely used Co catalysts for the Fischer–Tropsch synthesis is determined to a large extent by the nature of the zeolite support.²⁴ Thus the yield of liquid hydrocarbons on the Co catalysts supported on X and Y zeolites is higher than those on similar specimens based on zeolite A and mordenite. The highest yield of liquid products (166 g m^{-3}) over this series of specimens, attained on the Co–MgO/NaX catalyst, was 1.3 times higher than that on the Co–MgO/kieselguhr catalyst with the same component ratio (the latter catalyst was close in composition to the commercial one).

The nature of synthetic zeolites has a substantial influence on the polymerising and isomerising properties of Co catalysts for the Fischer–Tropsch synthesis.²⁵ An increase in the $\text{SiO}_2:\text{Al}_2\text{O}_3$ ratio in a zeolite results in an increased content of high-boiling products in the catalysate and in an increased proportion of normal aliphatic hydrocarbons in these products.

Catalysts containing A, X, Y or M zeolites in the H-form or with exchangeable Ca^{2+} , Mg^{2+} and ZrO^{2+} cations are less active in the synthesis of hydrocarbons from CO and H_2 than catalysts containing zeolites in the Na-form.²⁵ The highest yield of liquid hydrocarbons ($125\text{--}130 \text{ g m}^{-3}$) was achieved on catalysts containing NaX and NaY zeolites ($\text{SiO}_2:\text{Al}_2\text{O}_3 = 2.8\text{--}5$).²⁶ When more acidic catalysts were used, the proportion of iso hydrocarbons reached 50 mass %.

The composition of the products is substantially influenced by the nature of the exchangeable cation.²⁷ Thus introduction of Mg^{2+} by ion exchange into NaX zeolite used as a support increases the yield of liquid products 1.5-fold. Simultaneously, the proportions of branched hydrocarbons and alkenes in the catalysate decrease.

The catalytic properties of metal zeolite systems depend on the methods of their preparation and modification and on the operation conditions.⁶ For example, the cobalt particles in the Co/HZSM-5 catalyst prepared by impregnation of the zeolite with an aqueous solution of cobalt nitrate²⁸ are 3 times larger than those in the specimen prepared using dicobaltoctacarbonyl $\text{Co}_2(\text{CO})_8$.²⁹

The initial system used to produce the 9.5 mass % Co/HZSM-5 catalyst contains cobalt nitrate as amorphous particles with a size of ~ 20 Å.³⁰ After calcination in a flow of air, the nitrate is converted into the oxide Co_3O_4 . The reduction in a flow of hydrogen at 350 °C affords cobalt crystallites with a size of ~ 300 Å, which remain virtually unchanged during the Fischer–Tropsch synthesis, and the cobalt oxide CoO (~ 90 Å). The ratio of these components, equal to 4, remains approximately the same after treatment with synthesis gas, *i.e.* the catalyst is not reduced during the synthesis.

The Co/HZSM-5 catalysts prepared by impregnation contain cobalt in two states: exchangeable non-reducible Co^{2+} ions within the zeolite structure and crystalline Co_3O_4 on its external surface.¹⁵ The latter can be reduced with hydrogen to metallic cobalt and CoO. Specimens containing only exchangeable cobalt ions do not exhibit catalytic activity in the synthesis of hydrocarbons from CO and H_2 .

After preliminary reduction with hydrogen of the 30 mass % Co/HZSM-5 catalyst prepared by mixing basic cobalt carbonate with the support, the degree of Co reduction is 52%–58%.³¹ The rest of the cobalt occurs as Co^{2+} . Treatment of the catalyst with synthesis gas results in partial oxidation of the metal on the catalyst surface: the degree of Co reduction decreases to 31%–35% and Co_3O_4 (14%–17%) is formed. As the Si:Al ratio in the zeolite increases, the Co^0 surface concentration somewhat decreases, resulting in a decrease in both the total catalyst activity and the yield of liquid products.

Catalysts produced by impregnation or mixing and containing a metallic cobalt phase on the surface of HZSM-5 zeolite crystals are fairly active in the Fischer–Tropsch synthesis (the degree of CO conversion reaches 60%).¹⁵ At 280 °C, these catalysts permit the synthesis of aromatic hydrocarbons, the yield and composition of which depend on the composition of the catalyst and the method by which it was prepared. Thus the hydrocarbon mixtures obtained on the 8.5 mass % Co/HZSM-5 catalyst prepared by mechanical mixing of the components contained up to 49 vol. % of aromatic compounds, whereas the content of aromatics in the products of synthesis on 7.5 mass % Co/HZSM-5 catalyst prepared by impregnation was not more than 20 vol. %.

A number of Co/HZSM-5 catalysts containing from 3 mass % to 9 mass % of the metal and prepared by various methods have been studied.³² The following methods were used: decomposition of $\text{C}_5\text{H}_5\text{Co}(\text{CO})_2$ on the zeolite (specimen **I**), impregnation of the support by an aqueous solution of cobalt nitrate (specimen **II**) and mechanical mixing of cobalt oxide with the zeolite (specimen **III**). The conversion of synthesis gas at 2.1 MPa and 280 °C on any of these specimens increased with an increase in the cobalt loading. When the Co concentration was 9 mass %, the highest yield of liquid hydrocarbons C_{5+} (74%) was attained on catalyst **I**. This specimen contained much less ion-exchangeable cobalt than catalyst **II**. The rest of the cobalt in **I** occurred as Co_3O_4 on the external surface of the zeolite. Catalyst **III** did not contain exchangeable cobalt ions at all. Thus, the metallic component had no influence on the acidic properties of HZSM-5 zeolite, and this catalyst was best suited for the synthesis of aromatic hydrocarbons from CO and H_2 . The concentration of aromatics in the liquid products obtained on this catalyst was ~ 51 vol. %. The liquid products produced on specimens **I** and **II** were enriched in alkenes (their content was 14 vol. % and 22 vol. %, respectively).

The Co/HZSM-5 catalysts employed for the synthesis of aromatic hydrocarbons are prepared conventionally by mechanical (dry) mixing of Co_3O_4 and the zeolite to keep the latter in the H-form. Mixtures formed in the presence of these catalysts

contain up to 70 mass % of aromatic hydrocarbons.^{15, 25, 33} However, the yield of the products is not more than 10–20 g m⁻³, which is largely due to the low porosity of the catalyst samples. The yield of liquid aliphatic hydrocarbons in the presence of analogous catalysts prepared by co-precipitation (using basic cobalt carbonate) and promoted by magnesia reaches 150–170 g m⁻³.^{25, 34} It has been found³⁵ that the nature of the initial cobalt compound used to prepare the Co/HZSM-5 catalyst influences the yield and the composition of the liquid products formed. The syntheses were carried out at a pressure of 0.1 MPa, a temperature of 220–280 °C, volume ratio H₂:CO = 1 and a gas hourly space velocity of 100 h⁻¹. The use of basic cobalt carbonate makes it possible to increase the catalyst porosity (the specimen is loosened during reductive decomposition of the carbonate) and increases the yield of liquid products (up to 42 g m⁻³) and the selectivity of their formation (up to 44%). However, simultaneously the content of aromatic hydrocarbons decreases markedly (to 42%).

The introduction of 0.4 mass % to 1.5 mass % of ThO₂ into the 9 mass % Co/HZSM-5 catalyst prepared by mechanical mixing of the components substantially increases the degree of conversion of synthesis gas (up to 74%) and the selectivity of the formation of the petrol fraction of hydrocarbons (to 70%).³² The proportion of aromatic compounds in the liquid products decreases to 26% but, nevertheless, the octane number of the products is 90. It has been shown by IR spectroscopy that when the Co/HZSM-5 catalyst contains ThO₂, the relative concentration of the Brønsted acid sites in the zeolite diminishes; this accounts for the lower yield of aromatic compounds. A ⁵⁹Co NMR study has shown the presence of α - and β -cobalt phases in the Co/HZSM-5 catalyst.³³ The reduced Co–ThO₂/HZSM-5 specimen contained no hexagonal cobalt. In addition, upon the introduction of ThO₂, the size of the cobalt particles arising decreased from 40 to 10 nm;^{32, 36} this facilitated adsorption of synthesis gas and ensured higher product yields.³² However, after treatment of the catalyst with synthesis gas for 48 h at 280 °C, the size of Co crystallites again increased (apparently, due to sintering of metal particles) and the yield of aromatic hydrocarbons decreased. A similar decrease in the content of aromatic hydrocarbons in the liquid products of the synthesis on Co/HZSM-5 catalysts prepared using CoCO₃ has been observed upon introduction of 2%–3% of Mg, Zr or La oxides into the catalysts.³²

The synthesis carried out under relatively mild conditions (0.1 MPa, 250–280 °C) in the presence of the Co–Ni–ZrO₂/HZSM-5 catalyst gave aromatic hydrocarbons with a selectivity of 30 mass %–35 mass %.³⁷ A decrease in the space velocity, an increase in the temperature or an increase in the zeolite proportion in the catalyst resulted in a higher content of aromatic hydrocarbons in the C₆₊ fraction.

A study dealing with the adsorption properties of bifunctional cobalt–zeolite catalysts prepared by mechanical (dry) mixing of the components has shown that the adsorption isotherm deviates noticeably from the corresponding curve for the initial zeolite.³⁵ This implies destruction of the zeolite during the catalyst preparation, the degree of destruction being dependent on the duration of the mechanical impact on the specimen.

The hydrogenating activity of cobalt can be decreased by introducing Cu into the catalyst. The yield of methane on a mechanical mixture of 4% Co/SiO₂ and HZSM-5 zeolite is 1.7 times higher than that on the 4% Co/SiO₂ specimen itself (2.1 MPa, 280 °C, H₂:CO = 1). However, the proportion of methane formed in the presence of the 6% Co–0.05% Cu/SiO₂ + HZSM-5 specimen under similar conditions is only 1.2 times higher than that on 6% Co–0.05% Cu/SiO₂. Thus, the addition of copper decreases somewhat the efficiency of methane formation.³⁸

When developing and employing bifunctional catalysts, one should bear in mind that the rate of synthesis of aromatic hydrocarbons on these catalysts at a given temperature and at the optimum activity of HZSM-5 cannot be higher than the rate of

formation of alkenes on the metallic component of the catalyst (the Fischer–Tropsch component).⁸ The temperature for the synthesis of aromatic compounds is normally 280 °C. At this temperature, zeolite is active towards aromatisation of alkenes, and methane formation on the Fischer–Tropsch component is not too pronounced. The maximum rate of formation of aromatic hydrocarbons from alkenes at 280 °C is 0.084 g (g of HZSM-5)⁻¹ h⁻¹.⁸ At the same time, a catalyst for the Fischer–Tropsch synthesis (for example, 4% Co/SiO₂) can ensure formation of 0.123 g of alkenes per hour under similar conditions. It is the ratio of 0.084 to 0.123 that determines the ratio of the components in the bifunctional 4% Co/SiO₂ + HZSM-5 catalyst.

The main problem associated with the use of bifunctional zeolite catalysts is their deactivation during the interaction with synthesis gas. The deactivation is due to the following factors:⁸ deposition of inactive carbon on the metallic component, sintering of metal particles and coking of the zeolite component. The first and the second processes result in a gradual decrease in the overall rate of the synthesis gas conversion. The third process diminishes the selectivity of formation of aromatic hydrocarbons due to a decrease in the number of active sites capable of converting alkenes.

An attempt has been made to regenerate the Co–ThO₂/HZSM-5 catalyst by conducting redox cycles, because oxidative treatment favours the removal of the carbon deposits. However, in each regeneration cycle, cobalt particles sintered, and this retarded the reforming of synthesis gas. In order to suppress metal sintering during the oxidative regeneration of bifunctional zeolite-containing catalysts, the use of oxygen enriched in ozone was proposed.⁴⁰

Synthesis of branched alkanes from CO and H₂ can also be carried out in the presence of bifunctional catalysts containing Group VIII noble metals.⁴¹ Most often, these catalytic systems exhibit low activities. Conversely, Co/HZSM-5 catalysts are highly active: at an atmospheric pressure and a temperature of 175–200 °C, they permit production of liquid hydrocarbons (C₅–C₁₀), containing 60%–80% of isoparaffins, in 46%–59% yield with respect to the converted CO.⁴²

In the presence of 10% Co–6% MgO/HZVM catalysts (SiO₂:Al₂O₃ = 30–104) prepared by co-precipitation and containing high-silica zeolites, analogues of HZSM-5, the degree of conversion of carbon monoxide is 70%–100% at 175–200 °C.⁴³ On these catalysts, liquid hydrocarbons enriched in isoalkanes can be synthesised selectively in 70%–90% yield. The C₅–C₁₀ fraction prepared on a catalyst supported on a zeolite with a silica modulus (the SiO₂:Al₂O₃ ratio) of 30–68 contains 36%–46% of isoalkanes. The zeolite silica modulus has an influence on the yield of isoalkanes, the highest yield being attained at SiO₂:Al₂O₃ = 68. An increase in the reaction temperature from 175 to 220 °C permits selective synthesis of C₅–C₁₀ hydrocarbons containing more than 50% of isoalkanes.

The influence of the synthesis conditions on the formation of isoalkanes on Ru–Pt catalysts has been studied.⁴¹ It was found that the shorter the contact time, the higher the yield of branched hydrocarbons. When the *W*:*F* ratio (*W* is the mass of the catalyst, and *F* is the space velocity of synthesis gas through the catalyst) was proportional to the residence time and was equal to 7 (g of the catalyst) h mol⁻¹ (2% Ru–2% Pt/HY, 240 °C, 1.5 MPa, CO:H₂ = 2:3), the iso to normal ratio (iso/*n*) for C₄ and C₅ hydrocarbons was an order of magnitude higher than that expected from the thermodynamic viewpoint (this ratio cannot be achieved upon hydroisomerisation of linear alkanes). As the residence time increased, the iso/*n* ratio reached the theoretical (thermodynamic) value. This means that the ratio of branched to linear alkanes is controlled by kinetic factors, and an increase in the residence time leads to gradual hydroisomerisation of branched alkanes into linear alkanes.

It was found⁴¹ that the Fischer–Tropsch synthesis on Ru/zeolite catalysts yields alkenes as the primary products. The predominant formation of branched alkanes in the initial reaction

stage may be due to transformation of alkenes on the zeolite acid sites followed by hydrogenation on ruthenium. It can be expected that the ratio of the synthesis products would be determined by the relative reaction rates on the acidic and metallic sites. Since raising the temperature usually enhances the hydrogenating activity of a catalyst, the iso/n ratio simultaneously decreases. A decrease in pressure results in lower iso/n ratios, because hydrogenation is facilitated at low partial pressure of CO. The highest iso/n ratio (ranging from 10 to 40 for various C_{4+} hydrocarbons) on the 2% Ru–2% Pt/HY catalyst was attained at a pressure of 1.5 MPa.⁴¹ As the pressure increased, this ratio substantially decreased. The $W:F$ ratio remains constant upon a pressure increase, whereas the real residence time (*i.e.* the residence time of hydrocarbons in a catalyst layer) becomes longer, and this causes a decrease in the iso/n ratio. It was found that this ratio is inversely proportional to the selectivity of methane formation.

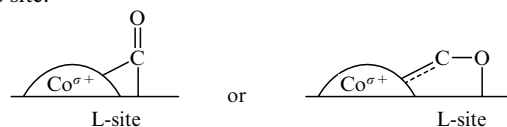
When the reaction is carried out on the 2% Ru–2% Pt/HY catalyst, the iso/n ratio in the C_{4+} hydrocarbons depends on the nature of the support and increases in the order $AS < CaY < DAHY < HY$ (where AS is a synthetic amorphous aluminosilicate, and DAHY is dealuminised HY).⁴¹ As the Si:Al ratio in the zeolite increases, the degree of CO conversion diminishes, whereas the selectivity of CH_4 formation grows. The H-forms of zeolites with higher silica moduli give lower yields of isoalkanes. These results are inconsistent with those obtained in other studies,^{44, 45} according to which Ru/zeolite catalysts with higher Si:Al proportions give products characterised by greater iso/n ratios. This inconsistency may be due to the fact that the iso/n ratio is determined by the relationship between the rates of various steps involved in the synthesis of isoalkanes from CO and H_2 , which depend on the nature of the metal and the type of the zeolite used. To elucidate the general regularities of the synthesis of hydrocarbons from CO and H_2 , it is necessary to study systematically various catalysts under identical conditions.

VI. The mechanism of the Fischer–Tropsch synthesis

The surface of supported Co catalysts contains two types of metal-containing active sites **A** and **B** (Scheme 1).^{46–49} Sites of type **A** are metallic cobalt crystallites; on these sites, CO undergoes dissociative adsorption giving surface carbon, which is hydrogenated yielding methane. Thus, sites **A** are responsible for CO methanation. On the same type of sites, as a result of CO dissociation, adsorbed oxygen appears, which is able to react with carbon monoxide to give CO_2 (or with hydrogen to give water). Type **B** sites comprise metallic cobalt and an oxide component. They might be located at the Co–oxide interface.⁵⁰ The oxide component can be represented by cobalt oxide resulting from incomplete

reduction of the initial cobalt salt, by an oxide support or by a surface mixed oxide formed upon interaction of cobalt, the support and an oxide promoter during high-temperature pretreatment of the catalyst (calcination and/or reduction).

On the metallic part of site **B**, reagents are activated giving intermediates of the type COH_x or CH_x ; these species spill over to the oxide part of the site on which they polymerise. The oxide part of site **B** is normally a Lewis acid site (L-site). It affects the neighbouring metallic cobalt in such a way that some of the electron density shifts from the metal to the support⁵¹ yielding $Co^{\delta+}$. Carbon monoxide is adsorbed on site **B** in the molecular form; apparently it binds simultaneously to both components of the site.



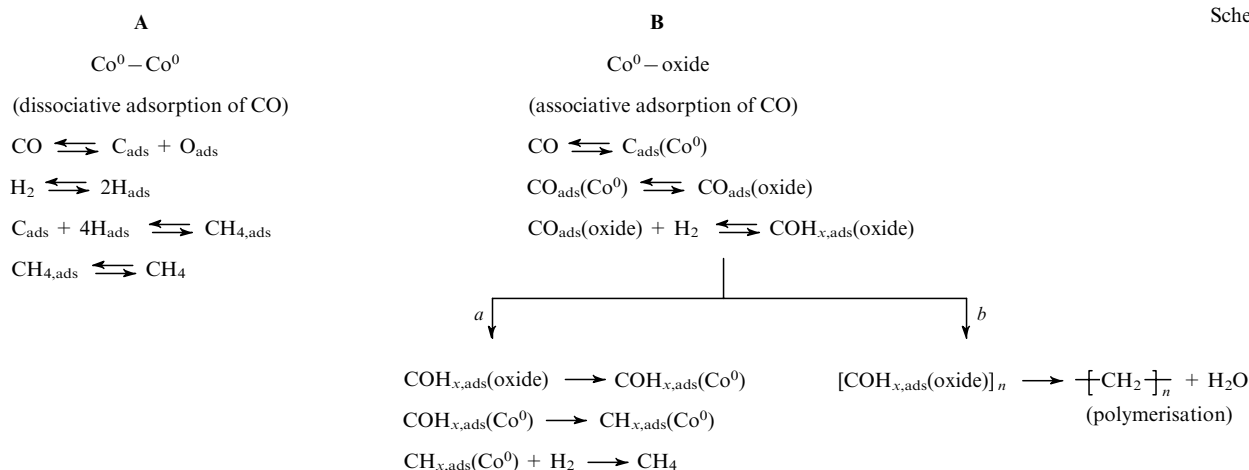
It is also possible that CO is adsorbed on the interface in such a way that its oxygen atom binds to the oxide component of the active site.^{52, 53} In this case, the Lewis acid site located near the Co–oxide interface weakens the C–O bond in the carbon monoxide molecule and increases the rate of its hydrogenation.⁵⁴

The role of metallic cobalt in active site **B** is not limited to adsorption of CO (which is also adsorbed efficiently by cobalt oxide); cobalt also ensures hydrogen activation and transport to the polymerisation site. In the case where hydrogen can be delivered to the polymerisation site without participation of the metal (for example, by dissociative adsorption of C_2H_2 on an oxide⁵⁵), CH_x radicals can polymerise directly on the oxide.

It should also be noted that in addition to the two types of metal-containing active sites mentioned above, the surface of Co catalysts for the Fischer–Tropsch synthesis contains Lewis and Brønsted acid sites of various strengths, which are located on the oxide surface and are able to participate in secondary transformations of the intermediates formed from CO and H_2 . In addition, the energetic characteristics of sites of a particular type (**A** or **B**) can differ owing to the inhomogeneity of the catalyst surface.

VII. Distribution of the products of the Fischer–Tropsch synthesis

The process of formation of hydrocarbons from CO and H_2 is an example of catalytic hydropolymerisation. The distribution of the products formed in this reaction can be described using the Schulz or Flory equations, which virtually coincide for high chain growth rates.⁵⁶ In particular, the Schulz equation is written as follows



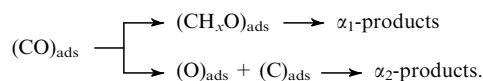
Scheme 1

(a) Proposed by Bartholomew in 1989; (b) proposed by Lapidus in 1991.

$$g_n = (\ln^2 \alpha) n \alpha^n,$$

where g_n is the weight fraction of a product containing n carbon atoms, and α is a factor of the hydrocarbon chain growth characterising the ratio of the probabilities of chain growth and chain termination.

In some cases, the distribution of the products of the Fischer–Tropsch synthesis does not conform to the classical Schulz–Flory distribution; this is due to the fact that there are at least two centres of chain growth on the catalyst surface, polymerisation on which occurs by different mechanisms.^{57–59} For example, it has been suggested⁶⁰ that hydrocarbons, the chain growth of which is characterised by factors α_1 and α_2 , can arise in the following way:



The ratio of the α_1 - to the α_2 -products is determined by the hydrogen pressure.

It has been assumed⁶¹ that on different active sites of the surface, different intermediates can be formed, which are converted, in their turn, into different surface compounds. According to these views, all the reactions occurring on the surface including the formation of the primary complex are reversible.

VIII. Secondary transformations in the Fischer–Tropsch synthesis

The deviation of the product composition from the Schulz–Flory distribution can also be explained by assuming that the alkenes formed from CO and H₂ are adsorbed once again on one or several active surface sites.^{62,63} In particular, the readsorption of alkenes substantially decreases the overall rate of the surface chain termination by changing the direction of the hydrogen elimination step, which leads to alkenes with a double bond located at the end of the molecule (terminal alkenes).⁶⁴

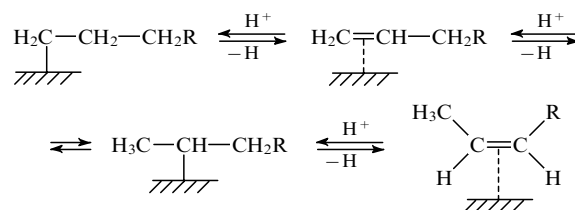
Study of the compositions of the products formed on the Fe/SiO₂ catalyst has demonstrated that there are two types of distribution, namely, a ‘classical’ distribution obeying the Schulz–Flory law and a ‘non-classical’ distribution, which does not obey this law.⁶⁵ The non-classical distribution appears because the primary reaction products can be rapidly converted into isomeric secondary products on the acid sites of the catalyst. The secondary transformations include double bond shift, *cis*–*trans* isomerisation, cyclisation and aromatisation.

There exists a direct correlation between the content of silica gel in a precipitated iron catalyst and the selectivity of this catalyst towards the formation of internal alkenes and branched hydrocarbons.⁶⁶ The content of alkenes with an internal double bond increases with an increase in the proportion of silica gel in the catalyst. Terminal alkenes are known to isomerise on silica gel,⁶⁷ alumina⁶⁸ and zeolites.⁶⁹ In the presence of these catalysts, alkenes undergo the following transformations (listed in order of increasing difficulty of transformation): *cis*–*trans* isomerisation, double bond shift, skeletal isomerisation, cyclisation, hydrogen transfer and polymerisation. These reactions occur on Brønsted and Lewis acid sites.

It is generally believed that termination of a growing alkyl chain upon elimination of a β -hydrogen atom yields terminal alkenes, whereas termination occurring by interaction of hydrogen with the α -carbon atom in the chain affords linear alkanes.⁷⁰ The formation of small amounts of *cis*- and *trans*-alkenes as the primary products occurs apparently in those rare cases where the growing carbon chain comes in contact with the active site of the catalyst through its β -carbon atom, the chain being terminated upon elimination of δ -hydrogen.

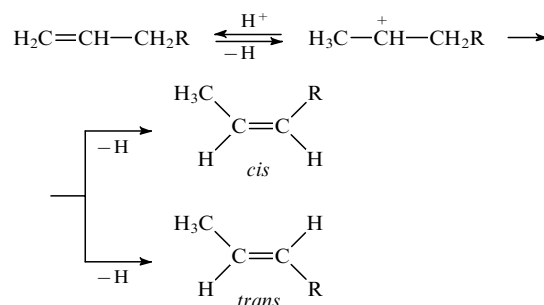
As the content of SiO₂ in the support of the Fe catalyst increases, the yield of alkenes with an internal double bond increases, whereas the amount of terminal alkenes simultaneously decreases; therefore, it can be concluded that internal alkenes

result from isomerisation of terminal alkenes on silica gel, which occurs according to the following scheme:⁶⁶



This mechanism implies that isomerisation proceeds on the same sites on which hydrocarbons are synthesised from CO and H₂ and that the two hydrogen atoms attached to the third carbon atom can be removed with equal probabilities to give *cis*- and *trans*-isomers in a ratio close to unity. This mechanism explains adequately the composition of the products formed on Fe catalysts supported on a material devoid of SiO₂.

In the presence of silica gel, the probability of isomerisation of terminal alkenes increases, because this support contains Brønsted acid sites. In this case, the scheme of formation of the *cis*- and *trans*-isomers can be represented as follows:⁷¹

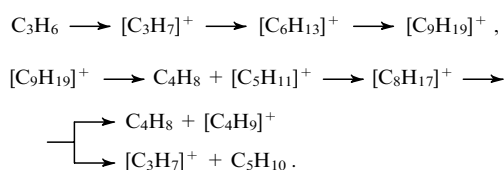


The interaction of an acid site proton with the double bond of an alkene yields a carbenium ion. Elimination of a hydrogen atom from the adjacent carbon gives rise to a *cis*- or *trans*-alkene. This mechanism accounts for the predominance of the *cis*-isomers in the reaction products, since it is known that on acidic catalysts (which include SiO₂) *cis*-isomers are formed predominantly.⁷²

The secondary transformations of the hydrocarbons produced from CO and H₂ have been studied using the precipitated catalysts 14% Co/SiO₂ (I) and 15% Co/SiO₂ + HZSM-5 (II).³⁸ In addition, a two-stage process was carried out using two consecutively connected reactors, one of which (the first stage) contained the 14% Co/SiO₂ catalyst, while the other one (the second stage) contained HZSM-5. The tests were carried out at a pressure of 2.1 MPa, a temperature of 280 °C, and the ratio H₂:CO = 1. The degree of conversion of CO on specimen I reduced at 350 °C reached 50%, and the content of C₅+ hydrocarbons in the carbon-containing products of the synthesis was 72%. The C₅+ fraction consisted of alkanes (63%), alkenes (34%) and aromatic compounds (3%). In the case of the two-stage process with catalyst I in the first stage and the zeolite at the second stage, the yield of liquid hydrocarbons somewhat decreased (to 65%). However, the C₂–C₄ alkenes formed in the first stage (~8%) were converted almost completely on HZSM-5. As a consequence, the content of aromatics in the liquid products increased to 33%. The proportion of C₃–C₄ alkanes markedly increased (from 7% to 21%), that of methane remained virtually unchanged (14%) and the content of C₅+ hydrocarbons diminished to 65%. When the 14% Co/SiO₂ catalyst was mixed with HZSM-5 (specimen II) and the synthesis was carried out in one stage, the methane formation was enhanced (up to 25%), whereas the yield of C₅+ hydrocarbons and the content of aromatics in them barely changed with respect to those attained in the two-stage process. This led to the assumption that methane is formed in a secondary reaction (apparently, hydrogenolysis of light alkanes) occurring on metallic cobalt. This assumption is supported by the fact that the yield of C₂–C₄

alkanes on catalyst **II** is lower than that in the two-stage process (15% and 21%, respectively). This type of side reaction proceeds to a noticeable extent only on catalyst **II** in which cobalt particles occur in tight contact with HZSM-5 zeolite.

Hybrid catalysts $\text{RuNaY} + \text{SO}_4^{2-}/\text{ZrO}_2$ consisting of a mechanical mixture of ion-exchange RuNaY zeolite and sulfidised zirconium oxide have been studied.⁷³ It was found that under the synthesis conditions (0.1 MPa, 250 °C, $\text{H}_2 : \text{CO} = 1 : 1$), the propene formed initially on the Fischer–Tropsch component (RuNaY) undergoes two subsequent transformations on the sulfidised zirconium oxide, which behaves as a superacid, namely, hydrogenation through hydrogen transfer to give propane and transformations giving C_4+ alkanes. The formation of C_4+ hydrocarbons from propene follows an oligomerisation–cracking mechanism with hydrogen transfer.¹¹



Propene is formed on the Fischer–Tropsch component and is readsorbed on the acid sites of the hybrid catalyst where it oligomerises to give heavier products. The resulting C_4 fragments can be converted into C_4 and C_5 surface groups, which, in turn, react with propene giving rise to C_7 and C_8 hydrocarbons, respectively. The probability of interaction with propene for the C_5 fragments is higher than that for C_4 , since heavier hydrocarbons are more readily adsorbed and more difficultly desorbed.^{74,75}

The formation of branched oligomeric intermediates during the conversion of alkenes on zeolites depends appreciably on the concentration and the strength of acid sites.⁷⁶ A higher concentration and a higher strength of acid sites lead to more branched oligomeric alkene intermediates. Oligomers synthesised on strong acid sites form larger amounts of isoalkanes.

The transformations of linear alkenes on acid sites of the catalysts can follow two routes:⁷³ (1) alkenes undergo direct skeletal isomerisation to isoalkenes and subsequent hydrogenation *via* hydrogen transfer; (2) oligomers formed on acid sites decompose. The fact that the amount of isobutane produced is larger than its equilibrium amount⁷⁷ indicates that isoalkanes are mainly formed *via* reaction (2).

It should be noted that hydrogen transfer is also catalysed by acid sites.^{78–80} Upon the hydrogen transfer reactions, some of the alkene molecules are saturated with hydrogen at the expense of other alkene molecules and/or oligomers attached to the catalyst surface. Consequently, oligomers giving off hydrogen become more unsaturated. Polymerisation of these highly unsaturated fragments results in the formation of coke precursors.⁷³

The presence of the metallic component in the hybrid catalyst stabilises its activity towards isomerisation of hydrocarbons.^{75,81,82} This can be explained in the following way. Molecular hydrogen is adsorbed on the metallic phase of the catalyst and undergoes homolytic dissociation. The atomic hydrogen thus formed spills over to the support, migrates to a Lewis acid site and then gives off an electron, being thus converted into H^+ . The interaction of the proton with oxygen located near the L-site affords a Brønsted site, which is also capable of participating in acid-catalysed reactions. This is accompanied by weakening of the L-site which has accepted the electron. Thus, the catalyst is deactivated to a lesser degree. Another possible explanation is neutralisation of carbocations on the catalytic surface by hydride ions, which result from heterolytic dissociation of hydrogen on the metal.⁷³ The appearance of hydride ions decreases the lifetime of intermediates and prevents their subsequent transformations.

The compositions of the products obtained upon cracking of oct-1-ene on DAHY zeolite and upon the Fischer–Tropsch

synthesis on the 2% Ru–2% Pt/DAHY bifunctional catalyst were found to be similar.⁸³ However, the products of catalytic cracking contain larger amounts of branched alkanes in the C_4 and C_5 fractions (especially in the initial stage of the reaction). This is explained by the increase in the lifetime of a carbenium ion due to the low reactivity of hydrogen in the absence of a metal, which results in a higher probability of isomerisation of the carbenium ion before it is desorbed. The presence of a metallic component in the catalyst favours hydrogenation of alkenes to alkanes;^{84,85} this promotes the formation of large amounts of linear saturated hydrocarbons and accelerates the spillover of hydrogen to acid sites. Therefore, to equalise the functions of hybrid catalysts, it is necessary that they contain similar numbers of metallic and acid sites.

The distribution of the Fischer–Tropsch synthesis products formed on the 2% Ru–2% Pt/zeolite catalyst shifts towards lighter hydrocarbons in the series $\text{NaY} < \text{HY} < \text{DAHY}$.⁸³ The number of strong acid sites of the zeolites determined by the method of temperature-programmed desorption of NH_3 ($T_{\text{max}} > 350$ °C) increases in the same sequence. Among the products of the synthesis catalysed by the DAHY-containing material, mono- and di-branched alkanes predominate. This is due to the fact that relatively strong acid sites are unsuitable for skeletal isomerisation.⁸⁶

Under conditions of the Fischer–Tropsch synthesis, the growing linear chain is chemically bound to the surface. This bond ruptures upon elimination of β -hydrogen from the hydrocarbon yielding a terminal alkene or upon α -hydrogenation giving rise to a linear alkane.⁸⁷ The latter is inert under the Fischer–Tropsch reaction conditions;⁸⁸ therefore, it does not participate in secondary transformations. Meanwhile, terminal alkenes can be partly hydrogenated or involved once again in the hydrocarbon chain growth after readsorption.^{89,90} Upon the repeated adsorption of alkenes, the possibility of chain termination as a result of hydrogenation decreases, resulting in a higher probability of chain growth and a greater alkane : alkene ratio.^{62,91}

The probability of secondary reactions involving terminal alkenes substantially increases with an increase in the number of carbon atoms in the molecule.^{92,93} Correspondingly, the alkane : alkene ratio^{94,95} and the probability of chain growth^{62,95} also increase. The probability of secondary transformations of alkenes is normally assumed to be proportional to the contact time. Some investigators^{63,93} believe that the contact time increases appreciably as the chain becomes longer, because hydrocarbons with longer chains are better soluble in heavy products of the Fischer–Tropsch synthesis, which fill the catalyst pores. However, the dependence of the solubility on the chain length cannot be determined or calculated; therefore, this parameter is difficult to use as a quantitative characteristic. In addition, this interpretation does not seem to be fully justified because the presence of a liquid phase does not influence the chemical potential and, hence, the secondary transformations.⁶² The dependence of the chain length on the residence time might also be due to transport limitations (*i.e.* diffusion). When there are no transport limitations, the components of the gas and liquid phases of the reaction system are in thermodynamic equilibrium. Therefore, in this case, neither the residence time of the products in the reaction area nor the kinetic driving force (volatility or chemical potential) depend on the presence of the liquid phase.⁶² The secondary transformations of hydrocarbons are not influenced by the liquid phase either. When there are external-diffusion limitations, the number of carbon atoms in the molecules being formed depends on the factor of the hydrocarbon chain growth α and on the concentration of alkenes. In this case, the residence time of hydrocarbons in the pores filled with a liquid increases and, hence, the probability of secondary transformations also increases.

An attempt has been made⁸⁸ to elucidate the reason for the dependence of the rate of secondary reactions on the hydrocarbon chain length using cobalt foil as a model catalyst. Diffusion

limitations were modelled using a foil coated preliminarily by wax. When a non-coated foil was used, there were no such limitations. Below we consider the results of this study in more detail.

The ratio of the rates of hydrogenation and repeated involvement of readsorbed alkenes in the chain is determined by a large number of parameters, in particular, CO and H₂O pressures.⁶² Under the conditions studied (0.1 MPa, 220 °C, H₂:CO = 1, polycrystalline cobalt), virtually all readsorbed alkenes should be hydrogenated. Thus, the distribution of hydrocarbons up to C₁₄ cannot deviate from the Schulz–Flory distribution, *i.e.* it cannot depend on secondary transformations. The chemisorbed intermediates which undergo hydrogenation differ from those involved once again in the chain growth.

To be repeatedly involved in the synthesis, an alkene should be chemisorbed on a vacant site on the catalyst surface. Under the conditions of the Fischer–Tropsch synthesis, vacant sites are scarce, because the surface is occupied almost completely by various fragments.⁹⁵ In order to occupy a growth site which has become vacant, an alkene should compete with CO and H₂. It is unlikely that an alkene molecule that has moved far away from a vacant active site would reach it before it is occupied again. Of all the alkenes present in the reactor, only those located in the close vicinity of a site have a chance to be readsorbed.

Thus, the probability of the repeated involvement of alkenes in the chain is intimately connected with their concentration at the interface in the physically adsorbed layer and with their average concentration over the whole reactor (*i.e.* the contact time). The alkene concentration at the interface is influenced, in addition to the transport limitations, by the preferred physical adsorption and solubility. Chemisorption of alkenes is a non-activated process. On passing from a physically adsorbed state to chemisorption, there is no competition between the reactions. Thus, the rate of readsorption is controlled only by the effective 'rate of collisions', which depends on the concentration of the molecules in the physical adsorption region at the interface, *i.e.* on the total contact time in the physically adsorbed layer and on the alkene concentration in wax. The chemisorbed phase occurs in a steady state; however, there is no equilibrium between the physically and chemically adsorbed phases.

As a consequence, at low degrees of CO conversion on the Co foil, the alkane/alkene ratio grows exponentially as the chain is lengthened. The coating of the foil with wax results in lower yields of alkanes and a less pronounced dependence of the alkane/alkene ratio on the chain length. These findings can be explained by the fact that the rate of readsorption of alkenes increases exponentially with chain length. A model was proposed which assumes competitive participation of alkenes in the readsorption, so that the readsorption rate is proportional to the alkene concentration at the catalyst–wax interface. Thus, the dependence of the alkane/alkene ratio on the chain length is determined by the solubility of hydrocarbons and by diffusion limitations; the latter, in turn, are caused by the predominant physical adsorption in the boundary layer. Under normal synthesis conditions (when the degree of CO conversion is high), the transport limitations are more significant.

IX. Conclusion

The foregoing leads to a number of general conclusions concerning the current state of the problem of catalytic synthesis of isoalkanes and aromatic hydrocarbons from CO and H₂.

The transformation of CO and H₂ on oxide catalysts giving mainly isoalkanes ('iso-synthesis') normally requires high pressures.⁹⁶ In this case, the yield of liquid hydrocarbons is low, and the overall catalyst activity is not sufficiently high.

A more promising method is the synthesis of isoalkanes as mixtures with linear alkanes on catalysts containing high-silica zeolites together with Group VIII metals. Apparently, either intermediates or alkenes which undergo skeletal isomerisation serve as the source of isoalkanes. Aromatic hydrocarbons can also be formed on these catalysts but this requires higher temperatures.

The zeolite component of the catalyst ensures the occurrence of isomerisation and aromatisation processes. Isomerisation occurs on the Brønsted and Lewis acid sites. Isomerisation of alkenes is more efficient on bifunctional metal-containing catalysts. Thus, the transformation of CO and H₂ on the Co–MgO/HZVM catalyst affords hydrocarbons (yield 70%–90%) containing 36%–40% of isoalkanes.⁴⁰

The 'two-sites' model for the Co catalysts for the Fischer–Tropsch synthesis that we proposed previously makes it possible to divide all the active sites on the catalyst surface into three main types, namely, methanation sites (Co⁰), hydrocarbon chain growth sites (Co^{δ+}–M_xO_y) and isomerisation and cyclisation sites (acid sites).

The deviation of the product composition from the Schulz–Flory distribution is due to the repeated adsorption of alkenes on one or several active sites. Readsorption of alkenes and their involvement in growing chains results in an appreciably decreased total rate of hydrocarbon chain termination and in a change in the step of hydrogen elimination giving terminal alkenes. Thus, readsorption of alkenes followed by their skeletal isomerisation and hydrogenation ensure the formation of isoalkanes. Yet another pathway to isoalkanes is decomposition of unsaturated branched oligomers on acid sites and subsequent hydrogenation.

Of course, it is as yet impossible to draw ultimate conclusions about the true mechanism of the formation of isoalkanes and aromatic hydrocarbons under the Fischer–Tropsch synthesis conditions. However, in all probability, a fairly important role in the processes catalysed by cobalt-containing catalytic systems is played by unsaturated intermediates and by their subsequent readsorption with involvement in the growing hydrocarbon chain or their oligomerisation and isomerisation.

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Promising aspects of the structural modification of polymers and polymer composites with the aid of high pressures

V A Beloshenko, A A Askadskii, V N Varyukhin

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Abstract. The results of studies on the structures and mechanical properties of polymeric materials subjected to isostatic treatment and extrusion in the solid state, mainly rigid-chain and network polymers, polymer blends, and reinforced compositions, are described systematically and surveyed. The bibliography includes 204 references.

I. Introduction

The modification of polymers, the manufacture of which has been undertaken on an industrial scale, is one of the principal trends in the creation of materials with a required set of characteristics. Various procedures for the deliberate alteration of the structures and properties, including methods such as chemical and physical modification, are employed. Despite the advances achieved on these lines, the search for new modification methods, among which methods involving treatment by the application of pressure are promising, is being continued.

A high hydrostatic pressure induces both reversible and irreversible changes in the physical and mechanical properties of materials, promotes the formation of their new modifications, and makes it possible to achieve the synthesis of products the preparation of which is impossible under normal conditions.^{1–7} The first experiments using high pressure were carried out more than 100 years ago but since then the interest in its employment for scientific and technological purposes has not weakened.

In order to obtain materials with the required performance properties, various methods based on the employment of high pressures, are used namely pressing, rolling, stamping, drawing, *etc.* They are distinguished by the scheme underlying the stressed state of the material and the hydrostatic component of the stress tensor.⁸ Among the technological processes based on the direct application of a high hydrostatic pressure, the greatest development has been achieved in isostatic pressing and hydrostatic

extrusion.^{7,9–17} The isostatic pressing method is used basically in the treatment of powders. Its advantages include extremely effective mechanical characteristics of the final products, the possibility of obtaining articles of any shape, however complex, the simplicity of equipment, and the ease of automation. Virtually all the advantages of the plastic deformation of materials, including the most favourable scheme underlying the stressed state, the reduction to a minimum of frictional forces, and the plasticisation effect determined by the application of pressure, are applied in the hydroextrusion method. Using the advantages of the method listed above, it is possible to alter the structure and the strain–strength characteristics of the treated material.

Compared with other substances, for example metals, polymers are much more sensitive to the effect of pressure, but the first few studies which considered various aspects of the influence of high pressure on polymers were carried out comparatively recently.^{18–22} Active interest in the study of the properties of polymers under pressure began to be manifested in the 1960s while the fundamental theoretical and experimental results, which clarify the role of high pressures in the establishment of a set of mechanical and performance properties of polymeric materials, were obtained in the 1970s–1980s, which may be regarded as the period of the most vigorous development of this field.^{23–30}

The methods for the treatment of polymers by the application of pressure, used for their structural modification, can be divided conventionally into two groups. The first comprises various procedures based on the application of an isostatic treatment; isostatic pressing of polymer powders, treatment by the hydrostatic compression of articles in the form of a block, and structure formation under pressure. This group of methods is characterised by a spherical external stress tensor. The second group includes methods based on the joint operation of a high pressure and shear stresses (the total external stresses tensor): deformation using Bridgman anvils, ultrasound, and shock waves; pressing; elastic-deformation grinding; solid-state extrusion; *etc.*

This review deals with structural modification methods, which are some of the most promising as regards practical employment — different versions of the isostatic treatment and solid-state extrusion. They are characterised by a high effectiveness, ease of technological application, and the possibility of treating comparatively large volumes of the polymeric raw material. The main bulk of studies devoted to isostatic treatment or solid-state extrusion have been carried out on flexible-chain amorphous or amorphous-crystalline homopolymers. Their results have been reflected to a large extent in a series of review articles and monographs, for example in the studies described in Refs 25, 26, 30, and 31. In the present review, attention is therefore

V A Beloshenko, V N Varyukhin A A Galkin Donetsk Physicotechnical Institute, National Academy of Sciences of Ukraine, ul. R Lyuksemburg 72, 340114 Donetsk, Ukraine. Fax (38-062) 255 02 08.
E-mail: bel@hpress.dipt.donetsk.ua (V A Beloshenko)

A A Askadskii A N Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, ul. Vavilova 28, 117813 Moscow, Russian Federation. Fax (7-095) 135 50 85. Tel. (7-095) 135 93 98.
E-mail: andrey@ineos.ac.ru

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concentrated on the less well known aspects of the problem, namely on questions concerning the modification of rigid-chain and network polymers and polymer composites. New aspects of the development of the structural modification methods under discussion, in particular the solid-state extrusion of a powdered billet, are examined in greater detail.

II. Isostatic treatment of crystallisable polymers

1. Crystallisation under pressure

The vast majority of studies on isostatic treatment have been devoted to crystallisation under pressure. The main bulk of such investigations have been carried out on polyethylene (PE).^{25,32–39} In the first experiments, it was already observed that pressure not only increases the crystallisation temperature but also induces certain structural changes in the polymer. Thus Matsuoka and Maxwell³² obtained at high pressures PE with an unusually high density, which they explained by more effective chain packing. Subsequently, Wunderlich⁴⁰ showed that crystallisation under a high pressure entails not only more satisfactory chain packing but also leads to the formation of crystals of a new type — crystallites with extended chains (CEC). The pressure corresponding to the onset of the formation of CEC is in the range 300–350 MPa according to the phase diagram.⁴¹

There are two main hypotheses concerning the appearance of CEC.³⁴ According to the first, the CEC are formed on nuclei consisting of straightened chains or packs of chains,³⁵ whilst according to the second, folded lamellae are thickened under pressure and are gradually converted into CEC.^{36,37}

The molecular mass distribution (MMD) has a significant effect on the course of crystallisation. For example, it has been shown³⁸ that the curves for the distribution of the thickness (length) of crystallites in the direction of molecular chains and of the molecular mass (M) distribution are identical for $M < 10\,000$. For $M > 10\,000$, mixed crystallites are formed. Fractions with narrow MMD crystallise in two stages,⁴² while the crystallisation of specimens with a broad MMD usually involves a single stage. In mixtures of fractions, fractionation and segregation take place during crystallisation, which results in the formation of a eutectic-like mixture of crystallites comprising fully straightened molecules with a low M and crystallites made up of molecules with a high M having both straightened and folded shapes.³⁹

The principal differences in the morphology of PE specimens, obtained at atmospheric and high pressures, are as follows. In the pressure-modified PE, the lamellar thickening occurs only up to a certain limiting extent, the twisting of the lamellae is not observed, and spherulitic formations with a fanlike structure are present. The latter are characterised by a tangential orientation of the C -axes.

The formation of CEC on crystallisation from the melt under pressure has been observed for a series of other polymers^{43,44} and copolymers.⁴⁵ Together with the formation of CEC, phase transformations occur in many polymers during crystallisation under pressure, as a result of which it is possible to obtain materials with a new crystal system. For example, it has been noted²³ that, together with the orthorhombic phase, a triclinic phase is present in PE crystallised at 436 MPa. If the crystallisation of syndiotactic polypropylene (PP) is carried out at pressures amounting to several hundreds of megapascals, it is possible to obtain a new crystalline modification.⁴⁶ Poly(vinylidene fluoride) (PVDF), crystallised at 507 MPa, consists of a mixture of two phases with different melting points (T_m); the PVDF obtained at atmospheric pressure consists of a single phase.⁴⁷ The transition to a new modification on crystallisation under high pressure has been noted also for polybut-1-ene.²⁵

The study of the crystallisation kinetics showed that a high pressure as a rule slows down the crystallisation process, *i.e.* a higher degree of supercooling of the melt is required in order to attain the same rate of crystallisation as at atmospheric pressure.^{48,49} At the same time a nonmonotonic dependence of the

rate of crystallisation of PE on pressure, due to changes in the kinetics of the growth of crystals and the phenomenon of topomorphy has also been discovered.⁵⁰

The structural transformations listed above, which occur in polymers as a result of crystallisation under pressure, induce changes in their properties. As a rule, denser packing appears in the polymers and the degree of crystallinity and T_m measured under atmospheric conditions increase.^{32,40} Thus the differences between the densities (ρ) of high-density polyethylene (HDPE) specimens, obtained at normal and elevated pressures, amount to 2%.³² The dynamic Young's modulus of pressure-modified polyethylene is twice as high, its strength is greater, but its plasticity is lower. A similar effect has been obtained for polytetrafluoroethylene (PTFE) and polypropylene.²⁵ The increase in the density of PE and the formation of CEC on crystallisation under pressure cause a decrease in its compressibility and in the intensity of γ -relaxation.³⁵

2. Annealing under pressure

The influence of annealing under pressure has also been investigated mainly in relation to PE.²⁵ It was established that, when PE specimens comprising crystals with folded chains (CFC) are annealed, the rearrangement of the structure with CFC to a structure containing CEC is observed in the corresponding temperature ranges.⁵¹ This has been confirmed by the appearance of a second (high-temperature) fusion peak and the results of morphological investigations; lamellae with transverse dimensions exceeding by more than an order of magnitude the dimensions of the lamellae in the unannealed specimens are formed after such annealing. There is a simultaneous increase in ρ for the annealed material, which reaches values characteristic of the structure with CEC. Slight changes in T_m , ρ , and morphology are observed during the annealing of specimens with the CEC structure, indicating a further improvement of their structural arrangement. It is assumed⁴⁰ that the formation of CEC during the annealing of PE under a high pressure takes place in accordance with a mechanism similar to the mechanism of crystallisation under the conditions of hydrostatic compression, *i.e.* via the isothermal thickening of lamellae.

Similar features (an increase in the degree of crystallinity, an improvement in the structure, and an increase in T_m and ρ) have also been established in the course of the annealing of other amorphous-crystalline isotropic polymer specimens.^{25,46} During annealing under pressure, oriented polymers exhibit a more complex behaviour. For example, uniaxially extended HDPE specimens undergo a phase transformation in addition to the increase in the thickness of the crystallites, in T_m , and in ρ already mentioned.⁵² A proportion of the material undergoes the transition from the orthorhombic modification to the oriented triclinic modification. At the same time, there is a sharp increase in the degree of crystallinity; the intensity of the amorphous halo for the annealed specimen is five times smaller than for the original specimen.⁵²

In the course of the annealing of oriented specimens of syndiotactic PP, the formation of a new high-pressure crystalline modification was observed.⁴⁶ The annealing of oriented PVDF specimens also induces a phase transition in the solid state with retention of the primary orientation.⁴⁶ The phase formed then has ρ higher by 10% compared with ρ for the low-pressure phase. Annealing under pressure (by crystallisation under pressure) of isotropic and oriented polymer specimens is reflected in their mechanical properties. In particular, a significant increase in the moduli of elasticity has been noted.^{53,54}

An improvement in the properties of the polymers can be achieved in a number of instances also by isostatic treatment at room temperature. The imposition of an hydrostatic pressure onto PTFE specimens with an increased porosity leads to the 'healing' of the micropores at pressures up to 80 MPa.⁵⁵ On further increase in pressure, the 'healing' process is retarded. Thermal activation analysis showed that the 'healing' of the

pores is associated with the viscous flow of the macromolecules. It continues until the free volume is 'exhausted'.

The contact between the polymer and the pressure-transmitting medium is very important in the isostatic treatment. In the absence of appropriate insulation, the negative effect of the medium can abolish the positive role of pressure or can impair the properties of the created material.⁵⁶

3. Isostatic treatment of powders

The component methods for the treatment of polymer powders are extrusion, pressing with subsequent free sintering, pressing with sintering under pressure, and casting under pressure.⁵⁷ The choice of a particular procedure is determined both by the properties of the polymer and by the nature of the technical problem to be solved. The advantage of the pressing-free sintering scheme consists in the possibility of the effective manufacture of long articles by separating the pressing and sintering operations. However, in order to obtain good-quality articles, it is necessary to achieve the highest possible density and uniformity of its distribution with respect to length and the cross-section of the billet. It has been shown in relation to PTFE of brands F-2M, F-4, F-4MB, F-40, and F-40-P⁵⁸ that the isostatic treatment makes it possible to obtain the above properties with retention of the specified form of the article, provided that this operation is carried out after preliminary pressing of the powder. Hydrostatic pressures of 200–250 MPa are sufficient for the attainment of the state with the minimum porosity (Fig. 1).

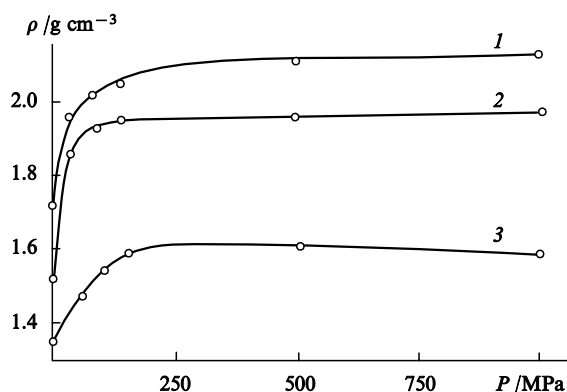


Figure 1. Pressure dependence of the density of polytetrafluoroethylenes for different powders: (1) F-4; (2) F-4MB; (3) F-2M.

A mathematical model describing the isostatic pressing of polymer powders and permitting the determination of the values of the principal technological parameter (the pressure) has been proposed.⁵⁹ The isostatic pressing process is regarded as consisting of two stages. The first stage is associated with the relative displacement and rotation of individual particles. The second involves elastic deformations of the particles filling the existing free space. After the removal of the external pressure, the polymeric material is loosened as a consequence of the reversibility of the elastic deformations and its density returns to the level attained at the end of the first stage. The relative density of the pressed polymer powder is therefore always less than unity. Comparison of the calculated and experimental $\rho(P)$ relations for PTFE confirms that the model is consistent with the isostatic treatment under consideration.⁵⁹

In the practical application of powder technologies, moulding methods, differing from isostatic pressing, for example pressing in a rigid die of complex shape or pressing in special shells are widely used. The technological problems arising under these conditions are associated with the determination of the force necessary to attain the specified density, with the estimation of the pressure exerted on the walls of the die, with the calculation of the

distribution of density with respect to the volume of the billet, *etc.* The parameters of the model,⁵⁹ found in experiments involving isostatic treatment, may be used to calculate the force parameters of the processes indicated.

III. Isostatic treatment of glassy polymers

1. The influence of pressure on the properties of amorphous polymers

There have been extremely few studies devoted to the influence of the isostatic treatment on the structure and properties of amorphous polymers. This is evidently associated with the possibilities for structural rearrangements which are much smaller than for crystalline polymers. Fairly detailed studies on polymeric glasses have been carried out.⁶⁰ It has been shown for a series of amorphous polymers that cooling of the specimens at 150 MPa from a temperature exceeding the glass transition temperature (T_g) to room temperature makes it possible to increase ρ compared with the original state by $\sim 1\%$. The state with increased density is metastable, but relaxation under atmospheric conditions proceeds slowly. With increase in temperature, this process accelerates, but at $T < T_g$ there is no complete transition to the original state. Compaction of the glass is characterised by increased values of the dynamic modulus of elasticity and a lower dielectric constant.

Higher values of ρ for a polymer vitrified under pressure have also been established in another study.⁶¹ Here the instability of the material was noted. The nature of the recovery of ρ when the material is heated depends on the pressure employed: in the original stage of the recovery of ρ , the rate of the process is higher the higher the pressure P .

There have been few technological studies devoted to the application of a high hydrostatic pressure for the structural modification of polymers. Among them, mention should be made primarily of Shturman's studies^{62,63} in which the favourable effect of annealing under pressure on the mechanical and performance characteristics of a series of polymers and polymer composites was demonstrated. For example, annealing of impact-resistant polystyrene promotes an increase in its strength, impact strength, and antifriction properties. A similar thermomechanical treatment of glass-reinforced polyamide specimens significantly increased their hardness together with an increase in the ultimate bending strength and impact strength. It is believed⁶² that the strengthening effect is due to the compaction of the surface layer and the appearance in the latter of compressive stresses which increase the cohesive strength of the polymers. The molecular mass of the polymers also increases under the influence of temperature and pressure (the content of low-molecular fractions diminishes), which is correspondingly reflected in their properties.

2. The structures and properties of network polymers obtained under the conditions of hydrostatic compression

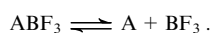
The chemical reactions as a result of which network polymers are formed are accompanied by the formation of a three-dimensional network structure. Compared with linear glassy polymers, one may expect new effects in the course of their isostatic treatment, in particular irreversible changes in structure and properties induced by the high pressure.

The study of the kinetics of the curing of network polymers under the conditions of hydrostatic compression showed that in the vast majority of cases the rate of this process increases with increase in pressure^{64–69} and the increase is extremely significant. For a series of epoxide compositions, the increase in the reaction rate constant (k) at 250–350 MPa reaches several orders of magnitude.^{64,67} The volume activation effect ($\Delta V^\ddagger$) for these reactions is negative and the increase in k with increase in pressure follows from the familiar relation.⁷⁰

$$\left(\frac{\partial \ln k}{\partial P} \right)_T = - \frac{\Delta V^\ddagger}{RT}.$$

The nature of the influence of pressure is determined both by the type of the reagents selected and their proportions. For example, in the presence of an excess of an epoxide oligomer (EO) there is a possibility of the solvation of the reaction centres, which prevents their interaction, as a result of which the intensity of the effect of the pressure diminishes.⁶⁹ The results of studies by different investigators^{64–69,71} involving the determination of k agree well. The shortening of the gel and glass formation times during the curing of EO by amines under the conditions of hydrostatic compression has been observed.⁷¹

Under the influence of pressure, the structure-formation process may be retarded as well as being accelerated. This result has been established, for example, in the curing of EO by an amine complex of boron trifluoride^{66,67} and is associated with the influence of pressure on the equilibrium constant (K) for the dissociation of this complex to the amine (A) and BF_3 , initiating the polymerisation



Under the influence of pressure, the equilibrium in this reaction shifts to the left and the concentration of BF_3 in the reaction mixture falls, which means that the rate of curing of the EO diminishes.

It has been established^{65–69} that the differences in the kinetics of the chemical reactions occurring at pressures from 0.1 to 250 MPa are quantitative. This makes it possible to postulate the absence of an appreciable influence of pressure in the selected range (0.1–250 MPa) on the curing mechanism and hence on the molecular level of the structural arrangement of the epoxide polymers (EP). At the same time, the data obtained for poly(ethylene glycol dimethacrylate)⁷² indicate that at sufficiently high pressures there is a possibility of changes in the structure of the molecular chains. Analysis of the IR spectra of poly(ethylene glycol dimethacrylate) showed that the nature of the disposition of the methacryloyl groups changes in the pressure range 600–2000 MPa, which is manifested by an increase in the probability of their 'tail to tail' addition. The most significant rearrangement of the molecular structure is observed at $P \leq 800$ MPa. An increase in pressure hardly influences the type of addition of the polymethacrylate chain units.

The influence of hydrostatic pressure on the topological and supermolecular structures of network polymers is more effective than its influence on the molecular level of the structural arrangement. Fig. 2 presents thermomechanical curves for specimens of a series of EP cured at different pressures.⁷³ The following compositions were employed: a blend of the epoxybisphenol A[†] resin

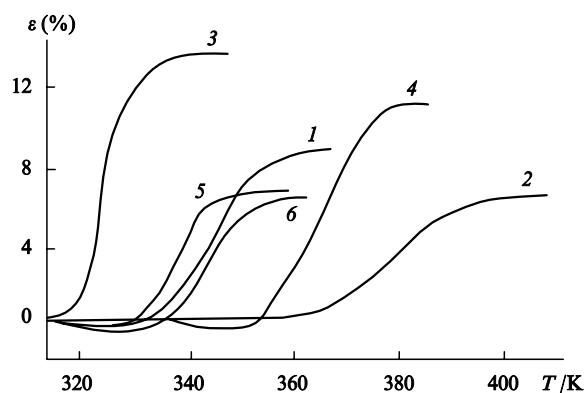


Figure 2. Thermomechanical curves for the epoxide polymers EP-4 (1, 2), EP-5 (3, 4), and EP-1 (5, 6) at different pressures (MPa): (1), (3), and (5) 0.1; (2), (4), and (6) 200.

[†] Bisphenol A ('dian' in Russian) is 2,2-bis(4-hydroxyphenyl)propane (Translator)

ED-20 and polyepichlorohydrin cured with monocycloethylenetriamine (EP-1); epoxyaniline resin cured with a eutectic mixture of aromatic diamines (EP-2); epoxybisphenol A resin cured with bis(4-amino-3-chlorophenyl)methane (EP-3); the epoxybisphenol A resin ED-20 cured with methyltetrahydrophthalic anhydride (EP-4); a blend of a flexible-chain block oligomer comprising an epoxide resin and acid oligomer and a diglycidyl ester cured with methyltetrahydrophthalic anhydride (EP-5); a blend of the epoxybisphenol A resin ED-20 and oligomeric diglycidyl esters based on diethylene glycol cured with triethanolamine titanate (EP-6); the epoxybisphenol A resin ED-16 cured with the methyltetrahydrophthalic anhydride (EP-7).

Curing under pressure results in an increase in T_g and in the initial temperature of forced rubber elasticity and a decrease in the deformability of the polymers in the region of rubber elasticity. These facts indicate the intensification of intermolecular interaction. Pressure exerts the greatest influence on EP with large units (EP-4) or long chains between cross-links (EP-5). The increase in T_g reaches 30 K and the relative decrease in the quasiequilibrium elastic deformation reaches 30%. The latter is equivalent to the corresponding increase in the equilibrium modulus of elasticity, *i.e.* the increase in the rigidity of the polymer network. In the case of EP with compact units (EP-1), the changes under consideration are less pronounced. These findings indicate that the change in T_g under the influence of pressure is caused predominantly by the change in the packing of the units. The structure produced is 'frozen' at $T < T_g$ and is retained after the removal of the pressure. The appearance of anomalies on the thermomechanical curves for the modified EP-1 and EP-5 specimens in the vicinity of T_g is apparently a consequence of the relaxation of the 'frozen' compressive stresses.

The main parameter of the topological structure of the type of polymers considered is the concentration of the network cross-links (ν). Table 1 presents the values of ν for certain EP investigated.⁷⁴ For all the compositions, the curing under the conditions of hydrostatic compression promotes an increase in ν and the highest values of $\Delta\nu$ are attained for EP-4 and EP-5 ($\Delta\nu$ was estimated as the ratio of the increment in ν , caused by the pressure, to the value of ν for the control specimen).

Table 1. Effective concentrations of network cross-links in EP.⁷⁴

Polymer	$10^{-20} \nu / \text{cm}^{-3}$	$\Delta\nu$ (%)	Polymer	$10^{-20} \nu / \text{cm}^{-3}$	$\Delta\nu$ (%)
EP-1	$\frac{7.3}{7.8}$	7	EP-4	$\frac{5.7}{8.1}$	42
EP-3	$\frac{12.1}{13.9}$	15	EP-5	$\frac{3.6}{4.4}$	22

Note. The values of ν above the horizontal line correspond to control specimens and those below the horizontal line were obtained at a pressure of 200 MPa.

The results of the thermomechanical analysis agree with pulse NMR data,⁶⁸ according to which structure formation under pressure increases the 'nuclear' glass transition temperature (T_g'), corresponding to the temperature of the appearance of two 'kinetic phases' with the nuclear magnetic transverse relaxation times T_{2b} and T_{2c} , and diminishes molecular mobility (Fig. 3). At $T > T_g'$, the changes in molecular mobility are observed only for the most mobile (T_{2b}) fragments of the polymer network, which indicates the influence of pressure also on the linear chains between the cross-links.

Differences between the internal friction spectra for the pressure-modified and control EP specimens have been demonstrated.⁷⁵ This indicates a lower intensity of the small-scale relaxation processes and a narrower set of relaxation times corresponding to these processes.

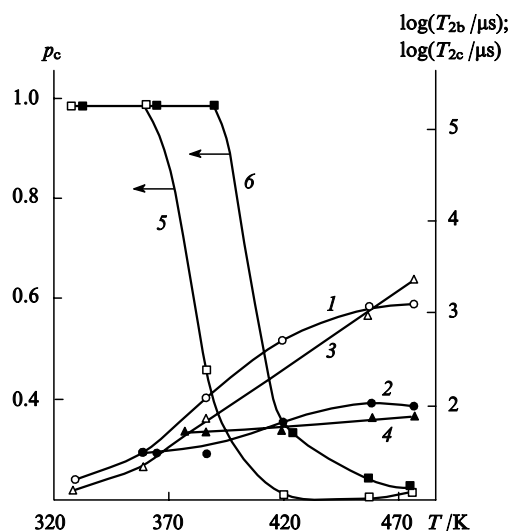


Figure 3. Temperature dependences of the nuclear magnetic relaxation times T_{2b} (1, 3) and T_{2c} (2, 4) and of the proton population p_c (5, 6) for EP-1 at different pressures (MPa): (1), (2), and (5) 0.1; (3), (4), and (6) 150.

Three endothermic maxima appear on the differential scanning calorimetric (DSC) curves for the cured EP specimens (Fig. 4). They correspond to regions with different scales of the 'unfreezing' of molecular mobility: the low-temperature maximum *I* is associated with the 'unfreezing' of the noncooperative motion of segments at sites with a lower packing density (β -transition); the maximum *II* at 440 K corresponds to the cooperative glass α -transition; the high-temperature maximum *III* at 490 K is due to the molecular mobility in the rubbery state.⁷⁶ Comparison of curves 1 and 2 in Fig. 4 shows that treatment with pressure leads to a decrease in the intensity of the maximum *I* and its shift towards higher temperatures (*I'* on curve 2), which is caused by the suppression of the small-scale molecular motion at the level of the segments (sections of the chain). The second maximum for the modified polymer is also located at higher temperatures (*II'* on curve 2). The intensity of the molecular motion does not then change.

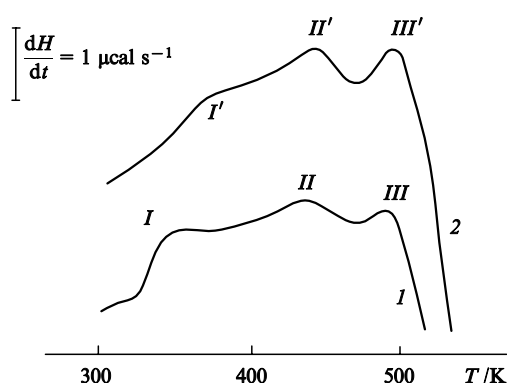


Figure 4. DSC curves for EP-1 at different pressures (MPa): (1) 0.1; (2) 100. *I*–*III* and *I'*–*III'* — see text.

Thus the set of data obtained by thermomechanical analysis, pulse NMR, internal friction spectroscopy, and DSC makes it possible to assume that the curing of the EP under the conditions of high pressures induces appreciable changes at the topological and supermolecular levels of the structural arrangement, manifested by an increase in the effective density of the cross-links and intensification of the intermolecular interaction.

This conclusion conflicts at first sight with the results of a study⁷⁷ in which the structure formation in EP was also investigated under the conditions of high pressures. According to these results, the specimens cured at 500–1000 MPa have lower values of T_g than those cured at atmospheric pressure. Estimation of the degree of cross-linking of the modified EP demonstrated that this process does not go to completion in the specimens indicated. Possibly the negative effect of pressure appeared because the investigators did not apply a correction for the temperature regime in the curing process. The change in T_g with increase in pressure is known to be $0.15\text{--}0.3\text{ K MPa}^{-1}$. By tradition, in the epoxide resin curing practice the final curing temperature for the composition is chosen so that it exceeds the expected glass transition temperature.⁷⁹ In this case, the highest degree of conversion is attained. When the temperature regime corresponding to atmospheric pressure is applied in the region $P > 500\text{ MPa}$, the specimen is vitrified, for the reason mentioned above, before it attains the necessary degree of conversion. The reaction is inhibited and an undesirable result appears as a consequence.

There is also a possibility of another mechanism of the loosening of the polymer network on curing EP under pressure, which is analogous to that of Ozerkovskii *et al.*⁷² In considering the pressure dependence of ν for PDMA, the authors of this investigation suggested that in the network polymer cross-linked to the limiting extent an equilibrium is established between the cross-links, leading to a decrease in the volume of the system and the loosening cross-links. Calculation showed that at high pressures ν decreases, because, starting with a certain critical concentration, the cross-links prevent the packing of the network skeleton.

In contrast to EP, for bis(methacryloyloxyethyleneoxycarbonyloxyethylene) oxide (MECDE) polymerised at 85–550 MPa, a decrease in the glass transition and enforced rubber elasticity temperatures as well as an increase in deformability in the rubbery state are observed with increase in pressure.⁷⁹ According to the authors,⁷⁹ this is caused by the changes occurring at the molecular level in the structural arrangement of MECDE. On polymerisation under pressure, there is an increase in the probability of the isotactic addition of units in the main macrochains of MECDE. Lower values of T_g are more characteristic of this modification than of the modification with the atactic type of addition of units.

A microstructure, the morphological unit of which is a globule, is at the uppermost level in the 'structural hierarchy' of network polymers.^{78,80,81} The globular character of the microstructure is manifested either on the surface of a section after etching or of the break produced by the application of a load. In the first case, the weakest sections of the polymer network are etched away, *i.e.* the globular relief reflects the chemical rupture front, the velocity of which is inversely proportional to the molecular packing density.⁸² In the second case, the rupture takes place at the interglobular boundaries.⁸³ This makes it possible to regard the globule as a local thickening of the three-dimensional network, manifested as a particle on etching or mechanical rupture.⁸²

Comparison of the microstructures of control EP specimens and specimens cured at high pressures shows that the dimensions of the globular formations and the thicknesses of the boundaries separating them diminish under the influence of hydrostatic pressure and the structure becomes more uniform.^{62,68,84,85} Table 2 presents the results of optical microscope studies of a series of epoxide compositions, illustrating this postulate. When the resolution of the microscope is high, it is seen that each globule consists of smaller formations. The results of electron microscope studies of the EP structure⁸⁴ are correlated with optical microscope data, which indicates a link between the observed morphological formations. The more finely disperse structure of the EP obtained under a high pressure compared with the structure of the EP cured at atmospheric pressure is due to the fact that the acceleration of the structure formation processes entails the

Table 2. The average sizes of the globules (d) and the content of groups of globules of different sizes at different pressures.^{62, 68}

Polymer	P /MPa	d /μm	Content (%) of groups of globules of different sizes /μm										
			1–1.4	1.4–2	2–2.8	2.8–4	4–5.6	5.6–8	8–11.2	11.2–16	16–22.4	22.4–32	32–44.8
EP-1	0.1	5.6	—	0.2	0.4	16.4	41.7	30.8	6.8	3.4	0.2	—	—
	200	3.5	—	4.4	29.2	35.8	19.9	9.5	1.2	—	—	—	—
EP-3	0.1	9.8	—	—	0.9	6.2	11.3	20.3	24.1	28.6	7.8	0.6	0.2
	100	6.7	0.6	5.6	5.8	11.6	18.5	26.9	19.4	9.4	2.0	0.2	—
EP-6	0.1	6.0	0.8	6.0	11.4	16.1	16.1	21.3	20.1	6.8	1.2	0.2	—
	200	5.6	0.8	7.2	9.0	19.8	23.2	21.8	11.4	6.2	0.8	—	—

formation of a larger number of centres with reacted reactive groups, which create a basis for the subsequent formation and establishment of the heterogeneous morphology of the EP.⁸⁶

The influence of pressure on the microstructure of MECDE is analogous to its influence on the structure of EP. Electron microscope studies⁷⁹ have shown that polymerisation under the conditions of hydrostatic compression is responsible for the decrease in the size of the globules from 500 Å (at 0.1 MPa) to 300–350 Å. Increasingly more pronounced aggregates with an elongated shape, consisting of a set of globules arranged one on top of another, are formed with increase in pressure.

An interesting result has been obtained in a study⁸⁷ devoted to the structure of a phenol–furfural composition based on iron tris(hydroxymethyl)phenoxide (Fe-TMP). In the original composition, the Fe-TMP forms ionic clusters which coagulate in the course of structure formation in the system with formation of associated species. High pressure promotes the latter process and leads to the appearance of larger metal-containing particles. At the same time pressure influences the physicochemical processes occurring in these particles during the curing of the composition, which alters their phase structure from amorphous to crystalline. The increase in the size of the cluster is accompanied by the appearance of a large amount of magnetite and an increase in the degree of order in its structure.

The pressure-induced changes at different levels of the structural arrangement of network polymers are reflected in their mechanical properties. In the first place, one should point to the increase in density, which has been noted in numerous investigations (see, for example, Refs 75, 79, and 85). This can be explained by the fact that pressure prevents the formation of macroscopic defects in the form of pores or cracks and promotes a decrease in free volume as a result of a more effective packing of the polymer. In the region of comparatively low pressures, the $\rho(P)$ relation is linear, but, as P increases, it approaches asymptotically a certain limiting value.⁷⁹

Table 3 lists the strain–strength characteristics of MECDE specimens at different pressures, established in compressive tests.⁷⁹ Evidently, with increase in pressure, the modulus of elasticity (E) and the ultimate tensile strength (σ_t) increase to certain values. In the range 425–500 MPa, these parameters diminish. The extremum change in mechanical properties may be caused by the competition between the changes at the microlevels (ρ) and topological levels (v) of the structure and at the level of the macrochains. At a comparatively low pressure, effects associated with the increase in ρ and v predominate. The mechanism of the

addition of methacryloyl groups predominates in the region ≥ 400 MPa.⁷²

The results of compressive tests on EP specimens cured at atmospheric and elevated pressures agree^{74, 85} with the data of the above study.⁷⁹ The more effective mechanical properties of the modified EP can be accounted for by the intensification of the intermolecular interaction and a decrease in structural inhomogeneity on curing under the conditions of hydrostatic compression. The most significant changes in properties are attained when the epoxide compositions deviate greatly from stoichiometry, whereupon the number of unreacted epoxide groups increases significantly. The intermolecular interactions at the boundary between the globular and interglobular phases are appreciably weakened under these conditions with a consequent sharp decrease in the strength characteristics of the control specimens. The density of the cross-links in the polymer increases under the influence of pressure (the degree of inhomogeneity diminishes) and the connectivity between the supermolecular formations is enhanced, which promotes the retention of fairly high strengths.

The data obtained in tensile tests on EP are similar. Fractographic investigations⁷⁵ have shown that modification by pressure does not entail a change in the rupture mechanism. The differences between the fractograms of the specimens compared are merely quantitative; in the modified EP, the structural elements of the fractograms are smaller.

A promising method of improving the mechanical properties of polymers is believed to be the cure under pressure of reinforced compositions, especially if one employs fillers with a low surface energy or fillers tending to undergo sedimentation. Fig. 5 presents the distribution of microhardness along sections of cylindrical

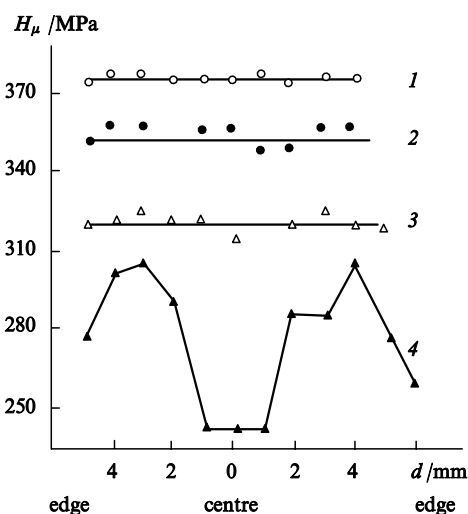


Figure 5. Distribution of the microhardness H_μ in cylindrical specimens of EP-2 (1, 2) and EP-2 with 10 mass% of graphite (3, 4) at different pressures (MPa): (2) and (4) 0.1; (1) and (3) 200. d = Diameter of the cylinder.

Table 3. The strain–strength properties of MECDE at different pressures.

P /MPa	$10^{-3}E$ /MPa	σ_t /MPa	P /MPa	$10^{-3}E$ /MPa	σ_t /MPa
0.1	2.20	230	340	2.60	250
85	2.35	235	425	2.55	245
170	2.35	220	550	2.40	230
255	2.45	230			

EP-2 specimens obtained at different pressures. The level of microhardness H_μ for the modified polymer is higher compared with the control specimen, while the scatter of the values is approximately the same. When finely dispersed graphite powder is introduced, the picture changes sharply: a slight increase in inhomogeneity in the distribution of H_μ is observed for the polymer obtained under the conditions of hydrostatic compression, while in the control specimens the maximum deviation of H_μ from the mean reaches 20% for a filler content of 10 mass%–30 mass%. Such a change in H_μ in the latter case is caused by the separation of the composition into layers as a consequence of sedimentation processes. The viscosity of the cured composition increases under the influence of a high hydrostatic pressure, with a consequent suppression of the sedimentation processes, the microstructure of the composite becoming more homogeneous.

The dielectric properties of EP obtained at atmospheric and elevated pressures have been investigated.⁷⁵ It was established that the specific electrical volume resistance (ρ_v) of the modified polymers is higher than that of the control specimens and that the highest differences between the ρ_v are observed for specimens in the rubbery state. The EP investigated exhibited the ionic type of conductivity and the increase in ρ_v is therefore accounted for by the decrease in the mobility of the ions induced by the higher values of ρ and v for the modified polymers. The temperature dependences of ρ_v , the dielectric loss factor ($\tan \delta$), and the dielectric constant (ϵ') are correlated.⁷⁵ The maxima in $\tan \delta$ and ϵ' caused by the α -relaxation in the modified EP, as well as the corresponding break in the $\rho_v(T)$ relation, are located at higher temperatures compared with the corresponding maxima for the control specimens. Furthermore, the modified polymers have lower absolute values of ϵ' .

Studies on the thermal stability of EP showed⁸⁸ that appreciable differences between the characteristic temperatures of the objects compared were not observed for specimens in the form of a block. When the modified specimens are ground, an increase in the original thermal degradation temperature compared with the corresponding temperature of the control specimen is observed. Analysis of the change in the thermal degradation temperature in the course of the annealing of the ground specimens in oxygen and under an inert atmosphere led to the hypothesis that curing under pressure influences the nature of the packing of the molecular chains, as a result of which the most 'vulnerable' chemical bonds are shielded from oxygen.

Polymers based on interpenetrating polymer networks (IPN) have great potential possibilities for structural modification. Such polymers are obtained by simultaneous or consecutive curing.⁸⁹ In a series of studies, Lee and Kim^{90–93} examined the influence of hydrostatic pressure on the structures and properties of simultaneously cured IPN in relation to the polyurethane–polystyrene (PU–PS) system. The characteristic features of the behaviour of the PU–PS compositions, consisting of blends of linear polymers or of polymers of the type of semi-IPN, were discovered. It was established that, in the course of synthesis under the conditions of hydrostatic compression, ρ of the final reaction product increases (the increase in ρ is observed in the range 0.1–250 MPa, while in the region of higher pressures ρ is independent of pressure). The nature of the temperature dependence of the mechanical loss factor also varies with increase in pressure. The $\tan \delta(T)$ relation for the compositions synthesised at atmospheric pressure has two maxima corresponding to each component of the composition (Fig. 6). In the synthesis under a high pressure, the positions of the temperature maxima are displaced towards one another and ultimately the maxima merge, forming a single peak. This peak is produced as a result of the degeneration of the PU maximum. The glass transition temperature of the dominant phase (PS) decreases with increase in pressure and this is the reason for the low slope of the relation $T_g(P)$ at ~ 1000 MPa. The authors associate the observed effect with the increase in the compatibility of the phases both for the blend of linear polymers and for the semi-IPN and IPN (Fig. 7).

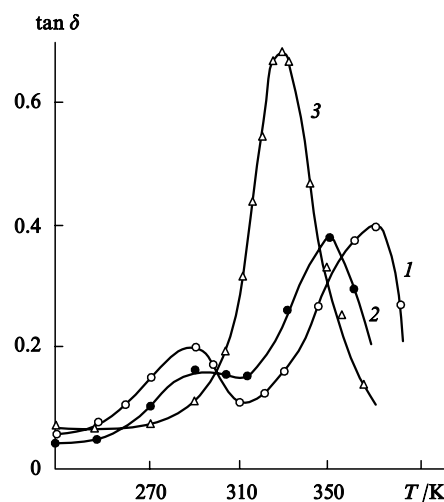


Figure 6. Temperature variations of the mechanical loss factor for the polyurethane–polystyrene IPN system containing 50 mass% polyurethane at different pressures (MPa): (1) 0.1; (2) 250; (3) 1000.

The results of electron microscope studies indicate that the morphology of the PU–PS system, synthesised at atmospheric pressure, consists of a fairly homogeneous structure made up of the PU and PS phases. With increase in the synthesis pressure, fully dispersed domains are formed in the PU phase, their size diminishing with increase in the compatibility of the phases. At 1000 MPa, the size of the domains is 30–50 Å, which corresponds to the molecular level of the blending. The size of the domains increases with increase in the cross-linking density in the IPN. The results of the study of the morphology of the IPN PU–PS system by dynamic mechanical analysis and electron microscopy agree satisfactorily.

In the case of the semi-IPN and the blend of linear polymers obtained at atmospheric pressure, the PU phase forms a matrix, but with increase in pressure a tendency towards the dispersion of this phase is manifested. Such a tendency is most notable for systems in which the PU component has a linear structure.

Prolonged annealing of the pressure-modified PU–PS blends at 0.1 MPa and $T < T_g$ promotes the partial restoration of the $\tan \delta(T)$ spectrum characteristic of control specimens synthesised under atmospheric conditions. With increase in the annealing temperature to $T > T_g$, complete phase separation (characteristic of the control specimens) takes place, which is indicated by the identity of the mechanical loss spectra of the annealed and control specimens.

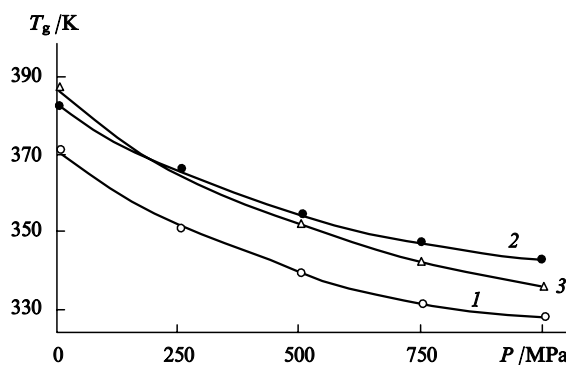


Figure 7. Dependence of the glass transition temperature T_g on the synthesis pressure for the polyurethane–polystyrene system. (1) IPN; (2) semi-IPN; (3) polymer blend.

The characteristic features of the structure formation in and the properties of the consecutively cured IPN synthesised under pressure have been investigated^{94–96} in relation to epoxide allyl polymers. Diethylene glycol bis(allyl carbonate) (DEGBAC) and epoxybisphenol resins (EO) were used as the allyl monomers. The study of the prepolymerisation (formation of the allyl network) kinetics by rotational viscometry and by measuring ρ_v showed that together with accelerating the process and increasing the average degree of polymerisation, pressure induces or intensifies the gel effect. Under these conditions, even a comparatively slight increase in the original DEGBAC concentration alters the direction of the reaction towards the formation of the network product.

The pressure-induced changes in the structure and properties of the prepolymer are inherited on final curing of the composition (curing of the epoxide component) at 0.1 MPa. According to the results of thermomechanical analysis, high glass transition and rubber elasticity temperatures are characteristic of polymers obtained under pressure, but the vitrification temperature range is comparatively narrow. Fig. 8 presents the dependences of T_g for epoxide allyl compositions on the DEGBAC concentration corresponding to different conditions in the synthesis of the prepolymer. The increase in DEGBAC concentration, starting from a certain value, leads to a linear growth of T_g . The change in v induced by an increase in the content of the allyl component and by pressure is correlated with the 'behaviour' of T_g (Table 4).

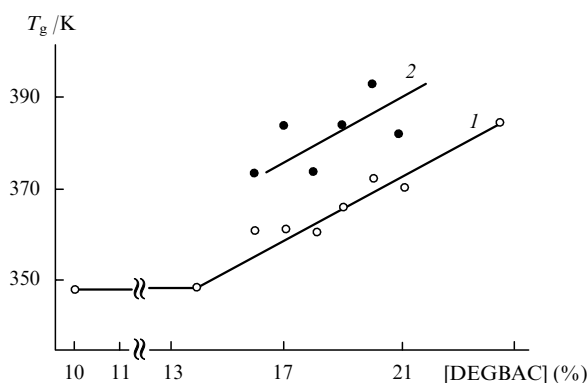


Figure 8. Dependence of the glass transition temperature T_g for epoxide-allyl polymers on the DEGBAC concentration. P (MPa): (1) 0.1 (control specimen); (2) 200.

Table 4. The structures and properties of epoxide-allyl polymers obtained at different pressures.

[DEGBAC] (%)	$10^{-20} \nu$ /cm ⁻³	T_g /K	ΔT_g /K	ΔC_p /kJ kg ⁻¹ K ⁻¹	H_μ /MPa
16	6.0	343	50	0.24	150
	7.8	353	30	0.21	180
	7.0	343	60	0.29	220
17	9.2	358	30	0.21	180
	7.6	343	60	0.38	250
18	9.2	358	20	0.21	185

Note. The quantities above the horizontal line represent the characteristics of the control specimens and those below the horizontal line represent the characteristics of the specimens obtained using a pressure of 200 MPa.

The study of the relaxation and thermophysical properties of the polymers obtained at DEGBAC concentrations ensuring the formation of type IPN polymer–polymer structures demonstrated the following. In the region of T_g , a symmetrical tan δ

maximum and a jump in heat capacity (ΔC_p) are observed. Higher values of T_g , a narrower vitrification range (ΔT_g), and lower values of ΔC_p have been noted in pressure-modified polymer compositions.

The existence of a single glass transition temperature and its linear dependence on the concentration of the allyl component in the compositions investigated indicate a high degree of interpenetration of the epoxide and allyl polymers.^{97,98} The influence of pressure on the change in the compatibility of the networks and the morphology of the polymers is difficult to trace for such systems. Nevertheless, the experimental results permitted a series of conclusions. The characteristic differences between the values of T_g , ΔT_g and ΔC_p for the polymers (Fig. 8 and Table 4), associated with the use of a high pressure in the prepolymerisation state, indicate the presence of a modifying effect of the pressure. Pressure affects primarily the degree of polymerisation of DEGBAC: for identical original concentrations of the allyl monomer, a higher degree of conversion of the prepolymer synthesised under the conditions of hydrostatic compression is observed and the probability of the formation also of a denser network of chemical bond cross-links therefore increases. In the curing of EO, the differences between the densities of the allyl networks are retained, which is reflected in the values of ν and T_g for the polymers compared.

The uniformity of the polymer structures may be inferred to some extent from the values of ΔT_g and ΔC_p : ΔT_g and ΔC_p diminish with increase in homogeneity.⁷⁶ Hence it follows that pressure promotes the homogenisation of the structures of polymer compositions. This is indicated also by the results of small-angle X-ray scattering studies: the scattering intensity in the case of specimens obtained using hydrostatic pressure is much lower than in the control specimens (Fig. 9). This effect may be induced by different causes, for example, by the extensive penetration of the EO into the allyl network in the preparation of the prepolymer under a high pressure and also by the formation of a less defective allyl network. Ultimately the factors considered improve the compatibility of the networks.

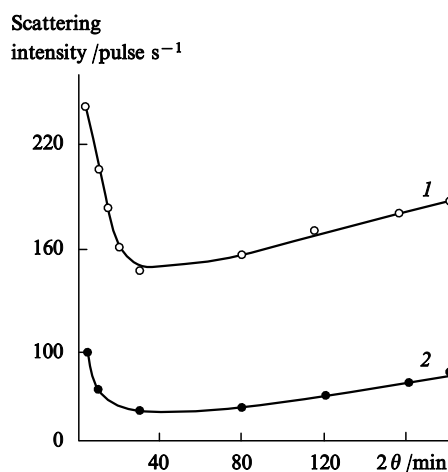


Figure 9. Results of the study of epoxide-allyl polymers (DEGBAC content 18 mass%) by the small-angle X-ray scattering method for prepolymerisation at different pressures (MPa): (1) 0.1; (2) 200.

The results of the measurements of the microhardness H_μ , which serves as a measure of the local plasticity (Table 4) agree with this conclusion. The lower values of H_μ for the pressure-modified polymers may be induced by the plasticisation phenomenon caused by the increase in the compatibility of the networks.⁹⁹

3. Preparation of oligomeric products by fusion under pressure

The modifying effect of pressure may be used not only for the preparation of network polymers and polymer-polymer systems but also in the synthesis of their reactive components. The effect of hydrostatic pressure on the fusion of the epoxybisphenol A resin ED-22F and bisphenol A has been examined¹⁰⁰ and a study has been made of the fractional composition of the reaction product. In a study of the fusion kinetics, use was made of the method involving the titration of the reaction groups: the epoxide (E), alcoholic OH (A), and phenolic OH (P) groups. The fractional composition was studied by the gel-chromatographic method.

Figure 10 presents typical chromatograms of the reaction product obtained on fusion of the epoxide resin for 1 h. The assignments of the peaks are presented in Table 5. The influence of the duration of exposure and pressure on the fractional composition of the epoxide resins is reflected in the data in Table 6 and the change in the molecular parameters is reflected in the data in Table 7.

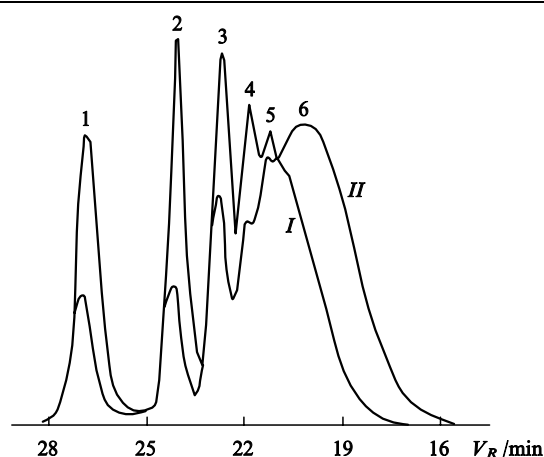


Figure 10. Chromatograms of the product of the fusion of an epoxide resin with bisphenol A. *P* (MPa): (I) 0.1; (II) 100; the numerals opposite the curves represent the numbers of the peaks in Table 5.

Table 5. The retention times (τ), the degrees of polycondensation (m), and the molecular masses of the product of the fusion of an epoxide resin with bisphenol A (Fig. 10).

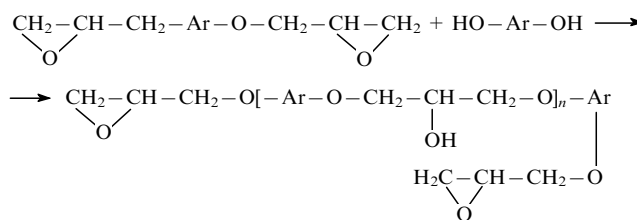
No. of peak	τ /min	m	M	No. of peak	τ /min	m	M
1	26.9	0	340	5	21.5	4	1476
			—				1364
2	24.2	1	568	6	20.2	5	1592
3	22.8	2	908		19.4 ^a	7	1936
			796		18.2 ^a	10	2620
4	22.0	3	1136		17.0 ^a	14	3532

^a These polymeric products are not represented by individual peaks on the chromatogram but are 'located' in the tail part of peak No. 6.

^a These polymeric products are not represented by individual peaks on the chromatogram but are 'located' in the tail part of peak No. 6.

Despite a certain scatter of the parameters presented in Table 7, the acceleration of the process by the pressure can be clearly traced. Pressure leads to an increase in the proportion of the high-molecular fractions and in the degree of polycondensation (Table 6). On the other hand, an integral parameter such as polydispersity changes comparatively little.

The synthesis (chain growth) under pressure of oligomeric products may be represented by the following simplified scheme:¹⁰¹⁻¹⁰⁵



It may be accompanied by a side reaction — chain branching:

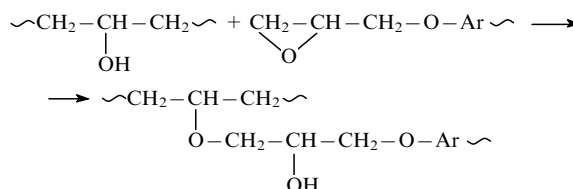


Table 6. Variation of the fractional composition of epoxide resins in the course of their synthesis.

Time /h	Content of fraction (%) for different degrees of polycondensation							
	0	1	2	3	4-6	7-9	10-13	≥14
1.00	17.9	19.0	19.6	14.9	23.9	4.1	0.6	—
	8.8	8.0	13.5	16.8	28.0	15.5	7.6	1.8
1.25	15.8	17.4	22.0	6.6	32.2	5.2	0.8	—
	8.0	6.0	14.0	19.0	27.1	15.8	8.0	2.1
1.50	14.6	16.5	18.3	14.1	29.7	5.8	1.0	—
	7.9	5.5	13.7	20.4	25.9	16.0	8.1	2.5
1.75	12.9	15.0	17.0	15.1	32.3	6.5	1.2	—
	7.5	5.4	13.4	21.1	25.5	16.1	8.2	2.8
2.00	10.7	14.4	16.2	14.5	36.0	6.8	1.4	—
	7.4	5.3	14.5	20.8	24.6	16.2	8.2	3.0
2.50	8.6	12.3	15.0	12.3	43.3	7.0	1.5	—
	7.3	5.1	13.3	22.2	24.4	16.3	8.3	3.1

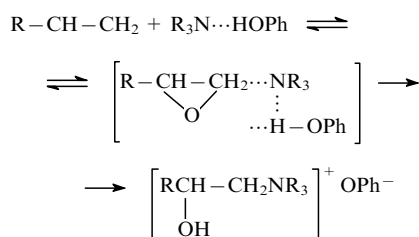
Note. Here and in Table 7 the quantities above the horizontal line were obtained for the control specimens and those below it refer to specimens synthesised at 100 MPa.

Table 7. Kinetic parameters of the synthesis and the molecular parameters of the epoxide resins obtained.

Time /h	$10^4 \ k$ /s $^{-1}$	b	$\bar{M}_n$	$\bar{M}_w$	$\bar{M}_z$	U	$\bar{f}_n^E$	$\bar{f}_w^E$	$\bar{f}_n^P$	$\bar{f}_n^A$
0.5	1.1	0.15	—	—	—	—	—	—	—	—
	1.4	0.04	—	—	—	—	—	—	—	—
0.75	1.1	0.15	—	—	—	—	—	—	—	—
	1.5	0.04	—	—	—	—	—	—	—	—
1.00	1.1	0.16	799	1100	1387	1.4	1.6	2.2	1.1	1.4
	1.6	0.04	1059	1548	1968	1.4	1.4	2.0	0.8	2.6
1.25	1.1	0.16	863	1215	1547	1.4	1.6	2.2	1.1	1.6
	1.6	0.04	1100	1600	2020	1.5	1.2	1.8	0.6	2.9
1.50	1.1	0.17	867	1227	1562	1.4	1.5	2.1	1.0	1.7
	1.5	0.04	1100	1600	2000	1.5	1.2	1.7	0.5	2.7

Note. The average molecular masses (the number-average $\bar{M}_n$, the mass-average $\bar{M}_w$, and z -average $\bar{M}_z$ molecular masses) were calculated using chromatographic data, while the average functionalities were obtained from the formulae $\bar{f}_n^E = \bar{M}_w c_E / 1000$, $\bar{f}_w^E = \bar{M}_z c_E / 1000$, $\bar{f}_n^P = \bar{M}_n c_P / 1000$, and $\bar{f}_n^A = \bar{M}_n c_A / 1000$, where c_E , c_P , and c_A are the concentrations of the E, P, and A groups in the polymer blend. The selectivity is designated by b .

It is believed¹⁰⁵ that the polar complex tertiary amine (R_3N)–phenol (HOPh) interacts with the epoxy-group in the main reaction and that the reaction proceeds in accordance with the scheme

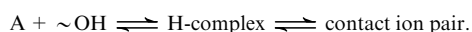


The kinetics of this process are described by the second-order equation

$$-d[E]/dt = k[E][R_3N]_0,$$

because the concentration of the reaction complex $R_3N \cdots HOPh$ is determined exclusively by the concentration of the tertiary amine. Bearing in mind that $[R_3N] = \text{const}$ in the course of the reaction,¹⁰² the process considered may be described by a first-order kinetic equation for the specified R_3N concentration.

In reality the process is much more complicate, because the complexes P_m , P_mE , and P_mA ($m = 1 - \infty$), where m is the degree of association of the phenol in the complex and A is the amine, are formed reversibly in the system. The complexes P_mA with $m = 1$ and 4 are reactive. All these features significantly complicate the kinetic description of the fusion process because H-complexes and (or) contact ion pairs may be regarded as the reactive species in the chain propagation and branching reactions:¹⁰²



The low acidity of the alcohol formed in the chain propagation reaction precludes its competition with phenol in the complex formation process. For this reason, the side reaction is hindered in the presence of phenol and may be neglected to a first approximation.^{101–103}

Table 7 presents the effective reaction rate constants (k) calculated from the consumption of the epoxy-groups (a first-order equation). Evidently, the approximate constancy of k is observed under the conditions investigated. This factor confirms the hypothesis that the main contribution to the rate of the given reaction comes from the amine–phenol complexes and not from the free ions.¹⁰²

The fact that the formal-kinetic descriptions of the reactions at 0.1 and 100 MPa are the same may be interpreted as evidence in support of the constancy of the mechanisms of these processes in the system investigated. This permits the employment of the known pressure dependence of k (Zhulin¹⁰⁶) for the calculation of the volume activation effect ($\Delta V_0^\ddagger$) corresponding to atmospheric pressure:

$$\log \frac{k_P}{k_0} = -\frac{\Delta V_0^\ddagger \Phi}{T},$$

where Φ is a function of pressure. With the aid of this relation and the values of k presented in Table 7 $\Delta V_0^\ddagger = -12.0 \text{ cm}^3 \text{ mol}^{-1}$ was found. The value of $\Delta V_0^\ddagger$ obtained differs significantly from that established for the analogous polycondensation process:⁶⁷ $\Delta V_0^\ddagger = -27.0 \text{ cm}^3 \text{ mol}^{-1}$ (interaction in the epoxide–amine system with formation of a network polymer). Consequently the influence of pressure on the interaction in the epoxide–phenol system is appreciably weaker than in the epoxide–amine system, which may be associated both with the differences in the transition states and with the solvation of the transition state in the epoxide–phenol system by oligomeric molecules, which may play the role of a ‘solvent’ (the volume activation effect for the viscous flow of such a solvent is positive¹⁰⁶).

Using the approach based on the cascade theory of branching processes,¹⁰⁷ the selectivity of the process investigated was estimated¹⁰⁰ as the ratio of the rate constants for the side and main reactions. It was established that the synthesis of epoxide resins under the conditions of hydrostatic compression improves the selectivity significantly.

IV. Solid-state extrusion of polymers and polymer composites

1. Crystallisable polymers

Porter and coworkers were some of the first investigators who studied solid-state extrusion.^{108, 109} They achieved the extrusion of PE through a capillary viscometer at temperatures close to the melting point. The transparent ultraoriented fibre thus obtained was characterised by high moduli of elasticity. In order to obtain a continuous oriented thread with the aid of a capillary rheometer, in a later study¹¹⁰ PE was crystallised under pressure, after which it was extruded at $T < T_m$. This resulted in the appearance of a rigid strengthened fibre.

The structure of the polyethylene fibres obtained by solid-state extrusion is microfibrillar and is in the main similar to the structure produced in the usual stretching. The main bunch of microfibrils (fibrilla) is ribbon-shaped. The microfibrils are linked sideways by penetrating chains, which has been confirmed by X-ray investigations.¹¹¹ The amorphous component of the extruded specimens is also oriented, although to a lesser extent than the crystalline component. The maximum orientation of the amorphous phase is attained at extrusion temperatures close to the α -relaxation temperature.¹¹²

The properties of the extruded fibres depend both on the extrusion conditions (extrusion temperature; draw ratio $\lambda = d_b^2/d_d^2$, where d_b^2 and d_d^2 are respectively the diameters of the billet and the calibrating aperture of the die; the geometry of the deforming instrument) and on the original morphology of the polymer. It has been shown for HDPE that there is an optimum ratio between the CEC and CFC in the original material, which makes it possible to obtain the best set of mechanical properties. On the other hand, the maximum tensile modulus of elasticity is attained on extrusion in the vicinity of the α -process temperatures.²⁵ An increase in external pressure also corresponds to an increase in the modulus of elasticity.¹¹³ The tensile strength is determined mainly by the value of λ .²⁵

The solid-state extrusion method, used to obtain ultraoriented fibres, may be employed also for the preparation of films, which are likewise characterised by effective mechanical properties.¹¹⁴ The solid-state coextrusion process has been frequently used in recent years for the uniaxial stretching of films.^{115–117} HDPE is usually the material of the shell in which the film is placed. The choice of HDPE is determined primarily by its satisfactory deformability.

The characteristic features of the solid-state extrusion of block specimens of isotactic polypropylene have been investigated.^{118, 119} The authors proposed a scheme for the process dynamics, incorporating nonstationary and stationary extrusion. The description of the process includes relations agreeing satisfactorily with experimental data. Within the framework of the chosen approach,¹¹⁸ taking into account the occurrence of the marked orientational strengthening of polymers, the formation of spiral defects on extrusion with high draw ratios λ becomes understandable.¹²⁰ For such values of λ , the yield point (σ_y) becomes close to the ultimate tensile strength (σ_t) and any local inhomogeneity in the flow leads to the rupture of the extrudate.

A new series of publications on this question appeared in connection with the development of the hydrostatic extrusion method. When a liquid is used to transmit a high pressure, the most favourable conditions are created for solid-state moulding and it is possible to obtain rod-like and tubular articles with different profiles and a satisfactory quality of the surface and performance properties.¹²¹

The vast majority of studies on hydroextrusion have been carried out in relation to PE (see, for example, Refs 120 and 122–132). The very significant role of the technological process parameters, particularly extrusion temperature, the rate of deformation, and the angle of the drawing die (α) has been noted. It has been established^{126, 128} that the most favourable deformation regime is the creep regime, in which the rate of emergence of the extrudate is $\sim 1 \times 10^{-3} \text{ m s}^{-1}$. The extrusion temperature range may be fairly broad but not unduly close to the melting point, where there is a possibility of the sticking of the material on the deforming instrument owing to its local fusion. At the same time, there is an optimum extrusion temperature for each draw ratio λ , which makes it possible to achieve the maximum effect (improvement of mechanical properties) due to orientation.

The data for the optimum value of α are contradictory,^{123, 128, 133} but it is at least clear that it is in the range $20^\circ \leq \alpha \leq 60^\circ$. For low conical angles of the discontinuity, the nonuniformity of the distribution of deformations on the cross-section of the extrudate is small, but, owing to the increase in the contact area, there is an increase in the friction of the billet against the die, which increases the extrusion pressure. For large angles, there is an increase in the nonuniformity of the distribution of the deformations, which promotes an increase in the extrusion pressure and has an unfavourable effect on the distribution of properties over the cross-section of the extrudate.

With increase in λ , the variation of the density of the extruded PE passes through a minimum,^{124, 126} the modulus of elasticity, the strength, and the hardness increase, while the plasticity diminishes.^{25, 31, 124, 128} It is noteworthy that the increment in the tensile modulus of elasticity induced by hydroextrusion with high draw ratios, may exceed two orders of magnitude, while the stress may exceed one order of magnitude.¹²⁸ The capacity for strengthening is determined to a large extent by the molecular mass: in high-molecular PE, the increment in the modulus of elasticity is smaller than in low-molecular PE for the same technical parameters of the hydroextrusion process.^{31, 124, 128} Together with the change in mechanical properties, an improvement of dielectric parameters has been noted for extrudates. Thus it has been observed¹²⁸ that the extruded HDPE is characterised by a greater resistance to the formation of incomplete electrical breakdown channels compared with the original material. This parameter increases with increasing draw ratio.

The study of the structures and properties of PE made it possible to put forward the following mechanism of the structural transformations in the hydroextrusion process.^{120, 127} For low values of λ , the material has a typical fibrillar structure with slightly skewed crystallites and intra- and inter-fibrillar layers. With increase in λ , the crystallites become thinner in a transverse direction, are displaced relative to one another in the direction of the extrusion axis, the fraction of the interfibrillar amorphous layers diminishes, and the layers are partly drawn into the fibrils. On further increase in λ , the interfibrillar layers vanish and a structure made up of layers perpendicular to the extrusion axis arises. Dense interfibrillar strands of the type of CEC appear in the amorphous sections. The increase in the modulus of elasticity for small and moderate draw ratios is due to the increase in the degree of orientation of the structural elements considered and in the degree of crystallinity, but for high values of λ it is caused by the uniform distribution of the mechanical load over all the fibrils and by the growing role of the increasing number of intercrystallite strands. Overall, the proposed mechanism agrees with that discussed by Ciferri and Ward.³¹

Fairly numerous studies have been carried out on the hydroextrusion of PP. Features in the main similar to those characteristic of PE have been established for this material.^{134, 135} In contrast to PE, the limiting draw ratios are significantly smaller for PP ($\lambda < 6$). A high degree of die swell (elastic recovery), characteristic of PP, reaching more than 30% for low values of λ , has also been noted.¹³⁴

The characteristic features of the hydroextrusion process and the properties of the extrudates have been investigated to a lesser extent for other representatives of the class of amorphous-crystalline polymers. The results of studies carried out on PTFE have been published.^{136, 137} The variation of the strength and elastic properties of fluoro-plastics as a function of the extrusion conditions obeys the same rules as in the case of other polyolefins, but the limiting degree of deformation on hydroextrusion does not exceed 4. The elastic and strength parameters for extension in the direction of the extrusion axis increase by a factor of 1.2–3.5. The breaking stress and tensile strength in the transverse direction also increase compared with the undeformed material. Extruded fluoro-polymers virtually lack cold fluidity.

The density, the mechanical properties in extension, and the linear coefficient of thermal expansion along the extrusion axis of hydroextruded poly- ϵ -caproamide have been investigated as a function of ratio.¹³⁸ The distribution of the densities of the axial and shear deformations has been obtained and comparative analysis of the experimental and calculated data on the extrusion pressure and the distribution of the deformations in the extrudates has been carried out.

An important performance characteristic of the oriented polymers is thermal shrinkage or the degree of recovery of the original dimensions (the shape memory effect). For HDPE, it does not exceed 10% and diminishes with increase in λ .¹²⁸ In the case of low-density polyethylene (LDPE), the degree of recovery is much greater: for low values of λ , it can reach $> 50\%$.¹²⁰ Numerous studies of the characteristic features of the thermal shrinkage of oriented specimens of crystallisable polymers have been carried out, but they were virtually all performed on films or fibres. The shrinkage characteristics and the shrinkage mechanism have been examined in detail for block specimens¹³⁹ in relation to LDPE deformed by hydroextrusion.

It was established that the thermal shrinkage of extruded LDPE specimens is a relatively rapid process in which the degree of shrinkage (ψ) increases with increase in the annealing temperature and with decrease in the extrusion temperature. Comparison of the maximum values of ψ for oriented PE films and specimens obtained by the hydroextrusion method showed that the latter exhibit a greater shape stability.^{140–143} The changes in the maximum shrinkage stresses ($\sigma_{m.sh}$) and linear dimensions of LDPE as a function of λ and extrusion temperature are similar (Fig. 11). The shrinkage stresses vanish completely at temperatures corresponding to the fusion of the crystallites in the oriented LDPE.

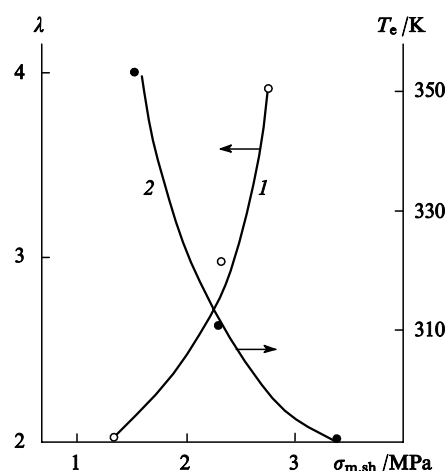


Figure 11. Relations between the draw ratio λ , the extrusion temperature T_e , and the maximum shrinkage stresses $\sigma_{m.sh}$ for LDPE. (1) $\sigma_{m.sh}(\lambda)$, $T_e = 313 \text{ K}$; (2) $\sigma_{m.sh}(T_e)$, $\lambda = 4$.

During the orientation of LDPE, layered structures consisting of crystalline lamellae arranged perpendicular to the direction of stretching, arise in the extrudates. Stressed tied chains or clusters also appear as a result of the orientation. Heating of the oriented specimens shortens the extended macromolecules or parts of them: under the influence of entropy factors, the crystalline framework is transformed, which makes possible the shortening of the molecules.^{140, 142, 144} The higher the temperature, the easier is the slip of individual sections of the macromolecules in the amorphous-crystalline polymer. With increase in extrusion temperatures, the number of stressed tied chains therefore diminishes, which decreases the stress and the degree of shrinkage. The decrease is caused primarily by the disappearance of the stressed tied chains in the defective crystallites, the disruption of which requires a low activation energy. At the same time, the displacement of the maximum on the temperature dependence of the shrinkage stress towards higher temperatures, which occurs with increase in the extrusion temperature,¹³⁹ is induced by the appearance of layers consisting of crystallites with increased transverse dimensions, the disruption of which requires a higher activation energy.

Yet another factor determining the structural rearrangement on heating of the extruded LDPE is the increase in the thickness of the lamellae during the annealing process. Individual segments are then 'drawn' into the body of the lamella, which induces the deorientation of the crystalline blocks and the appearance of internal stresses.^{145, 146}

All the results examined above for the solid-state extrusion of crystallisable polymers were obtained in the extrusion of low-porosity monolithic billets. When highly-porous polymeric billets are employed, a kind of anisotropic structure, which makes it possible to achieve a state with a negative Poisson ratio (μ), may be formed in the extrudates.^{147–149} The microstructure of such materials consists of grains joined by fibrils. These materials are interesting for a number of reasons: firstly, the effect of the negative μ may be used directly in clamps and seals; secondly, the presence of this effect influences favourably other mechanical properties, for example, the modulus of shear, the resistance to indentation, *etc.*^{150, 151} Finally, the complex microstructures responsible for the establishment of a negative μ may induce also other unusual phenomena associated with internal rotational degrees of freedom.^{152, 153}

Not only monolithic but also powder billet may be subjected to solid-state extrusion. Strips, which were subsequently placed in HDPE were prepared from superhigh-molecular polyethylene (SHMPE) powder^{154, 155} by pressing at elevated temperatures ($T < T_m$). Next the coextrusion process was carried out. Thus a highly modular high-strength state was achieved for the SHMPE. For example, the tensile modulus of elasticity achieved in one of the above investigations¹⁵⁵ amounted to ~ 60 GPa.

An even greater rigidity was attained on further stretching of the extruded materials by uniaxial extension. According to the data of Kanamoto *et al.*,¹⁵⁶ the modulus of elasticity of such films exceeded 100 GPa. Porter¹⁵⁷ obtained from powdered PTFE by the solid-state coextrusion method strips having a modulus of elasticity and an ultimate tensile strength of 3.2×10^4 and 3×10^3 MPa respectively. Oriented films have been obtained similarly¹⁵⁸ from polyacrylonitrile powder. They had effective strain–strength characteristics.

The difficulty of the process in which a polymeric billet is converted into a monolithic material, to be subjected to extrusion may in many instances render solid-state extrusion economically unjustified. This concerns particularly polymers with a high viscosity of the melt or reinforced compositions for which traditional highly productive processing methods (conversion of the billet into a monolithic material) are unsuitable. The solid-state extrusion method proposed in two investigations^{159, 160} makes it possible to solve this problem. The procedure includes the following operations: compaction of the powder billet at room temperature, free heating of the billet, and extrusion using a heated high-

pressure container and die. The process is fairly productive, since it can be made quasi-continuous, whereupon each successive billet, expels the mould residue from the preceding one.

It has been established empirically that the optimum extrusion temperature range for the extrusion of materials such as SHMPE is $(0.94–0.96)T_m$,¹⁶¹ while for the polyetherketone based on isophthalic and terephthalic acids (brand PKIT) it is $(0.95–0.98)T_m$. At lower temperatures, the extrudates are obtained in a nonmonolithic form whilst at higher temperatures the polymer sticks to the deforming instrument, inducing an increase in the extrusion pressure and the formation of an uneven surface on the articles obtained (SHMPE) or the cracking of the extrudates (PKIT).

With increase in the degree of extrusion, the moduli of elasticity of the polymers considered increase and the increment in the modulus of elasticity for the flexible-chain polymer (SHMPE) is greater than for the semirigid-chain polymer (PKIT) (Table 8). The extrusion-induced changes in σ_t are small in both cases. At the same time, the plasticity diminishes with increase in the draw ratio. The results of mechanical tests on extruded SHMPE specimens are consistent with the familiar rules established for flexible chain crystallisable polymers,^{126, 128} namely the increase in the modulus of elasticity is faster than the increase in the strength parameters associated with orientational extrusion. The conditions in the plunger extrusion of a polymeric powder billet differ fundamentally from the conditions in the traditional variants of solid-state extrusion and we shall therefore consider in greater detail the dynamics of the formation of the oriented structure in the extruded SHMPE specimens.

Figure 12 presents the dependence of the degree of crystallinity of SHMPE specimens on the draw ratio, obtained from

Table 8. The properties of polymer specimens obtained by the plunger extrusion of a powder billet.

Polymer	λ	$10^{-3}E$ /MPa	σ_t /MPa	ε_t^a (%)
PKIT brand	1.0	2.0	80	—
	1.7	2.4	75	—
	2.3	2.5	70	—
	2.8	2.6	73	—
SHMPE	1.0	0.6	28 ^b	9.7 ^b
	3.0	0.7	32	11.7
	4.0	0.8	30	11.0
	5.0	1.1	30	10.0
	6.0	1.2	34	10.6
SHMPE–kaolin	1.1	0.7	31 ^b	10.0 ^b
	2.0	0.6	28	11.8
	3.0	0.7	31	10.0
	4.0	0.8	41	10.3
	5.0	0.9	40	9.2
	6.0	1.3	43	7.1
	7.0	1.5	47	7.0
SHMPE–Al	1.0	0.7	26 ^b	8.1 ^b
	3.0	0.8	37	7.4
	5.0	1.2	41	5.3
	6.0	1.1	40	5.4
	7.0	1.1	38	4.8
	9.0	0.9	34	6.1
SHMPE–Al(OH) ₃	1.0	0.7	14 ^b	4.5 ^b
	3.0	0.8	19	3.0
	4.0	0.9	22	3.5
	5.0	0.8	17	3.0
	6.0	0.8	16	2.5
	7.0	0.4	13	4.9

^a ε_t is deformation at the rupture point; ^b σ_y and ε_y are quoted respectively instead of σ_t and ε_t .

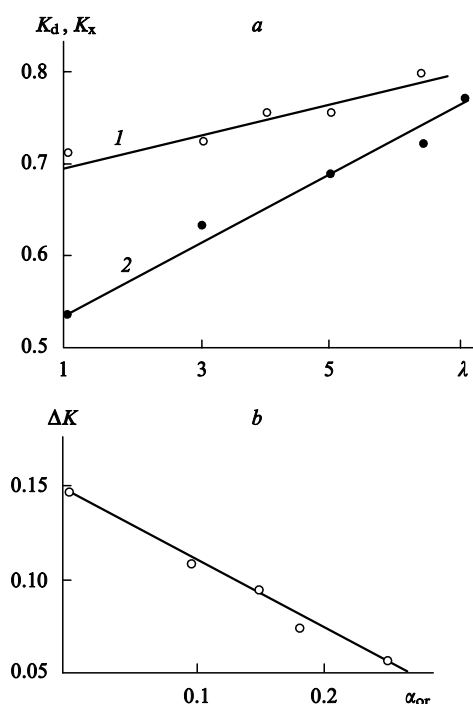


Figure 12. Dependences of the degrees of crystallinity K_d (1) and K_x (2) on the draw ratio λ (a) for SHMPE and of ΔK on the increment in the crystalline phase α_{or} (b).

X-ray data (K_x) and from density measurements (K_d).¹⁶² Evidently the absolute values of the X-ray degree of crystallinity are smaller than those found from the measurements of ρ . The observed difference between the values of K_x and K_d agrees with the available literature data^{163,164} and can have two explanations. According to Egorov *et al.*,¹⁶³ X-ray diffraction analysis yields the so called 'geometrical' degree of crystallinity, because the macromolecules arranged parallel to one another but without a three-dimensional order are detected by this method as disordered regions. On the other hand, in dilatometric measurements they can contribute to the crystalline phase. Mandelkern¹⁶⁴ expressed a different view, according to which the difference under discussion is caused by the presence of interfacial regions possessing a partial degree of order. In these regions, there is a smooth transition from long-range order (crystalline phase) to disorder (amorphous layers). Thus the quantity $\Delta K = K_d - K_x$ defines the fraction of either oriented macromolecules in the noncrystalline regions or the fraction of interfacial regions.

An increase in λ leads to an increase in the degree of crystallinity of SHMPE (Fig. 12), *i.e.* crystallisation due to orientation take place. The increment in the crystalline phase (α_{or}) can be expressed by the difference between the degrees of crystallinity (ΔK) corresponding to an arbitrary λ and $\lambda = 1$. The quantity K_x yields the true characteristic of the orthorhombic crystalline phase without taking into account the partial order in the noncrystalline regions and, by virtue of this factor, is accurate. It is therefore used to determine α_{or} . The parameter ΔK may be treated as the decrease in the fraction of oriented macromolecules in the noncrystalline regions¹⁶³ or in the volume of the interfacial regions.¹⁶⁴ Comparison of the data presented in Fig. 12 supports the second version, since, firstly, a decrease in the fraction of stretched through chains with increase in λ is unlikely; secondly, the values of ΔK for the undeformed SHMPE specimens are close to those established earlier by Mandelkern.¹⁶⁴

The $E(\lambda)$ relations for SHMPE¹⁵⁶ and HDPE,¹²⁴ obtained in compressive, bending, and tensile tests, are similar (Fig. 13). Without dwelling on the discussion of the differences between the absolute values of E , we may note that, with increase in λ , one

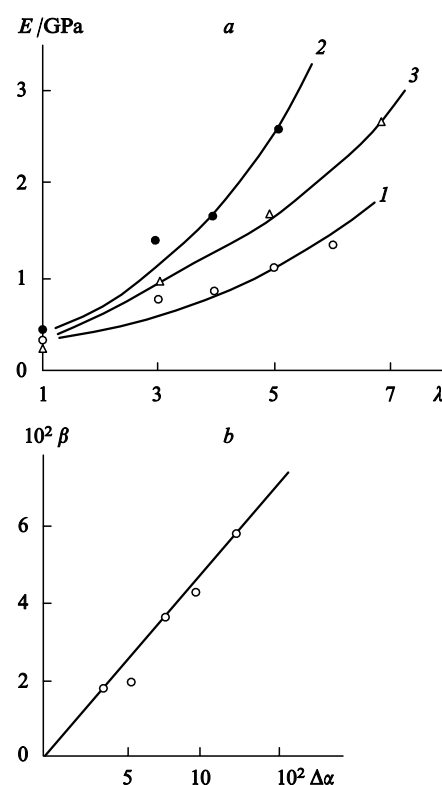


Figure 13. Dependence of the modulus of elasticity E for SHMPE and HDPE on the draw ratio λ (a) and of β on $\Delta\alpha$ for SHMPE (b). (1) SHMPE, compression; (2) SHMPE, bending; (3) HDPE, extension.

observes an increase in E which is steeper than a linear increase. There exist two limiting models describing the distribution of stresses in the oriented amorphous-crystalline monomers.³¹ In the first, one postulates a uniform distribution of stresses in the crystalline block, where the tied chains are fairly uniformly distributed among the microfibrils formed in the stretching process. In the second, one postulates the complete independence of the tied chains and the crystalline blocks, the internal regions of the crystals alternating with amorphous layers which do not contain tied chains. The $K(\lambda)$ relations of the type presented in Fig. 12a correspond to the first model.³¹ In this case, the volume fraction of the volume (β) occupied by tied chains is calculated by means of the simplified Takayanaga formula³¹

$$\beta = \frac{E}{E_{ax}(1 - K_x)},$$

where E_{ax} is the axial modulus of elasticity of the crystalline component.

Figure 13b presents the dependence of β on the fraction of the crystallised interfacial regions $\Delta\alpha$. The moduli of elasticity calculated from the results of compressive tests were adopted as E . A linear relation, passing through the origin of coordinates, is observed between β and $\Delta\alpha$. This means that the interfacial regions participate actively in the formation of the system of tied chains in the extruded SHMPE. The $\beta(\Delta\alpha)$ relation shows that $\sim 45\%$ of the macromolecules in the interfacial regions become tied chains. The result obtained agrees well with theoretical¹⁶⁵ and experimental¹⁶⁶ estimates.

Two components of the crystalline phase may be differentiated for the extruded SHMPE (taking into account the results examined above): the original crystalline phase transformed by deformation and the phase arising as a result of orientational crystallisation. The latter consists of crystallised amorphous sections and crystallised interfacial regions. Analysis of data on

the thermal shrinkage of extruded SHMPE specimens showed¹⁶⁷ that ψ increases with increase in α_{or} and $\Delta\alpha$, the absolute values of ψ and the corresponding α_{or} and $\Delta\alpha$ being similar. The above factors made it possible to postulate the fusion sequence for the components of the crystalline phase. The least perfect crystalline formations, obtained by the orientational crystallisation of the interfacial regions, melt initially. Their relatively high degree of imperfection can be explained by the presence in the interfacial regions of a large number of irregularities in the chains torn away from the crystallites. The next to melt are amorphous regions crystallised in the orientation process in which the number of irregularities is appreciably smaller. Finally, at higher temperatures the original crystalline phase melts. Thus the evolution of different structural components of SHMPE during the extrusion of a powder billet are described satisfactorily within the framework of the model of the three-component structure of the amorphous-crystalline monomer. The mechanism of this process has been examined in greater detail (resorting to fractal analysis and the cluster model of the structure of amorphous polymers) in another study.¹⁶⁸

X-Ray diffraction investigations carried out on extruded PKIT specimens showed that the degree of crystallinity of all the specimens studied is $\sim 40\%$ and changes little with increase in λ from 1 to 3. The specimens are characterised mainly by reflections which correspond to interplanar spacings of 5.71, 3.87, 3.19, and 4.79 Å. This state of PKIT is characteristic of an unstable crystalline modification,¹⁶⁹ *i.e.* the processing conditions are insufficient for a transition to the stable crystalline form having four principal reflections with interplanar spacings of 4.79, 3.91, 3.86, and 3.08 Å. Experiments showed that such an equilibrium form is formed on pressing at 623 K. It may be that the retention of the instability of the crystalline modification on extrusion in the temperature range 533–593 K is one of the causes of the insignificant change in the strain–strength characteristics of PKIT.

Porter and coworkers^{157, 170} investigated the processes involved in the solid-state extrusion of a high-molecular PTFE powder billet. The extrusion was carried out in the temperature range 373–613 K until the attainment of the maximum values of λ . It was established that at a temperature below 373 K or above 613 K (this is higher than the melting point, which amounts to 607 K), the process under consideration cannot be achieved. In the range 373 K $< T_e < 553$ K, the maximum value of λ is 10 and depends only slightly on T_e . On further increase in temperature, the limiting value of λ increases rapidly and amounts to 60 for $T_e = 603$ –613 K. The structure and properties of PTFE are determined by the values of λ and T_e . In particular, the dimensions of the crystallites in both parallel and perpendicular directions relative to the extrusion axis increase with increase in λ . The presence of microfibrils, having a transverse dimension (~ 45 nm) greatly exceeding that usually observed for oriented monomers (6–20 nm), is characteristic of the highly oriented PTFE. The maximum value of the flexural modulus elasticity, corresponding to the optimum extrusion conditions ($T_e = 613$ K, $\lambda = 40$) reaches 20 GPa.

The method involving the solid-state extrusion of a powder billet proved to be fairly effective also in the case of thermoplastic polyimides.¹⁷¹ The transition of the polymers to the molten state induces cross-linking of the macromolecules, which hinders their further processing. On the other hand, if the extrusion is carried out below T_m , using billets made up of powders pressed into discs beforehand, then for 563 K $\leq T_e \leq 593$ K it is possible to obtain high-quality articles with a high degree of crystallinity.

2. Glassy polymers

There have been few studies of the properties of flexible-chain amorphous polymers extruded in the solid state. An increase in E and σ_t with increase in λ is observed for polymeric materials of this class, as for the amorphous-crystalline polymers, although it is not quite so pronounced. A distinctive feature of the flexible-chain amorphous polymers is that their plastic characteristics increase

appreciably as a result of extrusion. For example, the deformation at the rupture point (ε_r) of poly(methyl methacrylate) subjected to tensile tests increased from several per cent for the control specimens to tens per cent for the extrudates.¹⁷² A severalfold increase in impact strength has been noted for impact-resistant polystyrene.¹⁷³ The sharp increase in the plasticity of these polymers is attributed to the orientation of the molecular chains along the extrusion axis and the breaking away of side chains.^{172–174}

The mechanical properties of polymers extruded in the solid state and of low-molecular substances, for example, metals, differ. The dependence of the strain–strength characteristic of oriented polymers on λ is determined to an appreciable extent by the scheme underlying the stressed state chosen in the test. Whereas on extension of polymers many investigators have noted an increase in the elastic and strength parameters with increase in the degree of orientation of the specimens, on compression the reverse effect is frequently observed or there are relations with a minimum. This applies both to crystallisable and flexible-chain amorphous polymers (Fig. 14).¹⁷⁵

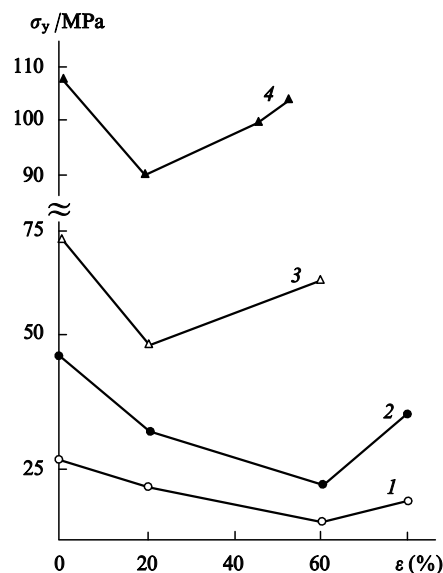


Figure 14. Dependence of the yield point σ_y in compression on the degree of deformation (ε) for polyethylene (1), polypropylene (2), poly(vinyl-chloride) (3), and poly(methyl methacrylate) (4).

The characteristic features of the solid-state extrusion of rigid-chain amorphous polymers have been scarcely investigated. In this connection, a definite interest attaches to data obtained in a study¹⁷⁶ of the influence of the deformation by hydroextrusion on the structure and properties of such materials in relation to the polyketones PAEKN (the product of the polycondensation of 4,4'-difluorobenzophenone and bisphenol A) and PAEKF (the product of the polycondensation of 4,4'-difluorobenzophenone and phenolphthalein, a card polymer). Table 9 presents the parameters of the hydroextrusion process: λ , T_e , the extrusion pressure P , and the properties of the extruded polyketones in compressive and microhardness tests. Evidently the pressure diminishes with increase in the extrusion temperature and increases with increase in the extrusion draw ratio. In the case of extrusion at room temperature, the extrusion pressure reaches such high values already at $\lambda > 3$ that the extruded materials are 'shot out' and break up.

Hydroextrusion improves the elastic characteristics of polyketones. For example, the modulus of elasticity of PAEKN increases with increase in λ and diminishes with increase in T_e . In the case of PAEKN, the highest value of E is observed at $T_e = 488$ K. The dependence of the characteristics σ_t and H_μ on

Table 9. The influence of hydroextrusion on the properties of polyketones.

λ	T_e /K	P /MPa	$10^{-3}E$ /MPa	σ_t /MPa	H_μ /MPa
Polymer — polyketone PAEKN					
1.0	—	—	2.0	80	180
2.2	293	800	2.5	70	170
2.4	293	900	3.0	70	165
2.8	293	1100	3.2	70	162
4.2	293	2000	—	—	—
2.5	488	30	3.6	120	237
Polymer — polyketone PAEKF					
1.0	—	—	0.7	56	143
1.8	443	3	0.9	63	135
2.6	443	25	1.1	58	126
1.8	453	1	0.7	55	130
2.6	453	3	0.8	48	122
4.0	453	15	1.0	59	127
6.0	453	27	1.3	64	133
1.8	463	1	0.7	40	135
2.6	463	3	0.7	38	132
6.0	463	17	0.8	50	136

the conditions in orientational extrusion is more complex. For PAEKN deformed at room temperature, these characteristics were lower than for the cast polymer ($\lambda = 1$). On the other hand, the extrusion of this material at an elevated temperature improves significantly the properties indicated. The values of σ_t and H_μ for PAEKF initially fall and then increase as λ increases, but the maximum values of these parameters for the deformed polyketone are smaller (H_μ) or of the same order of magnitude (σ_t) than for the original material. The measurements of the density of PAEKF indicate the compaction of the polymer on deformation. This factor is associated primarily with the decrease in the volume of the pores, which are present in large numbers in the cast PAEKF according to optical microscope data.

The pattern in the scattering of X-rays by specimens of the original PAEKF consists of an amorphous halo. Annealing of the specimens for 2 h at 488 or 523 K with subsequent slow cooling does not alter it. Hydroextrusion at room temperature also does not change the pattern. At $T_e = 488$ K, the separation of the centre of the amorphous halo into two broad low-intensity reflections is observed, which indicates the onset of the crystallisation of the polymer. Cast PAEKF specimens are amorphous. Analysis of the X-ray diffraction data showed that hydroextrusion does not lead to any appreciable changes in the structure of the specimens.

Comparison of the results of mechanical tests and X-ray diffraction studies makes it possible to understand the characteristic features of the changes in the strain–strength properties of the aromatic polyketones studied. The slight increase in E and the nonmonotonic variation of H_μ observed with increase in λ (Table 9) for specimens subjected to hydroextrusion¹⁷⁵ are induced (as for flexible-chain amorphous polymers) by the orientation of polymer chains and the values of these quantities are determined by the degree of orientation and the structure of the polymer. The higher the extrusion temperature, the lower the degree of orientation, other conditions being equal. This is responsible for the low-slope of the $E(\lambda)$ and $H_\mu(\lambda)$ relations observed for PAEKF as T_e increases.

The strength of the polymer is to a large extent determined by the presence of different kinds of defects in it. The presence of a large number of micropores in cast PAEKF specimens and their ‘healing’ (elimination of microdefects) during hydroextrusion probably account for the nature of the $\sigma_t(T_e)$ relation. The effectiveness of the ‘healing’ increases with increase in pressure,⁵⁴ so that σ_t increases with decrease in T_e (this is accompanied by an increase in pressure) (Table 9). The $\sigma_t(\lambda)$ relation corresponds to

the variation of the strength properties of flexible-chain amorphous polymers established by Nakayama and Inoue.¹⁷⁵

It was noted above that the creation of oriented order in crystallisable polymers enhances more significantly their elastic and strength properties than in the case of amorphous polymers. Extrusion with $\lambda = 2.5$ and $T = 488$ K entails the transformation of the amorphous modification of PAEKN into a semi-crystalline modification. This tends to improve the mechanical characteristics of the given material.

The relaxation properties are well correlated with the results of mechanical tests and structural studies. Hydroextrusion increases the original and equilibrium values of the relaxing modulus (E_r) and stress (σ). The highest values of E_r and σ characteristic of PAEKN correspond to the modification with a partially crystalline structure. With the aid of the ideas developed by Askadskii¹⁷⁷ it has been possible to describe in detail the kinetics of the relaxation processes in the extruded aromatic polyketones. In particular, it has been established that the rate of interaction of the relaxators in the extrudates is higher than in the cast materials. This is quite reasonable if relaxators are understood as different kinds of microheterogeneities which are converted into nonrelaxing structures faster the higher the level of internal stresses (the latter naturally increases on deformation).

Large single deformations occurring without the disruption of brittle materials such as network polymers have been achieved as a result of the plasticisation effect during hydrostatic extrusion after the attainment of the oriented state.^{68,75,178–180} EP — characteristic representatives of the class of network polymers — were selected as the object of study in the above investigations. It was established that the solid-state extrusion of EP induces a rearrangement of the structure at different levels of the structural arrangement, which is indicated by the results of NMR studies and optical-microscope studies.⁶⁸ Fig. 15 illustrates the variation of the molecular mobility of the structural fragments of high-crosslinked network EP, characterised by the nuclear magnetic transverse relaxation times T_2 for the mobile (T_{2b}) and more rigid (T_{2c}) ‘kinetic phases’ and also the variation of the fraction of relatively immobile protons (the p_c populations of the relatively

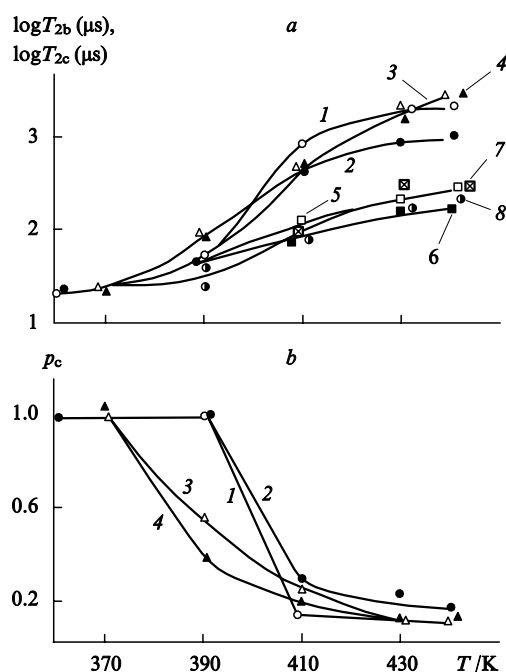


Figure 15. Temperature dependences of the nuclear magnetic relaxation times (a) and the proton population (b) for EP-7. (1)–(4) T_{2b} ; (5)–(8) T_{2c} ; ε (%): (1) and (5) original specimen; (2) and (6) 15; (3) and (7) 30; (4) and (8) 40.

immobile 'kinetic phase') as a function of the degree of deformation (ε) and temperature.

The differences between the kinetic properties of the fragments of the topological structure are induced by the differences between the numbers of degrees of freedom.¹⁸¹ From these standpoints, the more mobile protons (characterised by the values of T_{2b} and p_b) belong to the linear chains between the cross-links and defective fragments of the network — the trifunctional cross-links CL_3 and chain branches. The less mobile protons (characterised by T_{2c} and $p_c = 1 - p_b$) belong to the tetrafunctional cross-links CL_4 . The hierarchy of these fragments in order of decreasing mobility is as follows: linear chains between the cross-links and branches — CL_3 — CL_4 . Mainly the molecular mobility of the more mobile structural elements changes on hydroextrusion (Fig. 15). The decrease in T_{2b} in the case of $\varepsilon = 15\%$ compared with the control specimen may be a consequence of the occurrence of orientational processes. Some of the mobile fragments are converted into the less mobile 'kinetic phase', which is manifested by an increase in p_c at $T > 410$ K compared with p_c for the original material.

For $\varepsilon \geq 30\%$, an increase in T_{2b} and a decrease in p_c are observed. This is apparently associated with the predominance of disordering processes over orientational processes. However, the significant decrease in the 'nuclear' glass transition temperature indicates that the disordering processes are accompanied by the mechanodegradation of the network, in the first place of CL_3 and CL_4 cross-links. The results of thermomechanical studies agree well with NMR data.¹⁷⁸

The microstructure of the undeformed high-crosslinked network EP consists of globule-like formations made up of smaller elements. Hydroextrusion leads to characteristic changes in the morphology of the polymer. For $\varepsilon = 15\%$, the distinct boundaries separating the globules in the original material already vanish. A further increase in ε promotes the obliteration of the relief, which is observed on the etched surfaces of the specimens, bending, crushing, and twisting of the structural elements, and the formation of what resembles an 'eddy' structure.¹⁴

With increase in ε , the modulus of elasticity of the high-crosslinked network EP-7 ($v = 9 \times 10^{20} \text{ cm}^{-3}$) increases strongly in tensile tests and diminishes in compressive tests.¹⁷⁸ For individual specimens, deformed to the extent of 45%, the values of E obtained in extension exceed those for the control specimens by a factor greater than 2. The density varies nonmonotonically, reaching a maximum at $\varepsilon \approx 25\%$. The dependence of the strength parameters on ε , like the dependence on ρ , passes through an extremum (Fig. 16); on extension, σ_y and σ_t vary in parallel. In

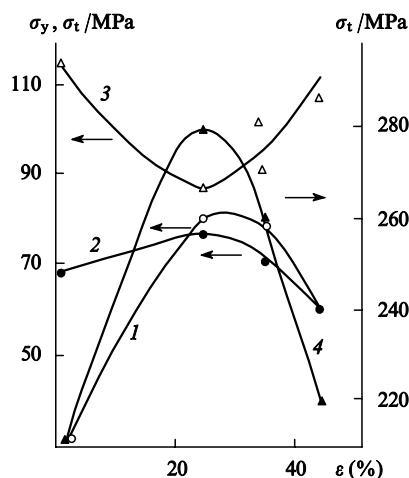


Figure 16. Dependence of the yield point σ_y (1, 3) and the breaking (tensile) stress σ_t (2, 4) on the degree of deformation ε for EP-7. (1) and (2) extension; (3) and (4) compression.

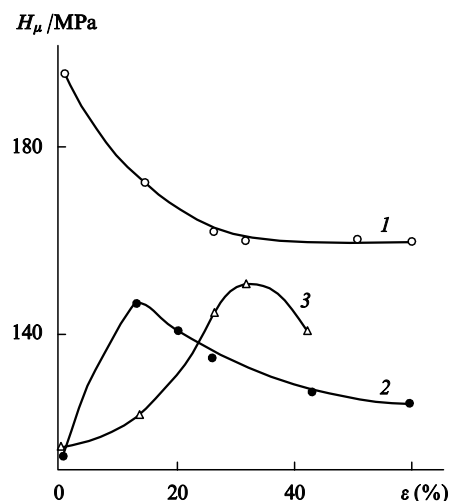


Figure 17. Dependence of the microhardness H_μ on the degree of deformation for EP-7 (1) and EP-5 (2, 3). T_c (K): (1) and (2) 293; (3) 358.

compressive tests, σ_y and σ_t reach minimum and maximum values respectively at $\varepsilon = 25\%$. In both types of tests, ε_r increases and then decreases with increase in ε to 25%, while H_μ decreases monotonically for EP-7 as ε increases (Fig. 17).

The nonmonotonic variation of the $\rho(\varepsilon)$ relation for hydroextrusion is associated with the following factors. Deformation under a high hydrostatic pressure promotes the 'healing' of the micropores formed in the EP curing stage^{25,80} and the orientation of the polymer chains in the direction of the application of force leads under these conditions to the greater ordering of the structure compared with the original structure. All these features are responsible for the increase in ρ . At the same time, as ε increases, the material becomes loosened with formation of interfaces and microcavities and the intramolecular and intermolecular bonds are broken,^{25,182,183} which leads in its turn to the appearance of cracks and a decrease in ρ . The changes in ρ noted above are undoubtedly reflected in the level of the mechanical properties of the hydroextruded polymer. This is indicated by the variation of σ_t and ε_r which is identical with that of ρ in both types of tests. The healing of the microcavities, predetermining to a large extent the strength of the continuous medium, leads to an increase in σ_t and ε_r , while the increase in porosity for $\varepsilon > 25\%$ induces an appreciable decrease in these quantities.

At the same time, the results of mechanical tests cannot be accounted for solely by the change in ρ . As already mentioned, processes involving the orientation of the chains of the macromolecules and mechanodegradation develop in EP on hydroextrusion. The orientation is probably achieved *via* the rotation of the elementary network, leading to the arrangement parallel to the direction of extrusion of the individual sections of the chains between the cross-links. For low values of ε , orientation processes predominate. They are responsible for the appearance in the polymer of internal microstresses, influencing the nature of the subsequent deformation of the specimen in tensile and compressive tests. As a result of the operation of the microstresses, the Bauschinger effect is observed:¹⁸⁴ the preliminary plastic deformation, induced by the extension, decreases the resistance to plastic deformation on compression. The moulding process during hydroextrusion can be regarded to a first approximation as deformation by extension (especially for a small angle of the die cone).³¹ Therefore the decrease in σ_y , observed in compressive tests for specimens with $\varepsilon = 25\%$ compared with the original specimen, may be induced by the identity of the signs of the microstresses in the extrudates caused by the tension in the linear chains between the cross-links, and of the applied stresses. It is noteworthy that the changes established in the mechanical properties of the deformed high-crosslinked polymer network are similar

to the changes in the strain–strength properties of oriented crystallisable and amorphous polymers,¹⁷⁵ which indicates the similarity of the mechanisms of their deformation.

The study of the relaxation properties of the high-crosslinked network EP carried out on the original specimens and the extrudates has shown that, for $\varepsilon = 35\%$ and 45% , there is a sharp increase in molecular mobility induced by the loosening of the material and the partial mechanodegradation of the network.¹⁷⁸ The relaxation of the stress in the deformed polymer proceeds more vigorously than in the control specimen with increase in ε , the stress required for the maintenance of the specified deformation diminishes, the rate of relaxation increases, and the relaxation continues until the attainment of lower stresses. The fitting of the experimental relations with the aid of new relaxation memory functions¹⁷⁷ made it possible to establish that the stress relaxation process in the extruded high-crosslinked network EP is determined with equal probability by the kinetics of the interaction of the relaxators (microheterogeneities) and the kinetics of the diffusion of the nonrelaxators.¹⁷⁸ Compared with the original material, the number of microheterogeneities in the extrudates diminishes.

In order to increase the probability of breaks in the network, experiments have been carried out⁷¹ on the hydroextrusion of an incompletely cured EP-1 epoxide composition. The curing of the specimens was completed after hydroextrusion. It was established that the elastic and strength properties depend only slightly on the degree of the preliminary deformation of the specimens. If the curing processes are not taken to completion, it is possible to detect at $\varepsilon = 50\%$ an increase in E by an order of magnitude compared with the undeformed specimens. Such an increase is induced by the orientation of the EP macrochain along the deformation axis. Probably a state with a high level of elastic and strength characteristics may be achieved for EP under appropriate experimental conditions when the time required for the completion of the curing of the extrudates is significantly shorter than the relaxation time of the oriented structure.

A study of the behaviour of the extruded EP having an open network ($v = 4 \times 10^{20} \text{ cm}^{-3}$) showed¹⁷⁹ that the nature of the dependences for σ_y and ε_r on ε in these materials is the same as for the high-crosslinked network EP. The difference consists only in the absolute values of σ_y and ε_r as well as the values of ε for which a change in the type of variation of σ_y and ε_r is observed; in the open network polymer (EP-5), the increase in σ_y and the fall of ε_r begin for higher values of ε . On the other hand, the dependences of E , σ_y and ρ on ε are qualitatively different. They increase over the entire range of ε . The microstructures of the original EP-5 specimens consist of globule-like formations of different dimensions. Deformation by hydroextrusion homogenises the microstructure and renders it finely disperse. On the other hand, an eddy structure is not formed up to $\varepsilon = 45\%$.

The observed differences between the changes in the microstructure, ρ , and the mechanical properties of the EP compared are associated with the different network densities and mobilities of the linear chains between the cross-links. In the more rigid polymer (EP-7), the plastic deformation processes accompanied by the rupture of the network of chemical bonds begin sooner and proceed more vigorously. In the case of EP with an open network (EP-5), they are scarcely manifested (for the range of ε investigated) in the behaviour of the integral macroscopic characteristics (ρ , E , σ_y , σ_t , ε_r). On the other hand, the use of a local method such as the procedure involving the measurement of microhardness made it possible to follow the evolution of network disruption processes even for low values of ε .¹⁷⁹ Fig. 17 (curve 2) illustrates the variation of H_μ in the extrusion of EP-5 in the glassy state. The nonmonotonic variation of H_μ with increase in ε indicates competition between the orientational strengthening and disordering processes caused by the loosening of the network. In the case of EP-7, in which the degradation phenomena develop sooner, such a maximum in H_μ is probably displaced towards $\varepsilon < 15\%$, and for this reason one observes on the experimental curve only its right-

hand (descending) branch (curve 1). It is logical to suppose that, in creating more favourable conditions for the orientation of the internodal fragments in EP, the maximum under consideration should be observed for larger values of ε . The $H_\mu(\varepsilon)$ relation, presented in Fig. 17 (curve 3), confirms this hypothesis. It was obtained for the EP-5 polymer deformed in the rubbery (non-equilibrium) state with subsequent ‘freezing’ of this state. Under conditions where the mobility of the linear chains between the cross-links increases significantly compared with the mobility of such chains in glassy polymers and the values of ε for which the disruption of the network is possible increase, this is reflected by the displacement of the maximum in the $H_\mu(\varepsilon)$ relation towards higher values of ε .

The behaviour in hydroextrusion of polymers of the IPN type with components differing appreciably in their rigidity is unusual. The results of studies^{179, 180} carried out on the polyurethane–polyesteracrylate (PU–PEA) system suggest that mainly the elastic component (PU) undergoes orientational strengthening. The strengthening effect is achieved because the rigid network (PEA) prevents the relaxation of the stressed PU chains, creating constraints in the form of macromolecular entanglements. At a low PEA concentration, the deformation-induced strengthening, caused by hydroextrusion, is insignificant, because the density of such entanglements is low and the elastic component relaxes readily. With increase in the PEA concentration, the degree of orientational strengthening increases, but mechanodegradation processes begin to be manifested already for a PEA content of 30%. Both elastic and rigid chains are probably disrupted. The latter follows from the fact that, for PU:PEA $\geq 50:50$, the possibility of the deformation of the IPN is reduced sharply.

The proposed explanation is supported by the following features. When the PU:PEA ratio changes from 90:10 to 70:30, the system undergoes phase separation.¹⁸⁵ This makes it possible to consider separately the evolution of the rigid and elastic networks during orientational stretching. It is known that in the solid-state extrusion of materials incorporating plastic and brittle (stronger) components with the former predominating, the weaker and more plastic component undergoes strengthening.¹⁸⁶ Under these conditions the brittle phase may be disrupted with increase in ε . The role of such phases in the PU–PEA composition is assumed by the PU and PEA networks respectively.

The characteristic features of the thermal shrinkage of network polymers have been investigated^{179, 180} in relation to EP and the PU–PEA system. It was established that the recovery of the original dimensions of the extruded EP when they are heated in a free state begins near the glass transition temperature ($T < T_g$) and terminates at $T \simeq T_g$ with attainment of the 100% effect. With increase in ε , the temperature of the onset of shrinkage diminishes. In contrast to linear amorphous and crystallisable polymers, network polymers have a narrower shrinkage temperature range and are characterised by the ability to retain the restored form at temperatures significantly exceeding T_g . The latter is known to be due to the presence of a network of chemical cross-links preventing the transition to the viscous flow state. The temperature of the onset of shrinkage is correlated with T_g (Fig. 18).

When extruded specimens with fixed ends are heated, the shrinkage stresses originally increase and then fall, this being accompanied by the disruption of the specimens in the vicinity of the clamps (Fig. 19). The maximum shrinkage stresses increase with increase in ε and v . The latter fact reflects the $\sigma_{m,sh}(T_g)$ relation (Fig. 18), since v and T_g vary in parallel in the case under consideration.¹⁸⁰ It is remarkable that the values of $\sigma_{m,sh}$ are approximately the same as for oriented block specimens of amorphous-crystalline polymers.

The characteristic features of the variation of the size of the oriented PU–PEA specimens during heating are on the whole similar to those established for EP: the shrinkage temperature range is comparatively narrow, the recovery of the original dimensions reaches 100%, and $T_{o,sh}$ diminishes with increase in ε . The temperature range in which the characteristic $\sigma_{sh}(T)$

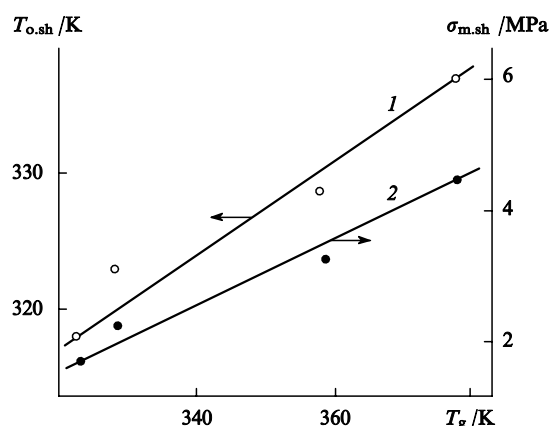


Figure 18. Dependence of the temperature of the onset of shrinkage $T_{o.sh}$ (1) and of the maximum shrinkage stresses $\sigma_{m.sh}$ (2) on the glass transition temperature T_g for EP-1.

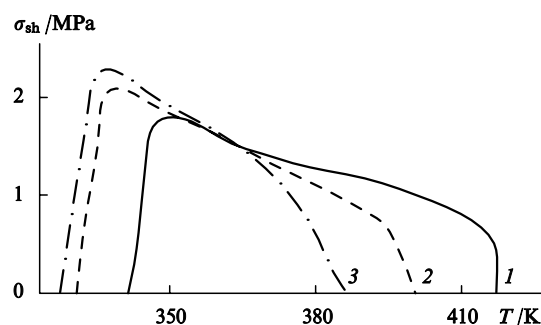


Figure 19. Temperature dependences of the shrinkage stresses (σ_{sh}) for EP-5, ϵ (%): (1) 15; (2) 20; (3) 25.

relations for the IPN investigated have an extremum (Fig. 20) indicates the dominant role of the elastic component, while the decrease in the half-width of the $\sigma_{sh}(T)$ maximum with increase in ϵ indicates an increase in the contribution of destructive processes (the specimens are disrupted earlier for the material with a defective structure in measurements of σ_{sh}) under these conditions. The fact that $\sigma_{m.sh}$ varies nonmonotonically (the relation has a maximum) with increase in ϵ is also striking. Such variation of σ_{sh} may be caused by the loosening of the network and hence by the partial relaxation of the stresses in the extrudate. The breaks on the right-hand branch of the $\sigma_{sh}(T)$ maximum for the

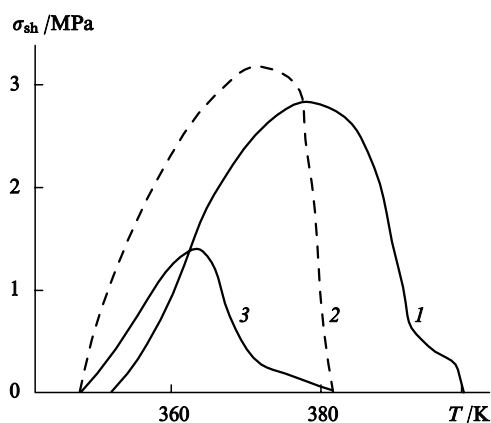


Figure 20. Temperature dependence of the shrinkage stresses for the PU-PEA IPN system containing 30 mass% of PEA, ϵ (%): (1) 25; (2) 30; (3) 40; $T_c = 358$ K.

PU-PEA system, preceding the disruption of the specimens, may be associated with the contribution of the rigid component.

The 'driving forces' of the thermal shrinkage of network and linear amorphous polymers^{187, 188} are apparently the same. The difference consists in the fact that in the case of network polymers the twisting process involves not molecular chains but internodal fragments oriented along the deformation axis during extrusion. Evidently, depending on the nature of the molecular mass distribution, the nature of the thermal shrinkage spectrum, especially its width, should also vary in these materials. For IPN with a high degree of segregation of the components, the stress relaxation processes in different networks are separated by a temperature range. This makes it possible to identify them on the basis of the $\sigma_{sh}(T)$ relation (Fig. 20): by varying the composition and ratio of the components, it is possible to control the form of the relation, obtaining different versions of the shrinkage spectrum.

For amorphous polymers (in contrast to crystallisable ones), the version of solid-state extrusion involving the use of a powder billet has not so far come to be widely employed. Nevertheless, individual investigations indicate that this processing procedure is promising for the establishment of an oriented structure. The extrusion process and the properties of extruded DF-10 (an aromatic polyester), consisting of a composition based on a polyarylate and a copolsulfoneformal, have been investigated.¹⁸⁹ The results of these studies have shown that the optimum process is achieved if the extrusion temperature is 0.95–0.98 of the temperature corresponding to the transition of the polymer to the viscous flow state and $\lambda \approx 6$ –7. Table 10 presents the strain–strength characteristics of DF-10 in tests involving compression and three-point bending (nicked specimens). Evidently, with increase in λ , the modulus of elasticity changes only slightly, whereas σ_y and σ_t increase appreciably. At the same time the plasticity of the material increases. These features are correlated with those established earlier for hydroextruded amorphous polymers.^{172–175}

Table 10. The properties of DF-10 specimens obtained by the plunger extrusion of a powder billet.

λ	Compression					Bending		
	E /GPa	σ_y , /MPa	ϵ_y (%)	σ_t /MPa	ϵ_r /MPa	E /GPa	σ_t /MPa	ϵ_r /MPa
1	1.5	82	6.0	81	37	1.1	108	13
3	1.4	95	6.0	130	44	1.3	109	12
4	1.5	91	6.0	120	40	1.4	118	12
5	1.5	91	6.5	140	40	1.3	115	12
6	1.5	103	8.0	175	58	1.2	115	12
7	1.6	107	8.0	180	50	1.4	129	18

3. Polymer blends and reinforced compositions

Polymer systems consisting of polymer blends and reinforced compositions have been vigorously investigated in recent years. One of the reasons for the increased interest of investigators in these materials is their great potential possibilities as regards regulation of mechanical properties. However, there have been extremely few studies on the solid-state extrusion of polymer blends and reinforced compositions. The possibility of obtaining oriented block specimens of the LDPE-PP system by the hydrostatic extrusion method has been examined.¹⁹⁰ Uniaxial solid-state extrusion of such compositions is difficult owing to the weak interfacial interaction of the components caused by their thermodynamic incompatibility. In order to eliminate this obstacle, various procedures are resorted to, for example, radiation-induced or photochemical cross-linking.^{191, 192} Deformation under the conditions of a high hydrostatic pressure made it

possible to abandon these procedures and to achieve higher values of λ without disruption of the material.¹⁹⁰

The change in the mechanical properties of polymer blend specimens on compression and extrusion as a function of λ corresponds to the change in these properties established for extruded PE and PP specimens.^{135, 175} The thermal shrinkage characteristics of the blends have a number of unusual features. An increase in the content of PP increases the shape stability of the extrudates (the residual deformation). At the same time there is an increase in the values of σ_{sh} and in the width of the shrinkage temperature range (Fig. 21). For all the PP concentrations, the increase in λ entails also an increase in $\sigma_{m,sh}$.

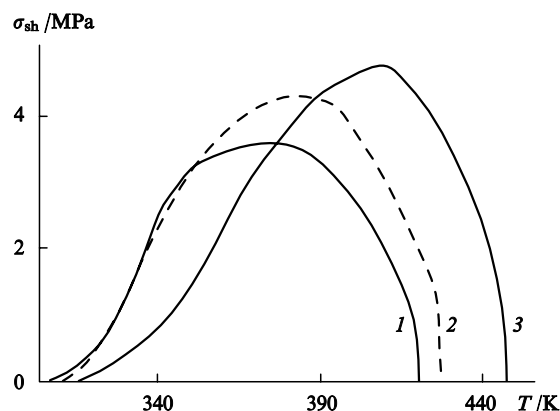


Figure 21. Temperature dependences of the shrinkage stresses σ_{sh} for the LDPE–PP blends. LDPE content (mass%): (1) 90; (2) 80; (3) 40; $\lambda = 3$

Analysis of the results of the study of Beloshenko *et al.*¹⁹⁰ established that the thermal shrinkage mechanisms in the LDPE–PP compositions and in LDPE are similar. At low PP concentrations, the stressed LDPE chains play the main role in the shrinkage process. With increase in the content of PP, the contribution of this phase to the establishment of the thermal shrinkage effect increases, which is manifested by the increase in $\sigma_{m,sh}$ and in the shape stability of the extrudates. The PP phase hinders the relaxation processes in the material: the temperatures at which the internal stresses are fully relaxed are displaced towards the region of higher T_m for the polyethylene phase. However, owing to the occurrence of phase separation, the observed changes are relatively small. The $\sigma_{sh}(T)$ relations for the blends in the region of the descending branch of the maximum differ from the relations established¹⁹¹ for crosslinked compositions: at $T < T_m$ for polypropylene, the right-hand branch of the maximum passes to a plateau. This fact can be explained by the formation during cross-linking of a network of chemical cross-links intensifying the interfacial interaction. In the hydroextrusion of noncrosslinked compositions, one is dealing merely with the appearance of additional physical cross-links, the network of which is unstable during annealing, and also with a decrease in the stresses at the interfaces compared with the stresses in the course of uniaxial extrusion as a result of the favourable deformation scheme. Nevertheless the result obtained is of definite practical interest, since the expansion of the range of σ_{sh} increases the functional possibilities of the material.

The behaviour of amorphous and crystalline films specimens of the polyether-ether-ketone–polyester-imide (PEEK–PEI) system subjected to uniaxial extrusion by the coextrusion method has been studied.¹¹⁶ The latter was achieved at temperatures below T_g (amorphous films) or below and above the crystallisation temperature (crystallisable films). The influence of extrusion on T_g , crystallisation and the degree of orientation was noted. In the case of amorphous films of the PEEK–PEI system, extrusion lowers the glass transition temperature of the polymer blend, although the density of the specimens increases somewhat under

these conditions. The degree of orientation of these films increases with increase in the PEEK concentration. In the crystallisable films, the density diminishes monotonically with increase in λ and extrusion intensifies the crystallisation process during the subsequent annealing of the films.

The traditional method for the preparation of reinforced polymer compositions is mechanical blending of the components. In the 1970s, a fundamentally new method for the introduction of fillers was proposed — the polymerisation filling method, which makes it possible to obtain polymer compositions directly in the course of the synthesis of the polymer.^{193, 194} One of the promising aspects of the polymerisation filling method involves the creation of compositions based on SHMPE. Such materials have strain–strength parameters similar to those of SHMPE, but are harder, have a higher modulus of elasticity, and are more resistant to wear.¹⁹⁵ At the same time they are greatly superior to activation-reinforced compositions as regards deformability and impact strength.¹⁹⁵ The characteristic features of the solid-state extrusion process and the mechanical properties of extrudates of reinforced compositions based on SHMPE have been investigated.^{161, 167, 196–200} The extrusion was carried out with the aid of the method proposed in a patent,¹⁵⁹ using polymer powder billets.

The extrusion parameters and the properties of the extrudates for a series of compositions investigated, measured in compressive tests, are presented in Table 8. The variation of E , σ_t , and ε_r for the SHMPE–kaolin system is analogous to that observed for SHMPE with the sole difference that the introduction of kaolin increases the limiting value of λ , the rigidity, and the strength, but reduces the deformability of the material. For other compositions, dependences of E and σ_t on λ with an extremum are observed, the values of λ corresponding to the maxima in the characteristics diminishing in the sequence kaolin $\rightarrow$ Al $\rightarrow$ Al(OH)₃. The last composition has the lowest level of strain–strength properties.

Comparison of the properties of the extruded compositions with those of control specimens obtained by hot pressing revealed an increase in rigidity and strength during solid-state extrusion for all the compositions investigated. The deformability diminishes at the same time. This feature is manifested even more strikingly in tensile tests.¹⁹⁶ Appreciable changes in ρ during the variation of λ have not been observed for the SHMPE–kaolin systems. For other compositions, ρ diminishes with increase in λ .

The extrusion draw ratio is known²⁰¹ not to reflect the real deformation of the macromolecules (λ'_m) in oriented polymers. For reinforced compositions, the discrepancy between λ and λ'_m is greater than for unreinforced ones, because the former quantity is calculated in relation to the entire volume of the polymer, whereas only part of it (the polymer matrix) is actually deformed. In order to eliminate this, a corrected molecular draw ratio has been introduced:¹⁶⁷

$$\lambda'_m = \frac{\lambda_m}{1 - \varphi},$$

where φ is the volume degree of filling. The inequality $\lambda'_m < \lambda$ holds for SHMPE and $\lambda'_m > \lambda$ is valid for reinforced compositions. This relation between the parameters considered reflects the differences in the mechanisms of the deformation of SHMPE and the compositions based on it. For higher values of λ , the polymer macromolecules are disrupted at the polymer–filler boundary, which lowers the effective density of the network of macromolecular entanglements. This tends to increase λ'_m and has a positive effect on E . However, owing to the loosening of the interfaces, the fraction of free cavities increases with increase in λ , which leads to a decrease in E . For $\lambda > 5$, the second effect predominates and this induces a decrease in E for the reinforced compositions (Table 8).

The above conclusion has been confirmed by measurements of ρ and by the results of a study of the rupture surfaces of the extrudates.¹⁹⁸ For low values of λ , the surface relief of the break is homogeneous, which indicates a satisfactory adhesion between

SHMPE and the filler. In the case where $\lambda \geq 7$, the inhomogeneity of the relief, induced by the loss of adhesion at the polymer–filler boundary and hence by the rupture of the material at this boundary, can be easily seen.

For the majority of the compositions investigated, σ_r varies with λ in parallel with E and reaches the maximum values in the region $\lambda = 4–6$ (Table 8). Fig. 22 presents the dependences of the limiting extrusion draw ratio corresponding to the rupture of the specimen in mechanical tests (λ_r) as a function of the extrusion draw ratio. The values of λ_r were determined from the formula²⁰²

$$\lambda_r = 1 + \varepsilon_r.$$

Evidently λ_r increases with increase in λ (for oriented polymers, an increase in λ diminishes λ_r as a consequence of the exhaustion of the mobility of the molecular chains).³¹ On the basis of the above findings, one can also postulate that the rupture of the extruded compositions is related directly to the presence of fillers, namely to the breakdown of the continuity of the specimens owing to the loosening of the polymer–filler boundaries and the formation of numerous microcracks. On deformation of the specimen in the course of mechanical tests, the microcracks formed during extrusion aggregate and the specimen is ruptured.

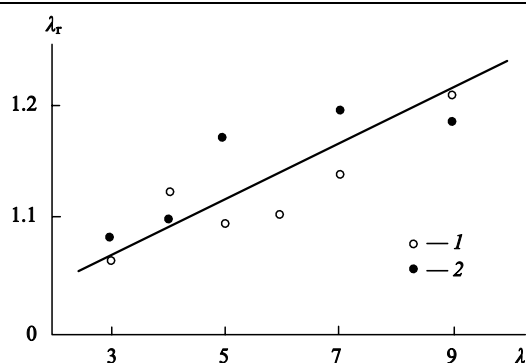


Figure 22. Dependence of the limiting draw ratio λ_r on the draw ratio λ for the SHMPE–70 mass% Al (1) and SHMPE–45 mass% of bauxite (2) systems.

The difference between the strain–strength properties of the SHMPE–kaolin compositions and the analogous properties of other compositions is caused primarily by the shape of the filler particles. The kaolin particles have the shape of plates, while the Al and $\text{Al}(\text{OH})_3$ particles are spherical. The presence of particles anisotropic as regards shape promotes the appearance of an intense interfacial interaction, manifested in the partially cohesive mechanism of the destruction of the SHMPE–kaolin compositions.²⁰³ At the same time, owing to the weak interaction at the polymer–filler interface, the fully adhesive rupture mechanism operates for the SHMPE– $\text{Al}(\text{OH})_3$ system.

A mathematical model has been proposed for the solid-state extrusion of polymer composites.²⁰⁴ It is based on the idea that the formation and ‘healing’ of microcavities are possible on deformation under conditions of high pressure. Relations have been obtained which make it possible to calculate the density of the extrudate and to plot it against λ . Comparison of the calculated and experimental values of ρ showed that the model describes adequately the plunger extrusion of a powder billet comprising polymerisation-reinforced compositions. At the same time, it can be used to predict the defectiveness of polymeric materials also in other processing schemes involving high pressures.

V. Conclusion

The data presented show that a high pressure is frequently used in theoretical and technological research and that its role in the structure modification of polymers is considerable and varied.

The methods involving treatment with pressure examined in the review may be used for the effective control of shaping processes and of the structure and properties of polymeric materials with different structures. However, the functional possibilities of the different ways of achieving the modifying effect of pressure are not the same. Thus crystallisation or curing under pressure make it possible to obtain objects in the form of a block, as a rule cylindrical in shape, which limits the range of their practical applications. On the other hand, the substances formed in series-connected IPN (preparation of a prepolymer) or in oligomeric products serve as starting components for more complex compounds. The latter are manufactured under traditional conditions, which tends to expand their applications. For example, the IPN can be used as adhesives and also for the preparation of bulky polymeric articles of different shape and for different purposes. Finished articles, which do not require further mechanical treatment, can be usefully subjected to annealing under pressure, because favourable changes in the material take place to the greatest extent in its surface layer.

The results of the study of solid-state extrusion indicate the considerable potential possibilities of this method in the processing of not only flexible-chain polymers but also of rigid-chain network polymers, polymer blends, and reinforced compositions. As a result of the plasticising effect under the influence of high hydrostatic pressure, it is possible to achieve an orientational order in polymers and polymer composites which are brittle and difficult to work. The appearance of such order is accompanied by an improvement in the strain–strength properties of the materials or by the establishment in the latter of a qualitatively new state (the shape memory effect, a negative Poisson ratio).

One may hope that further studies of the application of the isostatic treatment or solid-state extrusion for the structural modification of polymers will help in discovering new aspects of the influence of high pressure which are of interest from both theoretical and practical points of view.

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

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

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

Substituted androstanes as aromatase inhibitors

I S Levina

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Abstract. The synthesis and structure–activity relationships of inhibitors of steroid aromatase which catalyses the last stage of a multistep biotransformation of cholesterol into estrogens, *viz.*, aromatisation of C₁₉-steroids into C₁₈-phenolic steroids, are discussed. Compounds of the androstane series which are structurally related to the natural substrate, *viz.*, androst-4-ene-3,17-dione, are the subjects of consideration. The review encompasses problems of synthesis of various substituted androstanes and their aromatase-inhibiting activities and structural requirements for selective specific aromatase inhibitors based on *in vitro* and *in vivo* structure–activity studies of compounds synthesised, their biological properties and the results of clinical trials. Special attention is paid to practical applications of aromatase inhibitors in the treatment of hormone-dependent mammary and ovarian tumours as well as benign prostatic tumours. In writing this report, the author has used all the information currently available in the chemical, biochemical, endocrinological and medicinal literature as well as in patents. The bibliography includes 173 references.

I. Introduction

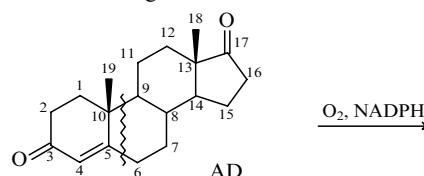
The search for selective and specific therapeutic steroid agents in the past few decades has given the main impetus to the development of synthesis of modified steroids. It is commonly known that many physiological processes occurring in the organism are controlled by a relatively small set of steroid hormones produced upon cholesterol biosynthesis. These compounds represent small hydrophobic molecules which penetrate easily through membranes and interact with their specific receptors thus regulating gene transcription. One most important factor that stimulated studies of steroids was the discovery that analogues of some endogenous hormones can be used for controlling the synthesis and modifications of steroids involved in proliferation of malignant tumours.

In many clinical situations, estrogens produced in normal or excess quantities play a prominent role in the pathogenesis of various diseases. Therefore, suppression of estrogen biosynthesis

is one of the ways to achieve progress in the treatment of such diseases as mammary and ovarian tumours, endometriosis, *etc.*^{1–4} The main efforts in the design of therapeutic preparations of the androstane series which are aromatase (estrogen synthase) inhibitors in their pharmacological effect have been directed at the synthesis of drugs against hormone-dependent mammary tumours. This approach has indisputable advantages over cytotoxic therapy which often causes serious complications.^{3,5}

At present, mammary tumours represent the most widespread type of malignant neoplasms and are the second major cause of mortality in women. In the USA alone, casuality of this disease amounts to about 130 000 annually.⁶ About a half of these malignant tumours require a source of estrogens for their growth and development. The present-day endocrine therapy relies upon the use of either antiestrogens which act on tumour cells directly, *via* their specific receptors, or high doses of progestins the mechanism of action of which has not been finally established. An alternative strategy consists in the application of aromatase inhibitors (AI) which suppress production of estrogens in the organism.

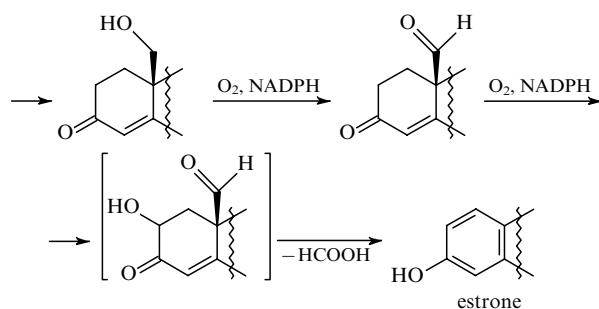
Aromatase represents an enzyme complex made up of two major components: a flavoprotein (NADPH-cytochrome P-450 reductase) which transfers electrons from NADPH to the terminal enzyme and a specific form of cytochrome P-450 commonly known as aromatase cytochrome P-450. This protein is involved in the binding of the C(19) atom of the steroid substrate and catalyses the multistep reaction resulting in the aromatisation of the ring A of the steroid.^{7–9} The conversion of Δ^4 -3-ketoandrogens into phenolic estrogens is the ultimate stage in the multi-enzyme transformation of cholesterol into female sex hormones. Although the details of this mechanism are still questionable, it is believed^{10,11} that aromatase performs three successive steps of the androgen oxidation. The first two steps yield 19-hydroxy- and 19-oxo-androgens. However, the site of incorporation of the third hydroxy group is not established. Presumably, hydroxylation occurs at C(2),¹² which results in aromatisation of the ring A of androst-4-ene-3,17-dione (AD). The loss of the angular C(19)-methyl group and *cis*-elimination of the hydrogen atoms from positions 1 and 2 give estrone and formic acid.^{3,12–19}



I S Levina N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 938 36 14

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The enzymic oxidation described above yields an enzyme-bound derivative, which in turn gives the aromatic steroid by virtue of rapid elimination and simultaneous recovery of the unchanged, active enzyme. It is obvious that various structural modifications of the natural substrate (AD) can alter this elimination in such a way that the steroid intermediate will remain covalently bound with the enzyme rather than undergo conversion into the aromatic steroid. Elucidation of the mechanism of androgen aromatisation and demonstration of its possible inhibition has led to successful design and development of a broad range of AI.

Since aromatisation is a unique reaction of steroid biosynthesis and estrogens are its final products, *in vivo* inhibition of aromatase does not affect other essential enzymes involved in this process. This is an important advantage of AI over other inhibitors recommended for therapeutic use (see Refs 4, 20).

Studies of the mechanism of aromatisation of the natural substrate (AD) have specified the type of its structural modification required for the design of AI. It consists in the introduction of substituents into the ring A or at adjacent positions with simultaneous preservation, in the majority of cases, of polar functional groups at C(3) and C(17). The sites for substitution have been identified as C(1), C(4), C(6), C(7), and C(19). The nature of the substituents varies widely depending on the substitution site.

Syntheses of AI often pose serious problems and are as such a considerable progress in both the design of synthetic approaches and their practical implementation. In each particular case, the synthesis of steroid AI employs original approaches which are based on modern methods of synthetic organic chemistry or a combination of several methods. Syntheses of structures with 2,19-bridges or a series of androsta-4,9(11)-diene-3,17-diones carrying a sulfur-containing group at C(10) (Section III.1) provide illustrative examples. Stereochemical aspects of the reactions are very important; modern physicochemical methods are employed for establishing the structure and stereochemistry of the reaction products.

From the standpoint of their chemical structure, AI can be classified according to the site of substitution in the AD molecule. It is this principle that is used in the description of AI syntheses in Section III of the present review. However, it should be remembered that classification of AI according to the mechanism of their action may be different. In this review, this classification was used to analyse the relationships between the structure of AI and their inhibitory activity.

The reviews on steroid AI that cover simultaneously the problems of their synthesis, relationships between their structures and biological properties and pharmacological data are virtually absent. One can mention the book by Zeelen 'Medicinal Chemistry of Steroids',²⁰ which includes the analysis of steroid and nonsteroid AI, as well as the surveys^{9,15,21} devoted predominantly to the mechanisms of action of AI and their inhibitory activity *in vitro*.

The present review describes the methods for the synthesis of substituted androstanes active as aromatase inhibitors, the relationships between the structure of AI and the extent of their binding with the enzyme as a criterion for directed search for selective AI, as well as biological properties and practical applications of the most potent steroid preparations currently available.

II. Classification of steroid aromatase inhibitors and methods for assessment of their activities *in vitro* and *in vivo*

Steroid AI have come under the scrutiny of science with the publication of the pioneering work by Brodie *et al.*²² in 1973. In the subsequent two decades, a vast variety of steroid compounds have been synthesised and assayed for AI activity.

In vitro inhibition of human placenta aromatase is the most common procedure used in the study of modified androgens.²³ This method is used primarily for testing steroids as candidates for AI. The inhibition is evaluated by several parameters. The most important of them are the inhibition constant, K_i , which is determined in experiments where both AI and a steroid substrate (AD) are introduced, and the concentration of AI that results in 50% inhibition (IC_{50}). The analysis of inhibition kinetics, which allows determination of the type of inhibitory activity for the given steroid compound, is also important.

The following methods are used for *in vivo* studies of AI: (1) inhibition of ovarian estrogen secretion; (2) inhibition of peripheral (extraovarian) aromatisation which is the main source of estrogens in post-menopausal women; (3) evaluation of the antitumour effect of AI in an experimental model of a 7,12-dimethylbenzo[*a*]anthracene (DMBA)-induced mammary tumour.

According to the mechanism of their action, AI are classified into reversible and irreversible ones. Compounds which, like usual androgenic substrates, reversibly bind with the active centre of aromatase to form a complex that does not undergo rapid dissociation can serve as rather efficient AI. Competitive aromatase inhibitors that are capable of binding with iron of the cytochrome P-450 heme (*e.g.*, due to the presence of a hetero atom with a specific stereochemical environment in their molecule) can sometimes manifest inhibitory activities both *in vitro* and *in vivo*. A great number of steroid AI are irreversible. Irreversible inhibition of the enzyme implies the conversion of a steroid substrate into an active complex which can irreversibly bind with the enzyme. These compounds are also referred to as 'suicide inhibitors'.^{9,24–26} The latter have a number of salient advantages over competitive reversible AI owing to their high specificity and the ability for irreversible inhibition. Thus, irreversible AI produce long-term inactivation of aromatase *in vivo*.

III. Methods for the synthesis of aromatase inhibitors of the androstane series and their activities

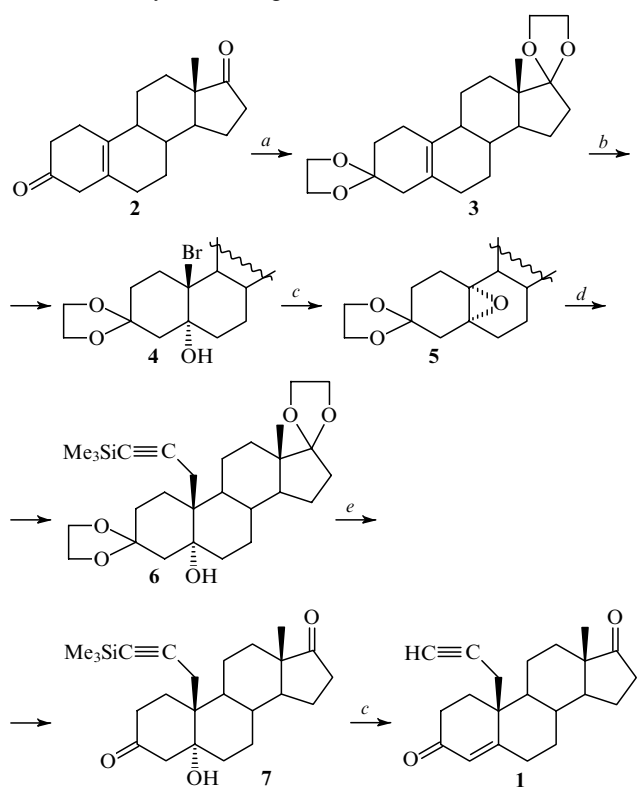
1. 19-Substituted androstanes

19-Substituted androstanes are the most numerous and diverse aromatase inhibitors. It is quite natural because many investigators consider the angular 19-methyl group to be the site of the primary enzyme attack leading to aromatisation.

Formally, the functionalisation of the 19-methyl group of the steroid molecule is a very difficult task. This class of steroids are synthesised mostly from compounds having a 5(10) double bond or from 19-hydroxy(oxo)androstanes using diverse methods of synthetic organic chemistry for their further transformations, such as epoxidation followed by oxirane ring opening with appropriate reagents; substitution of 19-mesyl(tosyl)oxy- and 19-halogeno-derivatives; fluorination; the Wittig, Corey, and Mitsunobu ethynylations, and other sophisticated approaches. All the known methods for the synthesis of 19-substituted androstanes are discussed below in detail.

10 β -Propynyl-steroids (19-ethynylandrostanes) synthesised in the 80's simultaneously and independently in several laboratories^{14,27–31} pertain to irreversible suicide inhibitors. Some 19-ethynyl-steroids of the androstane series have been described in patents.^{32–35}

19-Ethynylandrost-4-ene-3,17-dione **1** was obtained from commercially available estr-5(10)-ene-3,17-dione **2**. Diketal **3** formed upon protection of the carbonyl groups reacted with *N*-bromosuccinimide to give the bromohydrin **4** which was easily converted into the 5 α ,10 α -epoxide **5**. Epoxide opening with an alkynylcuprate reagent gave the 5 α ,10 β -disubstituted derivative **6** in 60% yield. Deprotection and elimination of the hydroxy group from position 5 of the 3,17-diketone **7** yielded the target androstane **1** in 23% yield starting from the oxirane **5**.¹⁴

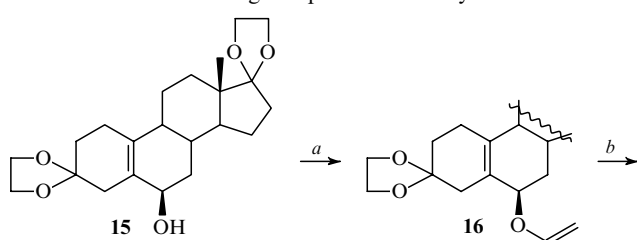


(a) HO(CH₂)₂OH, H⁺, PhH; (b) *N*-bromosuccinimide (NBS), DMF; (c) NaOMe, MeOH; (d) [Me₃SiC $\equiv$ CCH₂]₂CuLi, Et₂O; (e) H⁺, Me₂CO.

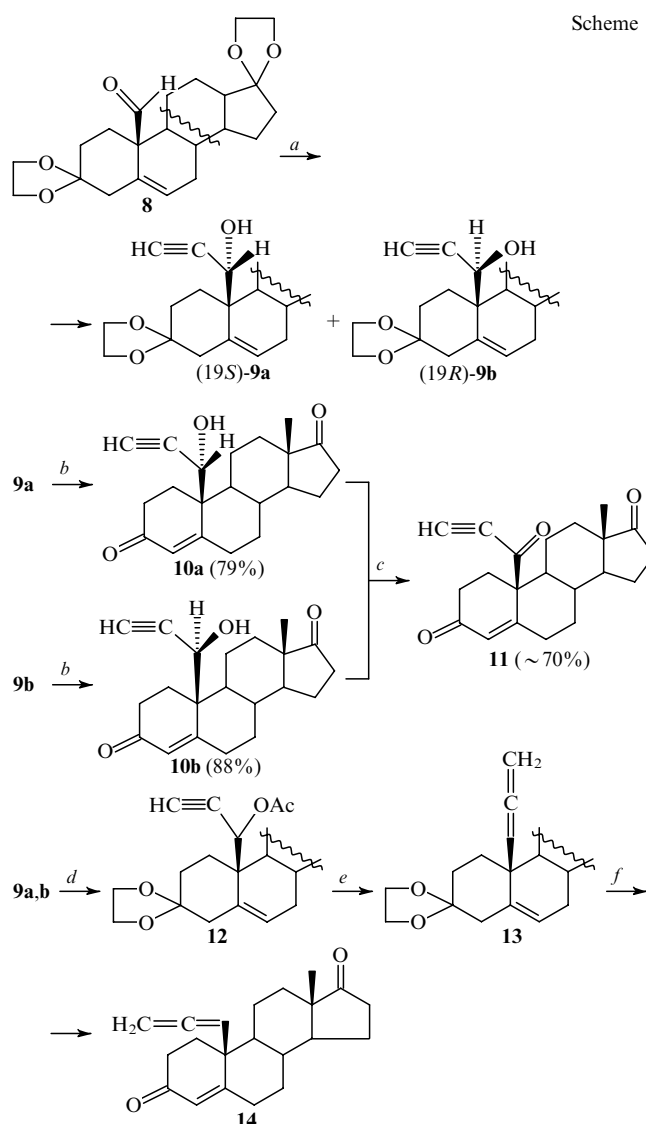
Structurally related diastereomeric 19-ethynyl-19-hydroxy derivatives **10a,b** were obtained from the bisketal-aldehyde **8**. The latter reacted with ethynylmagnesium bromide to give a chromatographically separable mixture of (19*S*)-**9a** and (19*R*)-**9b** derivatives in a 3 : 2 ratio (> 90% yield). The authors²⁷ ascribed the (19*S*)-configuration to the main product by analogy with the stereoselectivity of the reaction of the diketal-aldehyde **8** with methyl lithium. After removal of the ketal protection, the diketones **10a,b** were obtained in the individual state and further oxidised into the triketone **11**²⁷ (Scheme 1).

The acetate **12** prepared from 19-ethynyl-19-hydroxy-steroids **9a,b** served as the starting compound in the synthesis of an analogous allenic AI (**14**)²⁹ based on cuprate-initiated reductive elimination of acetic acid. The allene **13** was converted into the final product **14** after deprotection (see Scheme 1).

Yoshida *et al.*²⁹ have also developed an original procedure for the synthesis of 19-ethynyl-AD **1** using 6 β -hydroxystrenedione bisketal **15** as the starting compound. The vinyl ether **16** obtained

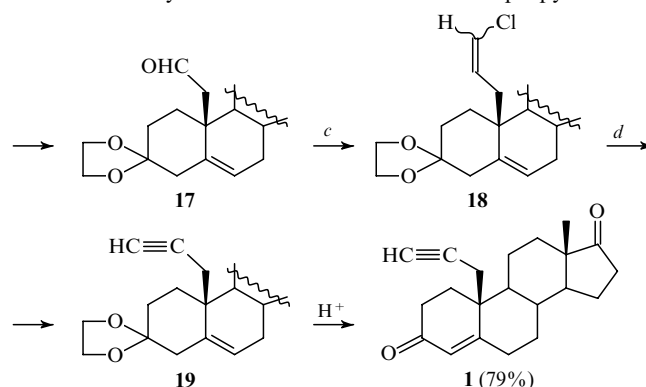


Scheme 1



(a) HC $\equiv$ CMgBr, Δ , THF, 2 h, 94%; (b) 10% H₂SO₄, Me₂CO; (c) CrO₃, H₂SO₄; (d) Ac₂O, Py; (e) MeLi, CuI, Et₂O, -78 °C, 50%; (f) *p*-TsOH, Me₂CO, 70%.

from it was subjected to the Claisen rearrangement (66% yield). The Wittig reaction of the aldehyde **17** with chloromethylene-phosphorane gave a mixture of *cis*- and *trans*-vinyl chlorides **18**, which were dehydrochlorinated with lithium diisopropylamide at

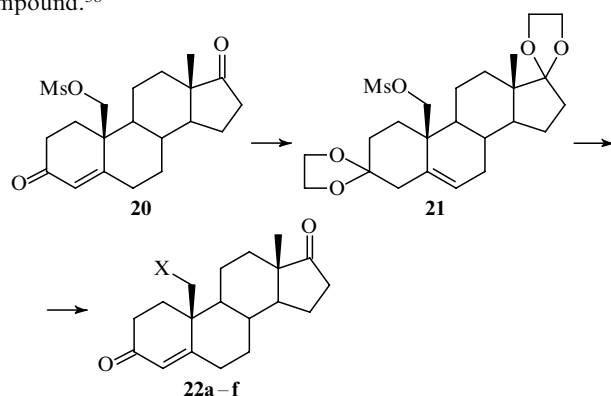


(a) H₂C=CHOEt, Hg(OAc)₂, 78%; (b) collidine, 165 °C, 4 h, 66%; (c) ClCH=PPH₃, 84%; (d) lithium diisopropylamide (LDA), -70 °C, 1 h, 95%.

–70 °C to yield the ethynyl derivative **19** in 95% yield. Removal of the ketal protection gave the final product, *viz.*, 19-ethynyl-AD **1**, in high yield.

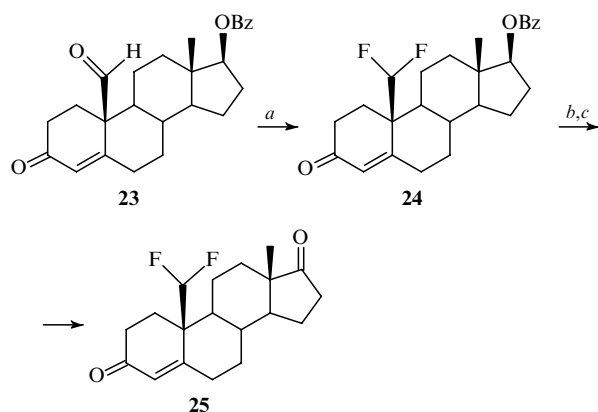
The steroid **1** and its derivatives have been extensively assayed as AI. It was found that 19-ethynyl-AD **1** and its 19-hydroxy- (**10a,b**) and 19-oxo-derivatives (**11**) are irreversible suicide inhibitors of aromatase and manifest high specificity^{14, 15, 26, 28, 29, 31, 36} (the data on their inhibitory activities are summarised in Table 1). The steroid **1** possessed high activity on oral administration with respect to the inhibition of ovarian aromatase. It is noteworthy that 19-ethynyl-17-propionyloxyandrost-4-ene-3-one manifests only *in vivo* inhibitory activity.³⁷ The allenic derivative AD **14** also pertains to irreversible AI and has rather high K_i value.²⁹

Several 19-halogeno-substituted androstanes **22** were obtained from the bisketal **21** by substitution of 19-methanesulfonates, which is well known in the series of Δ^5 -3-acetoxysteroids; 19-mesyloxy diketone **20** being used as the starting compound.³⁸



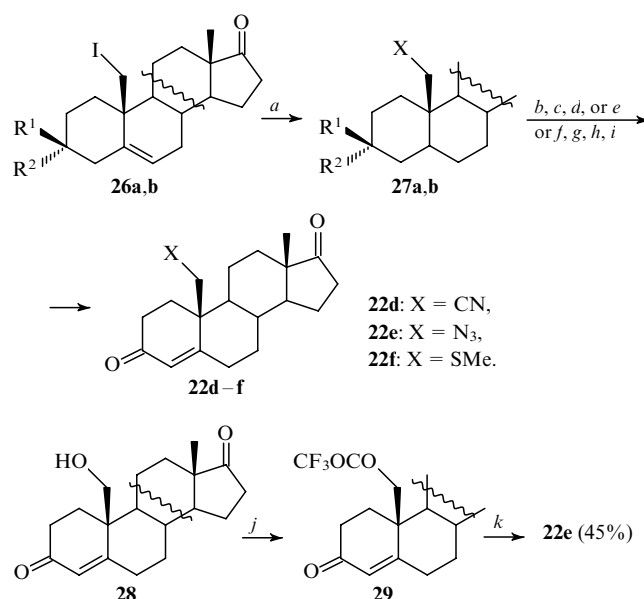
X = Cl (**a**), Br (**b**), I (**c**), CN (**d**), N₃ (**e**), SMe (**f**).

19-Difluoroandrostane **25** was obtained by selective fluorination of 17-benzoyloxy-3-oxoestr-4-en-19-al (**23**) with an excess of diethylaminosulfur trifluoride in a mixture of dichloromethane and trichlorofluoromethane. Removal of the benzoyl protection and oxidation of the resulting alcohol gave 19-difluoro-AD (**25**) which manifested moderate inhibitory activity^{39, 40} (see Table 1).



(a) excess Et₂NSF₃ (DAST), CH₂Cl₂–CCl₃ (1 : 1), 20 °C, 48 h;
(b) OH[–]; (c) CrO₃, H₂SO₄.

The synthesis of androstanes with functional groups at position 19 containing sulfur or nitrogen exploited the ability of 19-iodo derivatives **26a,b** for nucleophilic substitution without homoallylic rearrangement.⁴¹ This approach was used to obtain a series of 19-substituted androstanes **27a,b** and **22d–f**. It is appropriate to mention in this connection the synthesis of 19-azido-AD **22e** described in a patent.⁴² Compound **22e** was obtained by esterification of 19-hydroxy-AD **28** with trifluoroacetic anhydride with subsequent treatment of the ester **29** with sodium azide in DMF.



R¹ = OAc, R² = H (**a**); R¹, R² = O(CH₂)₂O (**b**);
X = CN, N₃, SSO₂Me;
(a) NaCN (X = CN); NaN₃, HMPA (X = N₃); NH₄SSO₂Me (X = SSO₂Me); (b) KOH, MeOH; (c) CrO₃, H₂SO₄; (d) Al(OPrⁱ)₃, cyclohexanone (CHex) (**27a**, X = CN, N₃); (e) (COOH)₂, EtOH (**27b**, X = CN, N₃); (f) LAH, THF; (g) MeI; (h) K₂CO₃; (i) Al(OPrⁱ)₃, CHex (**27a**, X = SSO₂Me); (j) (CF₃CO)₂O, Py; (k) NaN₃, DMF.

19-Substituted AD **22d–f** competitively inhibit aromatase.^{38, 42} Of special interest is the 19-methylthio derivative **22f** which is the first highly efficient AI (K_i = 1 nM); its inhibitory effect is determined not only by its interaction with the steroid-binding site of aromatase but also by coordination of the steroid sulfur atom with the heme iron of cytochrome P-450.⁴¹

The attention of several research groups was focussed on 10 β - and 19-sulfur-containing AD derivatives as aromatase inhibitors. Compounds with the sulfur atom linked directly with C(10) or separated from the C(10) atom by one or several methylene groups have been synthesised and assayed. Thus the introduction of the SH group at position 10 of estr-4-ene-3,17-dione resulted in an efficient suicide AI **32**. The opening of the 5 α ,10 α -epoxide ring of estrane **5** with potassium sulfide in ethylene glycol in the presence of 18-crown-6 gave 5 α ,10 β -disubstituted estrane **30** in 70% yield. The latter was converted in two steps into 10 β -mercaptoestr-4-ene-3,17-dione (**32**) via 5 α -hydroxy diketone **31**. The yield of the final product was 10% with respect to estr-5(10)-ene-3,17-dione **2**.¹⁴ The corresponding 17 β -hydroxy derivative possessing aromatase-inhibiting activity was synthesised by Bednarski and Nelson¹⁴ following an analogous scheme.⁴³ *In vitro* studies of the biological activity of the thiol **32** revealed that the free thiol group is required for the binding to the enzyme, because the corresponding acetylthio derivative was inactive.^{19, 43}

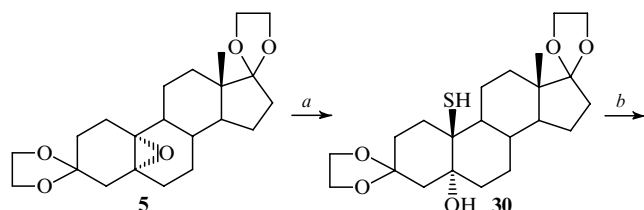
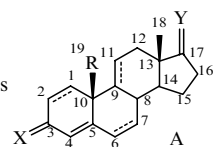


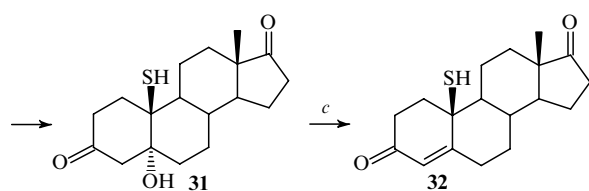
Table 1. Data on *in vitro* inhibition of aromatase from human placenta by 19-substituted androstanes

R	X	Y	The position of a double bond ^a			K_i /nM	IC_{50} /nM	Ref.
			Δ^1	Δ^6	$\Delta^{9(11)}$			
Me (ADD)	O	O	+	—	—	320		24
Me (114)	O	O	+	+	—	180		171
Me (183)	O	O	—	+	—	42		24
Me	H ₂	O	—	—	—	37		152, 145
Me	O	H ₂	+	—	—	1100		172
Et	O	O	—	—	—	9		15
(CH ₂) ₂ Me	O	O	—	—	—	3000		15
CH=CH ₂	O	O	—	—	—	3		15, 30
CH ₂ —C≡CH (1)	O	O	—	—	—	4.3		31
						23		28
						68		15
							31.3	9
CH ₂ —CH=CH ₂	O	O	—	—	—	13		31
						56		30
C≡CMe	O	O	—	—	—	—		31
CH ₂ C≡CMe	O	O	—	—	—	26		31
CH(OH)C≡CH (10)	O	O	—	—	—	49		31
COC≡CH (11)	O	O	—	—	—	350		31
CH=C=CH ₂ (14)	O	O	—	—	—	14		31
Me	CH ₂	O	—	—	—	13		148
CH ₂ OH	CH ₂	O	—	—	—	4.7		148
CHO	CH ₂	O	—	—	—	24		94, 148
CHF ₂ (25)	O	O	—	—	—	1000	1300	15, 40
CH ₂ N ₃ (22e)	O	O	—	—	—	22.5		31, 41
SH	O	OH	—	—	—	106		43
CH ₂ SH (35)	O	O	—	—	—	34		43
CH ₂ SMe (22f)	O	O	—	—	—	1	42	41, 46
(CH ₂) ₂ SMe (55)	O	O	—	—	—	0.5	22	49, 46
(CH ₂) ₂ SMe (40a)	O	O	—	—	+		12	46
(CH ₂) ₂ SEt (40b)	O	O	—	—	+		870	46
(CH ₂) ₃ SMe (51)	O	O	—	—	+		10000	46
(CH ₂) ₂ SAc (40c)	O	O	—	—	+		10000	46
(CH ₂) ₂ SPh (40d)	O	O	—	—	+		400	46
(CH ₂) ₂ S(CH ₂) ₂ OH (40e)	O	O	—	—	+		1000	46
(CH ₂) ₂ SCHF ₂ (40f)	O	O	—	—	+		1000	46
(CH ₂) ₂ SSC ₆ H ₃ (NO ₂) ₂ (40g)	O	O	—	—	+		1000	46
(CH ₂) ₂ SCH ₂ C≡CH (40h)	O	O	—	—	+		1000	46
(CH ₂) ₂ SCH ₂ Me (40i)	O	O	—	—	+		570	46
(CH ₂) ₂ SCH ₂ CH=CH ₂ (40j)	O	O	—	—	+		270	46
(CH ₂) ₂ SCH=CH ₂ (40l)	O	O	—	—	+		50	46
(CH ₂) ₂ SSMe (40m)	O	O	—	—	+		1000	46
(CH ₂) ₂ SPh (40n)	O	O	—	—	+		1000	46
(CH ₂) ₂ SC ₃ H ₅ -cyclo (40o)	O	O	—	—	+		1000	46
(CH ₂) ₂ SC≡CH (40p)	O	O	—	—	+		330	46
 [(19 <i>R</i>)- 59]	O	O	—	—	—	7		51
 [(19 <i>S</i>)- 59]	O	O	—	—	—	75		51
 [(19 <i>S</i>)- 60]	O	O	—	—	—	1		51
 [(19 <i>R</i>)- 60]	O	O	—	—	—	75		51
H ₂ C—  [(2' <i>S</i>)- 64]	O	O	—	—	—	22		55
 [(19 <i>R</i>)- 76]	O	O	—	—	—	3.4		56
 [(19 <i>S</i>)- 76]	O	O	—	—	—	56		56
 [(19 <i>R</i>)- 78]	O	β-OH	—	—	—	30		56
 [(19 <i>S</i>)- 78]	O	β-OH	—	—	—	693		56

Table 1 (continued).

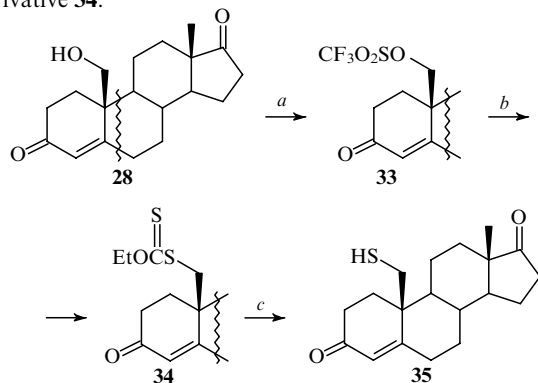
R	X	Y	The position of a double bond ^a			K_i /nM	IC ₅₀ /nM	Ref.
			Δ^1	Δ^6	$\Delta^{9(11)}$			
(CH ₂) ₃ -C(2)- β (86)	O	O	—	—	—	24		59
2 β ,10 β -(CH ₂) ₂	O	O	—	—	—	70		11
2 β ,10 β -CH ₂ CH(OH) [(<i>R</i>)- 82a]	O	O	—	—	—	870		11
2 β ,10 β -CH ₂ CH(OH) [(<i>S</i>)- 82b]	O	O	—	—	—	926		11
CH(OH)CH ₂ Br [(19 <i>R</i>)- 80]	O	O	—	—	—	27		11
CH(OH)CH ₂ Br [(19 <i>S</i>)- 80]	O	O	—	—	—	1130		11
CH(OH)CH ₂ Cl [(19 <i>R</i>):(19 <i>S</i>) = 9:1]	O	O	—	—	—	63		11
CH(OH)CH ₂ I [(19 <i>R</i>):(19 <i>S</i>) = 9:1]	O	O	—	—	—	11		11

^a Symbols + and — denote the presence and absence of the double bond in this position, respectively.



(a) KSH, HO(CH₂)₂OH, 18-crown-6, 70%; (b) H⁺, Me₂CO, 78%;
(c) NaOH, MeOH, 32%.

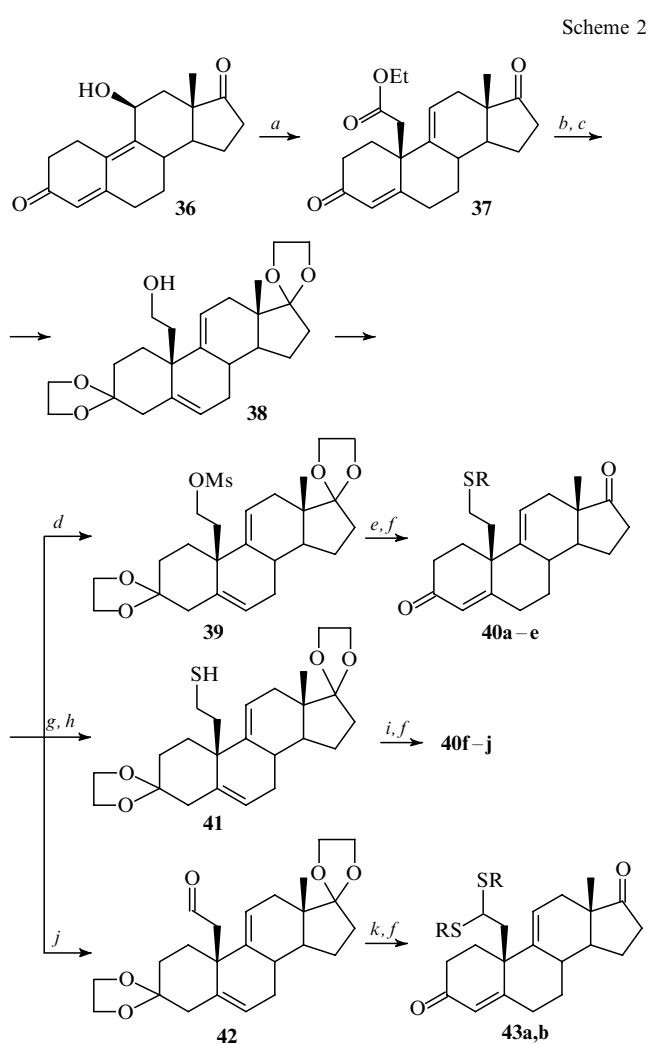
The homologous 19-mercapto-AD **35** was obtained by the reaction of the 19-triflate **33** with potassium ethyl xanthate in the presence of 18-crown-6 with subsequent cleavage of the thio derivative **34**.⁴³



(a) (CF₃SO₂)₂O, Py; (b) EtOCSK, 18-crown-6, THF, 20 °C, 20 h;
(c) H₂N(CH₂)₂NH₂, THF.

The inhibition constant of the steroid **35** is 34 nM.⁴³ It represents an irreversible AI; its activity is 16 times as high as that of formestane both *in vitro* and *in vivo* (see Section II). However, the thiol **35** has a limited use because of its insufficient pharmacological stability due to the presence of a free thiol group. To overcome this limitation, its ethylthio derivative, *viz.*, 19-ethylthio-AD, has been synthesised⁴⁴ (for the relevant patent, see Ref. 45).

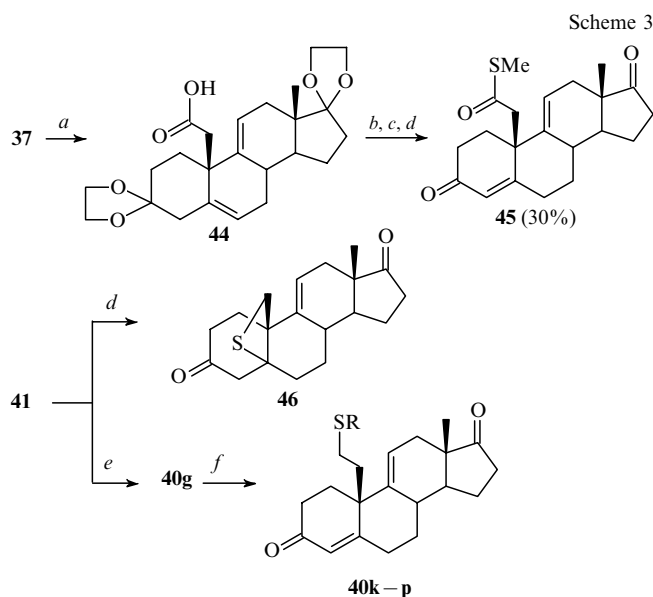
One of recent papers devoted to 19-functionalised androstanes presents the results of extensive studies on the synthesis and structure–aromatase affinity relationships of several series of androstane-4,9(11)-diene-3,17-diones carrying a sulfur-containing group, [(CH₂)_{*n*}SR], at the C(10) atom, where *n* = 0–3 and R stands for various alkyl, acyl and aryl substituents.⁴⁶ 19-Ethoxycarbonylandrosta-4,9(11)-diene-3,17-dione **37** obtained from the allylic alcohol **36** by the [3.3]-Claisen rearrangement was used as the starting compound in these syntheses (Scheme 2).



R = Me (**a**), Et (**b**), Ac (**c**), Ph (**d**), (CH₂)₂OH (**e**), CHF₂ (**f**), 2,4-

(NO₂)₂C₆H₃S (**g**), CH₂C≡CH (**h**), CH₂SMe (**i**), CH₂CH=CH₂ (**j**);
(a) (EtO)₃CMe, EtCO₂H, 137 °C, 4 h, 81%; (b) HO(CH₂)₂OH, CH₂Cl₂, Δ, 8 h, 71%; (c) LAH, THF, –50 to 20 °C, 2 h, 85%; (d) MsCl, Et₃N, CH₂Cl₂, 0 °C, 100%; (e) RNa, DMF; (f) HCl; (g) AcSH, PPh₃, diethylazodicarboxylate (DEAD), THF, 20 °C, 2.5 h, 60%; (h) NH₂NH₂, THF, –30 °C, 72 h, 97%; (i) Bu^tOK, THF, RHal; (j) (COCl)₂, DMSO, CH₂Cl₂, –50 °C; (k) RSH, BF₃·Et₂O, –78 to 20 °C.

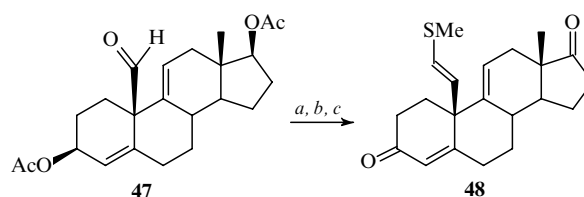
Thus the reaction of steroid **36** with triethyl orthoacetate in the presence of propionic acid gave the ethoxycarbonyl derivative **37** in > 80% yield.⁴⁷ The latter was reduced to alcohol **38** via the biscetal. Several methods presented in Scheme 2 have been elaborated for its conversion into various 19-thiomethyl androstane derivatives. One of them consists in conversion of the alcohol **38** into the corresponding mesylate **39**, subsequent substitution of the mesyloxy group by various thiolates and deprotection to give compounds **40a–e**. The first member of this series, *viz.*, 3,17-diketo analogue of compound **41**, could not be obtained using this approach; various attempts at its deprotection gave compound **46**, which is the product of intramolecular Michael addition (Scheme 3).



40: R = C≡CSiMe₃ (**k**), CH=CH₂ (**l**), SMe (**m**), SPh (**n**), cyclo-C₃H₅ (**o**), C≡CH (**p**);
 (a) KOH, MeOH, 18 h, 95%; (b) ClCO₂Et, Et₃N, 20 °C, 1 h; (c) MeSNa, DMF, 2 h; (d) HCl; (e) 2,4-(NO₂)₂C₆H₃SCl, Py, CH₂Cl₂, 20 °C, 0.5 h; (f) RM, THF.

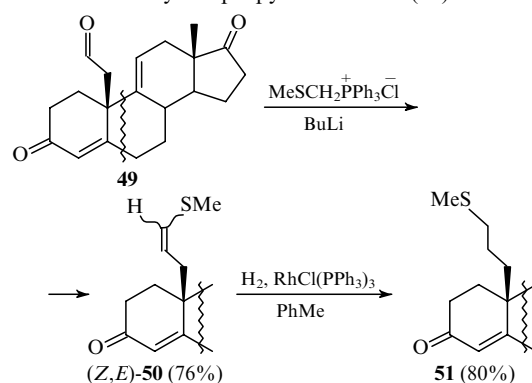
The thiol **41** was used as the starting compound in the synthesis of thio derivatives **40f–j**. This has been obtained by the Mitsunobu reaction from the alcohol **38** and thioacetic acid in the presence of PPh₃ and diethyl azodicarboxylate followed by hydrazinolysis. Alkylation of the thiol group of compound **41** with alkyl halides or 2,4-dinitrophenylsulfenyl chloride gave compounds **40f–j** in good yields (see Scheme 2). Thioacetals **43a,b** were prepared by the reaction of the aldehyde **42** obtained by the Swern oxidation of the alcohol **38** with methane- or ethanethiol, respectively, in the presence of boron trifluoride etherate. Compounds **40k–p** were synthesised by the reaction of the disulfide **40g** with various organometallic reagents. The methyl thiocarboxylate **45** was obtained from the key compound **37** in three steps which included hydrolysis of the ester function, activation of the resulting acid **44** with ethyl chloroformate and reaction with sodium methanethiolate (Scheme 3).

Methylthiovinyl steroids **48** and **50** have also been described.⁴⁶ The acetoxy derivative **47** was deacetylated into the corresponding 3,17-diol which was introduced into the reaction with diethyl methylthiomethylphosphonate and butyllithium. The thus prepared (10*E*)-methylthiovinyl derivative was further oxidised into steroid **48**.

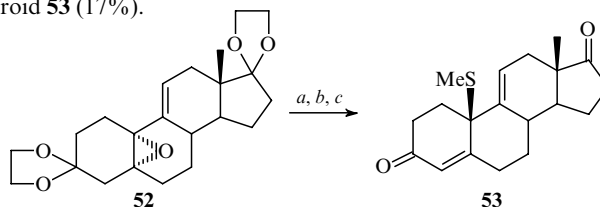


(a) KOH, MeOH (78%); (b) MeSCH₂PO(OEt)₂, BuLi (76%); (c) Al(OPr)₃, CHex (74%).

An analogous reaction of the homologous aldehyde **49** with (methylthiomethyl)triphenylphosphorane gave a 1 : 1 mixture of chromatographically separable *E*- and *Z*-isomers **50** in total yield 76%. Hydrogenation of this mixture in the presence of the Wilkinson catalyst gave compound **51** in 80% yield which contained a 3-methylthiopropyl residue at C(10).

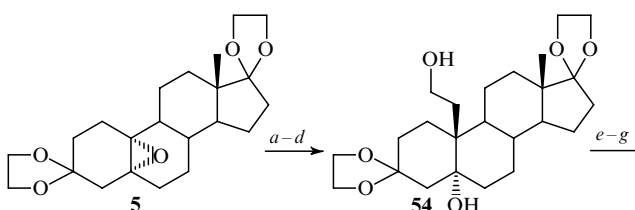


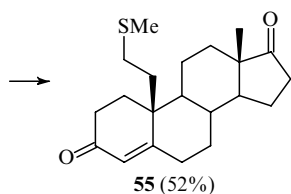
And, finally, the opening of the 5 α ,10 α -epoxide ring of estrane **52** with lithium methanethiolate which is analogous to that described above for compound **5**,^{14,43} and subsequent deketalisation and elimination of the 5 α -hydroxy group resulted in $\Delta^{4,9(11)}$ -steroid **53** (17%).



(a) MeSLi, THF, 1 h, 20 °C; (b) 6 N HCl; (c) 0.1 N NaOH (17%).

The opening of the 5 α ,10 α -epoxide ring of the estrane **5** with monolithium acetylide with subsequent partial hydrogenation of the hydroxy alkyne and hydroboration of the resulting alkene gave the diol **54**. Its mesylation and subsequent reaction of the mesylate with sodium methanethiolate followed by acid hydrolysis gave the ring C-saturated analogue of the steroid **40a**, *viz.*, 19-methylthiomethyl-AD **55**.



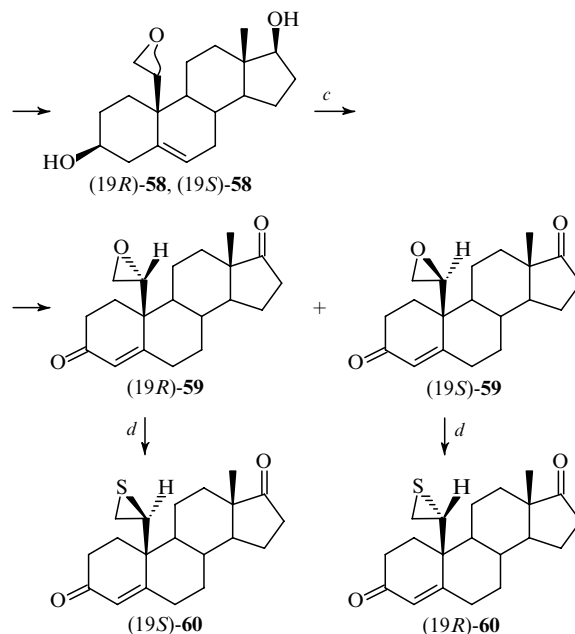
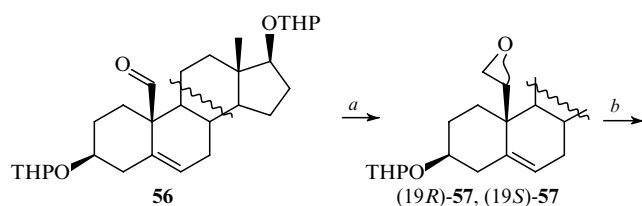


(a) $\text{LiC}\equiv\text{CH}$, ethylenediamine (EDA), 50 °C, 96 h, 81%; (b) H_2 –10% $\text{Pd}(\text{OH})_2/\text{BaSO}_4$, EtOAc-Py ; (c) $\text{BH}_3\cdot\text{Me}_2\text{S}$, THF, 35 °C, 4 h; (d) 30% H_2O_2 , NaOH, 0 to 20 °C, 12 h, 67%; (e) MsCl , Et_3N , CH_2Cl_2 , 0 °C, 45 min; (f) MeSNa , DMF, 20 °C, 1 h; (g) HCl , EtOH, 20 °C, 3 h.

The results of *in vitro* and *in vivo* studies of activities of the majority of compounds synthesised by Lesuisse *et al.*⁴⁶ suggest that the steroids with one- or two-carbon chains having a terminal thioether function at position 10 (e.g., **22f**, **40a,b**, **55**) are the most efficient AI. The presence or the absence of the 9(11)-double bond does not practically affect their inhibitory activity.⁴⁸ Compound **40a** was the most reactive among other compounds assayed and was considered⁴⁶ to be one of the best AI available to date. On the contrary, the steroids with the sulfur atom attached directly to the steroid skeleton (**53**) or separated from it by three carbon atoms (**51**) have practically no affinity for the enzyme. The key property of the efficient AI of this series is the ability of the sulfur atom to react with the heme iron of the porphyrin moiety of the enzyme (compounds **22f**, **40a** and **55**), whereas compound **53** reacts only with the lipophilic steroid-binding centre of the enzyme. This behaviour is consistent with the hypothesis^{14,41} that the incorporation of one methylene group between the sulfur atom and position 10 of the steroid skeleton alters the character of the interaction of the steroid substrate with the enzyme. The fact that AI with a two-carbon chain at C(10) react most efficiently with the heme $\text{Fe}(\text{III})$ allowed Lesuisse *et al.*⁴⁶ to suppose that the iron atom is separated from the 19-methyl group of the substrate by a distance equivalent to two methylene groups at the oxidation steps of AD. This hypothesis is consistent with the generally accepted mechanisms of aromatisation.^{15,16} The effect of the substituent at the sulfur atom in the molecule of AD analogues on the inhibition of aromatase has also been studied. Sulfur-containing steroids with methyl, vinyl or ethynyl substituents at the sulfur atom (compounds **40a**, **1** and **p**, respectively) possessed the highest affinity for the enzyme. Substitution of the ethyl group (**40b**) for the methyl group (**40a**) decreases the activity of the steroid substrate 72-fold. Compounds with hydroxyethyl (**40e**) and cyclopropyl groups (**40o**) are completely devoid of activity, while compounds with allyl (**40j**), phenyl (**40d**), prop-2-ynyl (**40h**) and methylthiomethyl (**40i**) groups possess certain activity. Disulfides **40g,m,n**, thioacetals **43a,b** and analogues **48** and **50** with a double bond in the side chain at C(10) are also inactive as AI.

Compound **40a**, which is the most active in this series, decreases the estradiol level and inhibits the growth of endocrine tumours *in vivo* when used at a dose of 0.4 mg kg^{-1} .⁴⁹

Yet another type of 19-substituted androstanes, *viz.*, 10 β -(oxiran-2-yl)- and -(thiiran-2-yl)-steroids, represent competitive reversible AI. The synthesis of diastereomeric 10 β -(epoxyethyl)estr-4-ene-3,17-diones (19*S*)-**59** and (19*R*)-**59** was carried out in four steps.^{50–52}

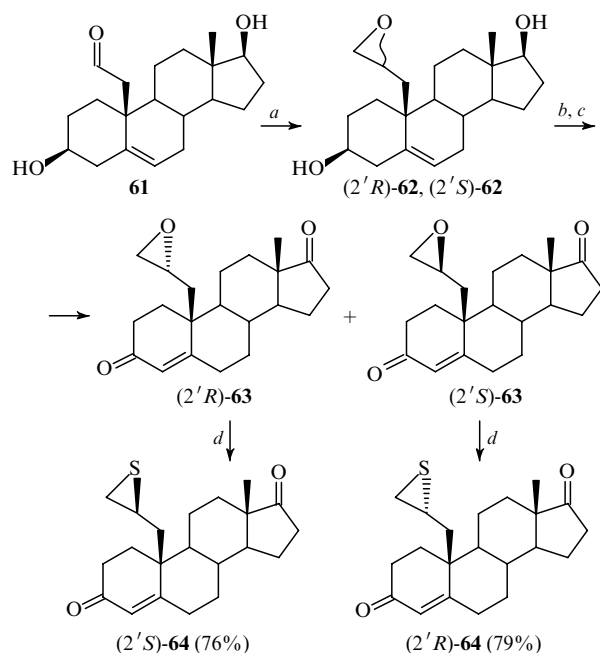


(a) Me_2SCH_2 (or Me_2SOCH_2), THF or DMSO; (b) $\text{Py}\cdot\text{HSO}_3\text{C}_6\text{H}_4\text{Me}$, 20 °C, 4 h; (c) $\text{Al}(\text{OPr})_3$, CHex; (d) Ph_3PS is picric acid, PhH, 80 °C, 16 h.

Reaction of the tetrahydropyranyl derivative of 19-aldehyde **56** with dimethylsulfonium methylide (or dimethylsulfoxonium methylide) in THF gives a mixture of oxiranes (19*R*)-**57** and (19*S*)-**57** in 26% and 74% yields, respectively. Under other reaction conditions, *i.e.*, in DMSO in the presence of dimethylsulfonium methylide at 0 °C, the ratio of diastereomeric products is changed: the (19*R*)-**57** isomer becomes predominant.⁵¹ Deprotection and chromatographic separation of diols (19*R*)-**58** and (19*S*)-**58** with subsequent Oppenauer oxidation of each of the diastereomeric alcohols gave individual isomers (19*R*)-**59** and (19*S*)-**59**, respectively. Steroid thio analogues (19*R*)-**60** and (19*S*)-**60** were obtained from oxiranes **59** by reaction of the latter with excess of triphenylphosphine sulfide and picric acid in benzene.⁵³

The configuration of isomeric 10 β -oxiranes **59** (*R* or *S*) was established from X-ray analysis. It was shown that the oxirane ring in the stereoisomer (19*R*)-**59** is positioned over the ring *A* in the direction towards C(1) and C(2) in a manner similar to that of the 19-hydroxy group in 19-hydroxy-AD **28**. On the contrary, the three-membered ring in the molecule of (19*S*)-**59** is positioned over the ring *B* and directed toward C(6).^{31,51,54} Presumably, it is these stereochemical peculiarities that are responsible for the difference in the binding and inhibitory activities of these compounds. Both of them are potent competitive AI with K_i 7 and 75 nM, respectively. Thiiranes (19*R*)-**60** and (19*S*)-**60** manifest an even greater stereoselectivity of binding: K_i for (19*R*)-**60** is 1–2 nM and that for (19*S*)-**60** is 75 nM.⁵¹ In another study⁵⁴ it was shown that (19*R*)-isomers of oxiranes and thiiranes are more active (36-fold and 80-fold, respectively) than the corresponding (19*S*)-diastereomers. Spectroscopic studies with purified aromatase showed that the inhibition involved reversible binding of the oxygen (or sulfur) atom of the oxirane (or thiirane) with the heme iron of the enzyme.^{15,51,54} The knowledge of the spatial structure of these compounds made it possible to assume that the modified steroid inhibitor is bound in exactly the same way as does the natural substrate (AD) and that the heme iron is localised in close proximity to the 19-methyl group of the androgen molecule.⁵⁴ It is of note that with neither 19-hydroxy, nor 19-methoxy derivatives of AD is such coordination possible.¹⁵ Thus, coordination with the heme iron of the enzyme, together with the binding selectivity inherent in 10 β -(oxiran-2-yl)- and -(thiiran-2-yl)-steroids make these AD analogues highly specific aromatase inhibitors.

The synthesis of homologous 19-(oxiran-2-yl)- (**63**) and 19-(thiiran-2-yl)-AD (**64**) continued the series of investigations aimed at establishing the localisation of the aromatase heme iron during its binding with the steroid substrate.⁵⁵

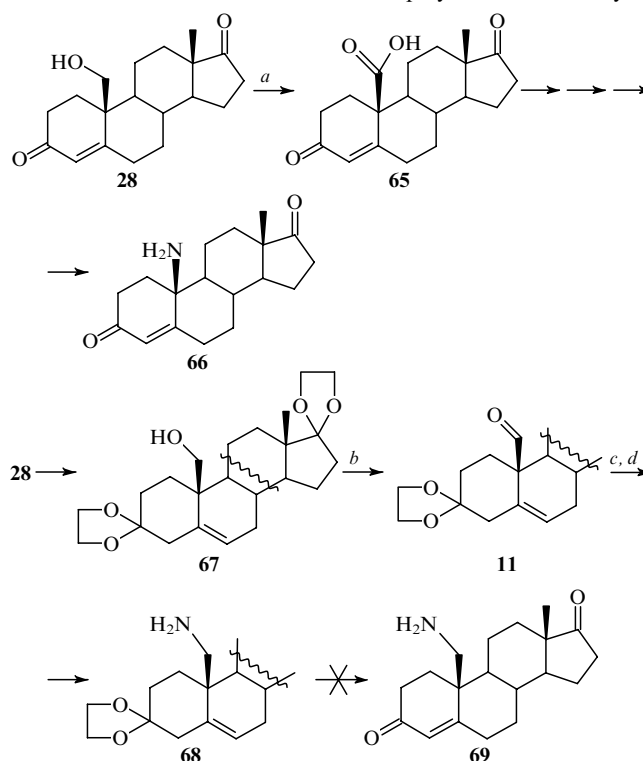


(a) $\text{Me}_2\text{SCH}_2^+$ (or $\text{Me}_2\text{SOCH}_2^+$), THF, 4 °C (75%); (b) $\text{CrO}_3 \cdot \text{Py}$, CH_2Cl_2 , 25 °C, 20 min; (c) diazabicyclononene (DBN), CH_2Cl_2 , 25 °C, 18 h; (d) Ph_3PS , PhH , Δ , 18 h.

The methodology of the synthesis of these compounds is analogous to those used in the synthesis of 10 β -(oxiran-2-yl) and -(thiiran-2-yl) steroids⁵² with 3 β ,17 β -dihydroxyandrost-5-ene 19-carbaldehyde **61** as the starting compound.³⁰ Unlike the 10-formyl analogue **56**, this reacted with both dimethylsulfonium and dimethylsulfoxonium methylide to give a chromatographically separable mixture of diastereomeric oxiranes (2'*R*)-**62** and (2'*S*)-**62** of the same composition (3 : 1) in 75% yield. This result is rationalised by higher spatial accessibility of the aldehyde group in the molecule of compound **61**. After separation into individual diastereomers, epoxy diols **62** were converted into diketones (2'*R*)-**63** and (2'*S*)-**63** by the Collins oxidation with subsequent isomerisation of resulting Δ^5 -3,17-diketones with diazabicyclonene. The configuration of epoxide (2'*R*)-**63** was established by X-ray analysis. Reaction of this oxirane with triphenylphosphine sulfide and picric acid gave thiirane (2'*S*)-**64** in 76% yield. Analogously, thiirane (2'*R*)-**64** was obtained from (2'*S*)-**63** in 79% yield. The *R*- and *S*-configuration of thiiranes **64** was ascribed on the basis of the established stereochemistry of the oxirane precursors and the known stereochemical regulation of thiirane formation.⁵⁵ Oxiranes **63** and thiiranes **64** are competitive AI; the latter possess higher activity than the corresponding oxiranes. (2'*S*)-Isomers of both compounds are more efficient inhibitors than 2'*R*-diastereomers. The inhibition constant of the strongest inhibitor, *viz.*, the thiirane (2'*S*)-**64**, is 22 nM. The oxygen and sulfur atoms in the oxirane (2'*S*)-**63** and the thiirane (2'*S*)-**64** molecules coordinate with the aromatase heme iron during their interaction with the enzyme similarly to the corresponding (19*S*)-diastereomers **59** and **60**. Here, the weaker inhibitor possesses weaker affinity for the heme iron of cytochrome P-450. The configuration of the 2'-centre of the three-carbon chain at C(10) is crucial for the stereoselectivity of inhibition.⁵⁵ Thus, strong competitive inhibition of aromatase and coordination of the heteroatom in the steroid substrate are observed even in those cases where the oxygen or the sulfur atom in the three-membered ring are separated from C(10) by a methylene group (*cf.* Ref. 46).

Having considered the AD analogues containing an oxygen or a sulfur atom at positions 10 or 19, one may conclude that sulfur-containing steroids are the most potent inhibitors and that compounds with a methylene group between the steroid skeleton and the heteroatom manifest higher inhibitory activity. A characteristic feature of compounds of this series is the stereoselectivity of their interaction with the enzyme.

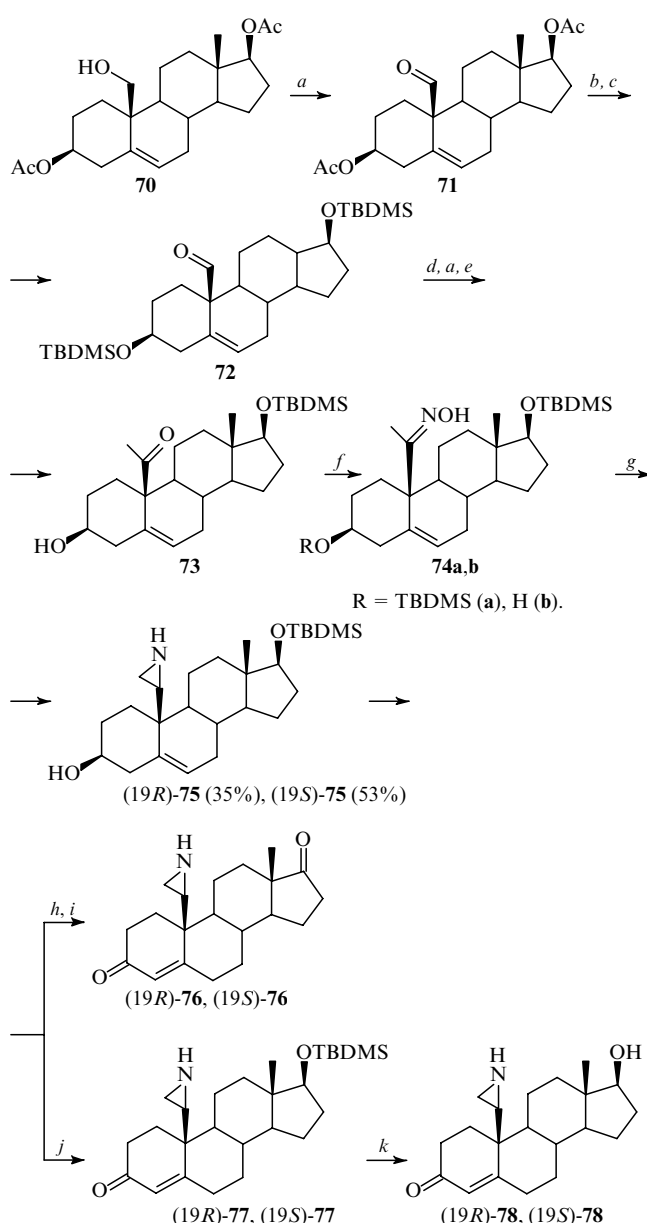
Synthesis of AD derivatives containing nitrogen at position 19, which bind with iron of the aromatase heme by virtue of coordination similarly to sulfur-containing steroids was described by Robinson in 1993,⁵⁶ although attempts to synthesise such derivatives were undertaken earlier.⁵⁷ Thus 10 β -aminoestr-4-ene-3,17-dione **66** was obtained by the Curtius rearrangement of the corresponding derivative of 19-acid **65**. However, all the attempts to obtain its homologue, *viz.*, 19-aminomethyl-AD **69**, failed, although its diketal derivative **68** was obtained in high yield from 19-hydroxy-AD **28**. Compounds **66** and acetamido and trifluoroacetamido derivatives of diketone **69** displayed low AI activity.⁵⁷



(a) $\text{CrO}_3 - \text{H}_2\text{SO}_4$; (b) $\text{Py} \cdot \text{CrO}_3$ (93%); (c) $\text{NH}_2\text{OH} \cdot \text{HCl}$ (88%); (d) Ni/Ra , EtOH, 2 M NaOH (89%).

Oxime **74** obtained from the accessible 3,17-diacetate of the triol **70** in seven steps (Scheme 4) was the key compound in the synthesis of 10 β -(aziridin-2-yl)-steroids.⁵⁶ Oxidation of compound **70** with tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide as a co-oxidant gave 19-aldehyde diacetate **71** in high yield; the latter was further converted into diol and then into bis-*tert*-butyldimethylsilyl ether **72**. Methylation of the aldehyde **72** with methyl lithium occurred in quantitative yield. Oxidation of the 19-hydroxy-19-methyl derivative and selective desilylation of the thus obtained 10 β -acetyl derivative gave 17-silyl ether **73**. The latter was refluxed with hydroxylamine hydrochloride in pyridine to give a mixture of key oximes **74a,b** in 70% yield. On treatment with lithium aluminium hydride in THF, the oxime **74b** was converted into a mixture of (aziridin-2-yl)-steroids (19*R*)-**75** and (19*S*)-**75** isolated in the individual states with 35% and 53% yields, respectively. Each of them was further converted into (19*R*)- and (19*S*)-10 β -(aziridin-2-yl) diketones **76** (in 39% and 41% yields, respectively) *via* the corresponding diols. 17 β -Hydroxy analogues (19*R*)- and

Scheme 4



(a) Tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO), CH₂Cl₂, 20 °C; (b) 10% KOH, MeOH, 90%; (c) Bu^tMe₂SiCl ((TBDMS)Cl), DMF; (d) MeLi, Et₂O; (e) TBAF, THF; (f) NH₂OH·HCl, Py, Δ; (g) LAH, THF, Δ, 18 h; (h) HF, H₂O, EtOH, 20 °C, 2.5 h; (i) Al(OPrⁱ)₃, LAH; (j) Al(OPrⁱ)₃, 4-methylpiperidone; (k) HF, H₂O, MeCN, 20 °C, 2 h.

(19*S*)-**78** were synthesised from the aziridines (19*R*)- and (19*S*)-**75** via intermediate Δ⁴-3-ketones **77**. The stereochemistry of these compounds was established by deamination of diastereomeric aziridines **76** and **78** with sodium nitrite in aqueous acetic acid into the known 10β-vinylestr-4-ene-3,17-diones and the corresponding 17β-alcohols. The configuration of the (aziridin-2-yl)-steroid (19*R*)-**78** was also confirmed by X-ray analysis.

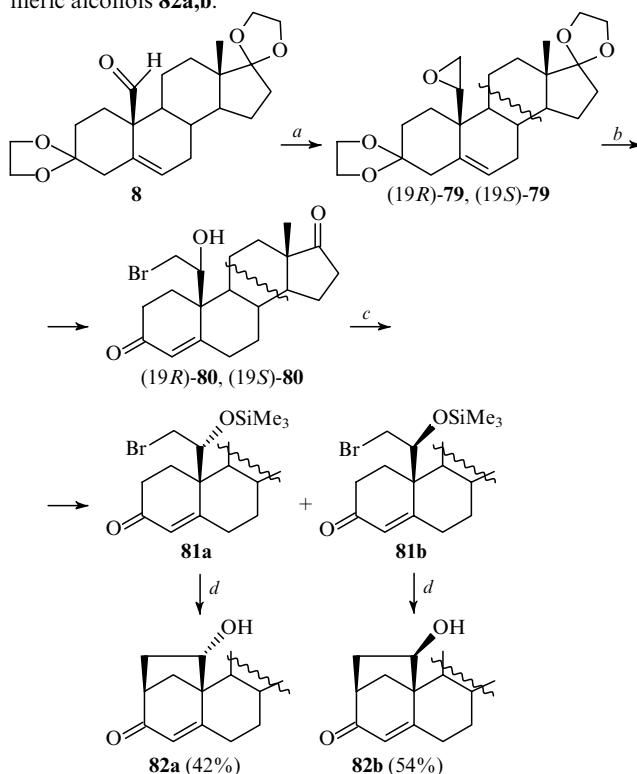
Compounds (19*R*)- and (19*S*)-**76** as well as (19*R*)- and (19*S*)-**78** are potent stereoselective AI with *K*_i = 3.4, 56.0, 30.0 and 693 nM, respectively. 10β-(Aziridin-2-yl)-steroid (19*R*)-**76** manifested the highest efficiency. Spectroscopic analysis of its interaction with preparations of microsomal aromatase have shown the coordination of the nitrogen atom of the aziridine ring with the iron atom of the cytochrome P-450 heme. Earlier, such a coordination was established for 19-azido-AD **22e**.¹⁷ These results suggest that the orientation and accessibility of the nitrogen

atom are crucial for efficient coordination.⁵⁶ It should be noted that *N*-acetylation of compounds **76** strongly decreases their inhibitory activity.⁵⁶

The recently described 10β-aziridinoestr-4-ene-3,17 dione was less active in comparison with the 10β-aziridine (19*R*)-**76**.⁵⁸

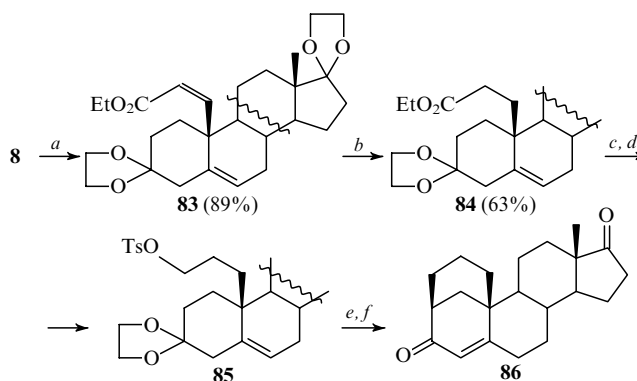
The synthesis of hydroxylated 2,19-bridged structures related to AD was described in 1991.¹¹ The key compound in this synthesis was 10β-epoxide **79** [a mixture of (19*R*)- and (19*S*)-isomers] obtained by reaction of the aldehyde **8** with dimethylsulfonium methylide.

The opening of the epoxide ring and removal of the ketal protection with 48% HBr in acetone gave a mixture of bromohydrins **80** [the (19*R*)-**80**/(19*S*)-**80** ratio was 7 : 1]. Chromatographically separable trimethylsilyl derivatives **81a** and **81b** were obtained by the action of bis(trimethylsilyl)-acetamide in DMF. Intramolecular alkylation at C(2) under the action of lithium bis(trimethylsilyl)amide in THF and subsequent treatment of the reaction mixture with an acid complete the synthesis of diastereomeric alcohols **82a,b**.



(a) Me₃Si⁺, NaCH₂SOCH₃, DMSO, THF, 98%; (b) HBr, H₂O, Me₂CO; (c) CH₃C(=NSiMe₃)OSiMe₃ (BSA), DMF; (d) LiN(SiMe₃)₂, HCl, THF.

The synthesis of diketone **86**, which is homologous to these bridge structures, was carried out in five steps.^{59, 60}

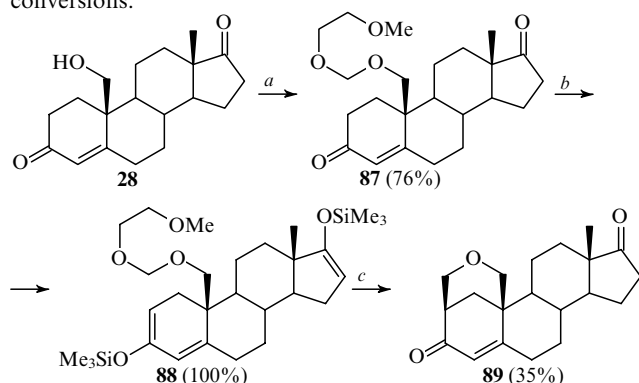


(a) (EtO)₂P(O)CH₂CO₂Et; (b) Mg, MeOH; (c) LAH (93%); (d) TsCl, Py, 60%; (e) H⁺ (60%); (f) LiN(SiMe₃)₂, THF, -78 °C (62%).

In this case, too, the same bisketal **8** was used as the starting compound. Its reaction with triethyl phosphonoacetate gave the unsaturated derivative **83** in high yield, and the double bond was reduced with magnesium in methanol. The ester function in the thus prepared compound **84** was reduced into the alcohol function which was then tosylated. Removal of 3,17-diketal protection in the tosylate **85** and cyclisation of 19-(2-tosyloxyethyl)-AD with lithium bis(trimethylsilyl)amide in THF gave the final product, 2 β ,19-ethylene-AD **86**.

The section devoted to bridge structures can be completed by the description of a synthesis of 2 β ,19-methyleneoxy-AD **89**.

The methoxyethoxymethyl ether (MEM) **87** prepared from 19-hydroxymethyl-AD **28** was converted into the homoannular dienol **88** silyl ether. The latter underwent Lewis acid-catalysed intramolecular alkoxyalkylation at C(2) involving the acetal carbon atom of the MEM-protective group to give the bridge steroid **89**. It is noteworthy that the MEM ether group played the role of both the protective group and the reagent in these conversions.



(a) $\text{ClCH}_2\text{OCH}_2\text{CH}_2\text{OMe}$, $(\text{Me}_2\text{CH})_2\text{NEt}$, CH_2Cl_2 , 20 °C, 20 h;

(b) LDA, Me_3SiCl , THF, -20 °C, 0.5 h; (c) TiCl_4 , CH_2Cl_2 , -20 °C, 0.5 h.

Some sulfur-containing analogues of the steroid **89** have been recently patented.⁵⁹

2 β ,19-Bridged steroids **82a,b**, **86** and **89** appeared to be sufficiently active AI.^{11, 59–61} Bromohydrins **80** also manifested a certain AI activity (see Table 1).¹¹

2. 4-Substituted androstanes

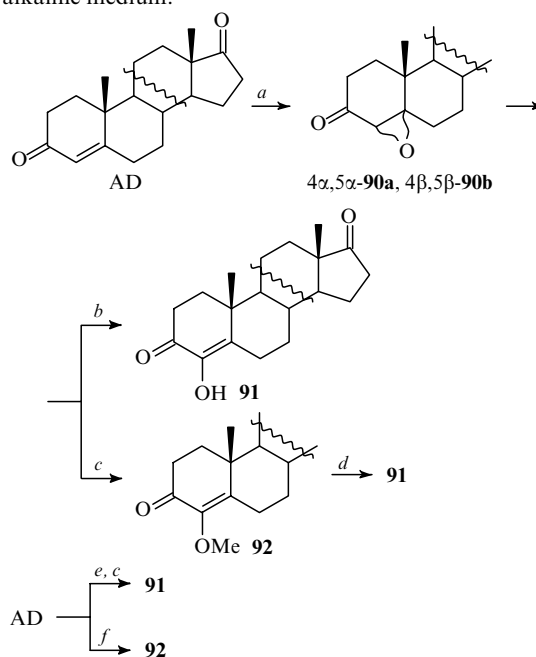
Of all substituted androstanes, particularly of those substituted at position 4, 4-hydroxyandrost-4-ene-3,17-dione (4-OHA) **91** is the most popular and well-studied. It was first described in 1977⁶² as a competitive AI. Later, it was shown to represent a suicide irreversible AI; according to different estimates, its K_i ranges from 1 to 50 nM.^{19, 55, 62–64} This steroid is the basis of one of a few (if not the only) steroid inhibitors of aromatase that is already used in clinical practice.⁶⁵ This compound is known under the trade name 'formestane' and is used for the treatment of hormone-dependent mammary tumours in women in the post-menopausal period.^{8, 15, 48, 66–71}

All the syntheses of 4-OHA **91** described in the literature involved acid- or base-catalysed opening of 4,5-epoxides **90a,b**. The latter are obtained by treatment of AD with hydrogen peroxide in an alkaline medium.

Epoxidation of conjugated steroid ketones is a well-known reaction. In the case of Δ^4 -3-ketones, it affords a mixture of 4 α ,5 α - and 4 β ,5 β -oxides in which the latter predominates. The conditions for this reaction have not practically changed since the publication by Bible *et al.*⁷² in 1957. However, the overall yields described therein were rather low and poorly reproducible. Various modifications of reaction conditions failed to increase the yields considerably,^{73–75} although a successful synthesis of epoxides **90a** and **90b** (1 : 5, total yield 90%) is documented.⁴⁸

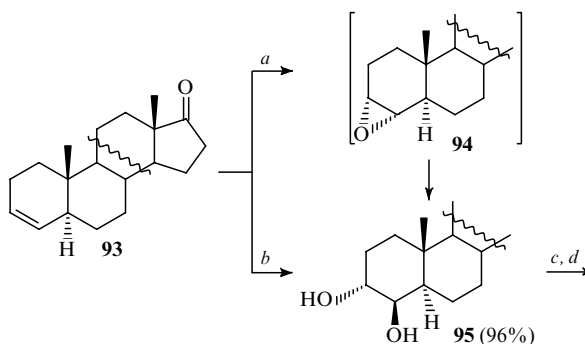
The opening of the epoxide ring in compounds **90a,b** results in 4-hydroxy-substituted AD **91** in up to 50% yields.^{14, 48, 74–78} The

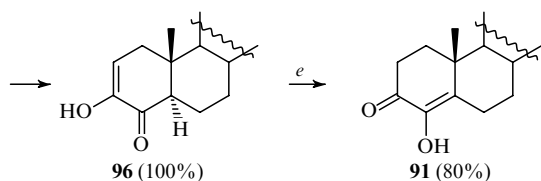
steroid **91** was also obtained in a satisfactory yield by opening of the isomeric epoxides **90a,b** and hydrolysis of the ether **92**.¹³ Rearrangement of the epoxides **90a,b** in the presence of boron trifluoride etherate in benzene and chromatographic separation of side products (*e.g.*, 4-nor-3-oxo-5 α -carbaldehyde) gave the target steroid **91** in 34% yield.¹⁴ The ether **92** was synthesised in 25% yield by treatment of AD with *o*-iodosylbenzoic acid and alkali in methanol.⁷⁹ Special mention should also be made of a recently developed procedure for the synthesis of 4-OHA **91** (47% yield) which involves hydroxylation of AD with $\text{OsO}_4/\text{H}_2\text{O}_2$ with subsequent dehydration of the resulting mixture of 4,5-diols in an alkaline medium.⁷⁰



(a) H_2O_2 , OH^- ; (b) AcOH, H_2SO_4 , or Me_2CO , H_2O , H_2SO_4 , or HF, Py, or $\text{BF}_3 \cdot \text{Et}_2\text{O}$, PhH; (c) MeOH, NaOH (62%); (d) HCl, dioxane, Δ (53%); (e) OsO_4 , H_2O_2 , Bu^tOH, 20 °C; (f) $\text{OIC}_6\text{H}_4\text{CO}_2\text{H}$, MeOH, KOH (25%).

Introduction of 4-OHA **91** into the clinical practice and the steadily increasing number of publications devoted to the analysis of the topography of the active site of aromatase using various analogues of 4-OHA **91** (see, *e.g.*, Refs 80 and 81) have stimulated the search for alternative efficient methods of its synthesis. A recent publication,⁸² which describes a new approach to the synthesis of 4-OHA **91** by oxidation of easily accessible 5 α -androst-3-en-17-one (**93**), is an example. The latter was obtained by reduction of AD with zinc in acetic acid.⁸³ Treatment of steroid **93** with performic acid generated *in situ* gives *trans*-diaxial diol **95** in 96% yield. Oxidation of androst-4-ene-3-one **93** in dichloromethane resulted in 3 α ,4 α -epoxide **94** as the only identified and isolated reaction product. Further oxidation of the diol **95** with dimethyl sulfoxide activated with trifluoroacetic anhydride gives hydroxy ketone **96** in quantitative yield. The latter is isomerised into the final steroid **91** on treatment with a base.

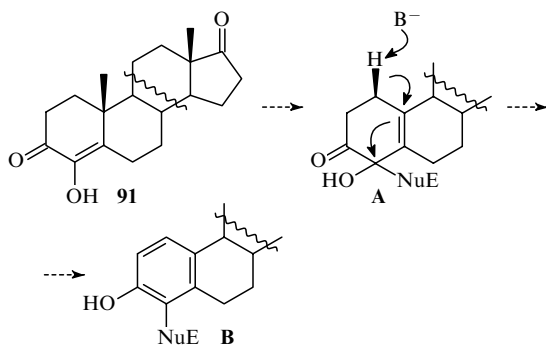




(a) H_2O_2 , HCO_2H , CH_2Cl_2 , 20 °C, 6 h; (b) H_2O_2 , HCO_2H , 20 °C, 1 h;
(c) DMSO, $(\text{CF}_3\text{CO})_2\text{O}$, -60 °C, 3 h; (d) Et_3N , -60 °C, 15 min;
(e) NaOMe , 20 °C, 1 h.

High yields in all the stages of this synthesis and the accessibility of the starting steroid **93** (the authors propose to use a mixture of 5 α - and 5 β -isomers) illustrate the high outlook of this approach.

The mechanism of the inhibitory effect of 4-OHA **91** on aromatase has not been completely elucidated. An inactivation mechanism, which involves the formation of a covalent bond between the enzyme and position 4 of the steroid substrate (which, in turn, changes the direction of the final stage of elimination), has been proposed by Covey.²⁴ Protonation of the hydroxy group at position 4 of the substrate and its elimination as a water molecule occurs in the enzyme-bound intermediate **A** (instead of removal of the enzyme as the nucleophile, which normally takes place).



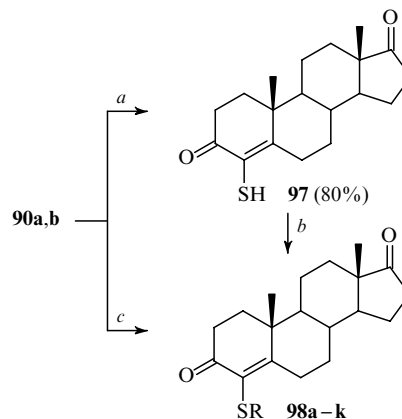
Nu is the nucleophile, E is the enzyme.

Inactivation of the enzyme, which cannot 'kick off' the steroid substrate, follows aromatisation of the steroid ring **A** with the formation of structure **B**. A great number of 4-OHA **91** analogues have been synthesised aimed at elucidating the mechanism of its action and obtaining more efficient aromatase inhibitors. Thus its 6 α -methyl analogue obtained by hydrolysis of the corresponding 4,5-epoxide in a mixture of acetic and sulfuric acids has been described.⁸⁴ 4-Acetoxy-AD^{63,64,85} possessed inhibitory properties, whereas 4-methoxy-AD **92** was inactive.⁷⁴ However, recent *in vitro* studies have shown that 4-methoxy-AD **92** suppressed the proliferative activity of cancer cells.⁸⁶

Although 4-OHA **91** is an active AI, it is characterised by low bioavailability and short-term action and manifests *in vivo* activity only on subcutaneous administration, which is due to the ease of its glucuronidation.^{67,87,88} The quest for the synthesis and analysis of its various analogues thus becomes understandable. Besides, these studies were aimed at establishing the structural demands for the design of novel AI.

A prominent role among formestane **91** analogues belongs to 4-alkylthio- and 4-arylthio-AD. Several compounds of this series (**98a–e**) were obtained in the 80's^{89,90} by the opening of epoxides **90a,b** with the corresponding thiol reagents. All of them appeared to be efficient competitive AI with K_i ranging from 36 to 73 nM.⁹⁰ It was found that the chain length at C(4) of alkylthio analogues of such steroids should not exceed three carbon atoms in order to preserve a sufficiently high inhibitory activity.⁹⁰ 4-Phenylthio-AD **98d** (25 and 50 mg per kg per day) inhibited the growth of mammary tumours in rats.⁹¹

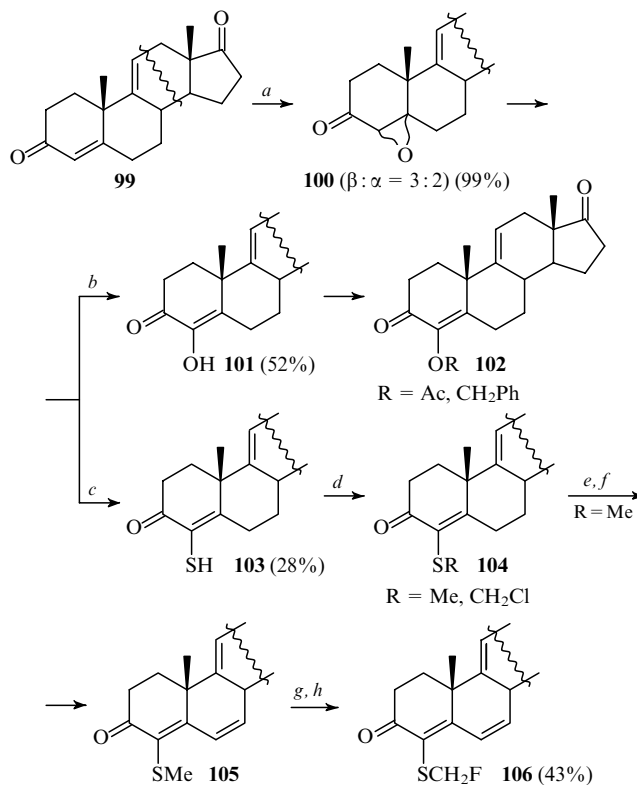
The thiol **97** was synthesised in high yield by the opening of epoxides **90a,b** with thioacetic acid in dioxane. Its subsequent alkylation with various functionalised alkyl halides gave a series of



(a) AcSH , dioxane, MeOH , HCl ; (b) RX , Bu^tOK , THF ; (c) RSH ; $\text{R} = \text{Me}$ (**a**), Et (**b**), Pr (**c**), Ph (**d**), CH_2Ph (**e**), CH_2F (**f**), CH_2Cl (**g**), CHF_2 (**h**), CH_2CN (**i**), CH_2OMe (**j**), CH_2SMe (**k**).

4-alkylthio-AD **98f–k** containing hetero atoms in the substituent at C(4).^{48,92}

4-Thio-substituted **98f–h** were comparable in activity with 4-OHA **91** (see Table 2). The difluoromethyl analogue **98h** was found to be a reversible AI, whereas the fluoromethyl and chloromethyl analogues **98f** and **98g** are suicide AI with $K_i = 30$ nM (*cf.* K_i for 4-OHA **91** is 27 nM⁴⁸). *In vivo* activity of compound **98f** is comparable with that of 4-OHA **91** and, like the latter, it is inactive on *per os* administration.⁴⁸ It is noteworthy that the presence of an additional 9(11)-double bond in these analogues, like in 19-sulfur-containing steroids **40a–o**, does not influence their affinity and inhibitory activity with respect to aromatase. A similar conclusion was made from the biochemical analysis^{48,88} of some 4-alkyl(aryl)thio- $\Delta^{9(11)}$ -AD **102–106** (their synthesis is shown below). The most active compound of this series is the steroid **104** ($\text{R} = \text{CH}_2\text{Cl}$) ($K_i = 27$ nM).⁴⁸

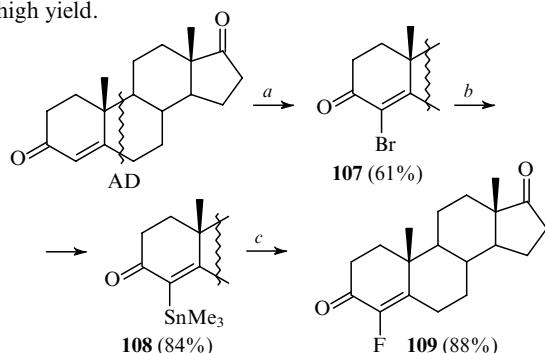


(a) H_2O_2 , NaOH , CH_2Cl_2 , MeOH , 4 °C, 1 h; (b) H_2SO_4 , AcOH , 4 h, 20 °C; (c) AcSH -dioxane, MeOH , HCl ; (d) RX , Bu^tOK , THF ; (e) $\text{HC}(\text{OEt})_3$, EtOH , *p*-TsOH; (f) chloranil; (g) MCPBA; (h) DAST, CHCl_3 , Δ .

Table 2. Data on *in vitro* inhibition of aromatase from human placenta by 4-substituted androstanes.

R	The presence of a $\Delta^{9(11)}$ double bond	K_i /nM	IC ₅₀ /nM	Ref.
OH (91)	—	10–37		31
		27	48, 123	
		50	55	
		67	124	
			43.7	9
OPh (176)	—	412		80
NH ₂ (112)	—	37		15
SH (103)	+	72		48
SCH ₂ Cl (98g)	—	30		48
SCH ₂ Cl (104)	+	27		48
SCH ₂ F (98f)	—	30		48
SCH ₂ CN (98i)	—	169		48

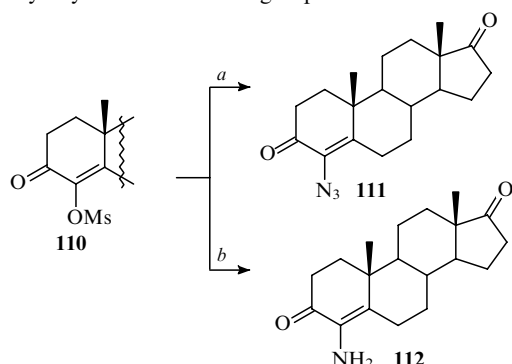
Other 4-substituted AD have been also obtained and assayed as AI. Thus 4-fluoro-AD **109** has been recently prepared from 4-bromo-AD **107**.⁹³ Conversion of bromide **107** into the 4-trimethylstannylated steroid **108** by hexamethyldistannane catalysed by tetrakis(triphenylphosphine)palladium and its subsequent treatment with cesium fluorosulfate gave 4-fluoro-AD **109** in high yield.



(a) Br₂, AcOH, Δ , –30 °C; (b) Pd(PPh₃)₄, (Me₃Sn)₂, PhMe; (c) FOSO₃Cs, CH₂Cl₂, MeOH, N₂, 0 to 20 °C.

4-Fluoro-AD **109** is comparable with 4-OHA **91** in its inhibitory activity; however, its practical application is limited due to its low bioavailability.⁹⁴ The synthesis of 4-chloro-AD is given in a patent.⁹⁵

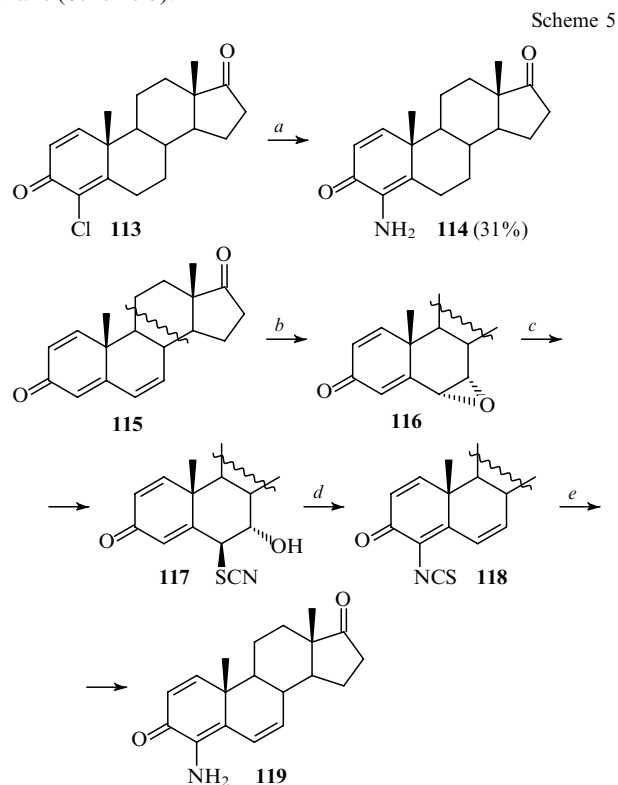
Among other 4-substituted AD, special mention should be made of 4-azido-AD **111** and 4-amino-AD **112** prepared from 4-mesyloxy-AD **110** according to patent data.⁹⁶



(a) NaN₃, H₂O, 60 °C, 1 h; (b) NaN₃, 100 °C, 1.5 h.

Highly active 4-amino-androstenediones **114** and **119** present special interest. One of them, 4-aminoandrosta-1,4,6-triene-3,17-dione **119**, appeared to be an efficient AI and was recommended for treatment of mammary tumours. This compound has passed successfully clinical trials under the trade name of 'minamestane'.^{97–99}

4-Aminoandrosta-1,4-diene-3,17-dione (**114**) was obtained by ammonolysis of the corresponding 4-chloro derivative **113**⁹⁵ in dioxane (Scheme 5).



(a) 30% NH₄OH, dioxane, 24 h; (b) 2 KSO₅ · KHSO₄ · K₂SO₄ – phosphate buffer, Me₂CO, 5–10 °C, 15 min; (c) KSCN; (d) DMF, 110–135 °C, 1.5 h; (e) dioxane–H₂O, 35% NaOH, 0.5 h.

The oxirane **116** obtained by selective epoxidation of the trienedione **115** was the key compound in the synthesis of minamestane **119**. Its reaction with potassium thiocyanate gave the 6-thiocyanate derivative **117**. Heating of the latter in DMF resulted in 4-isothionate **118** and its alkaline hydrolysis yielded the target compound, 4-aminotrienedione **119** (see Scheme 5).¹⁰⁰ Its 6- and 7-substituted analogues have been described in the patent.¹⁰¹

Studies of structure–activity relationships revealed the enhanced rate and selectivity of aromatase inhibition upon introduction of additional 1,2- and 6,7-double bonds into the molecule of 4-amino-AD **112**.⁹⁸ Steroids **114** and **119** are highly efficient and manifest *in vivo* antitumour activity both on subcutaneous and oral administration.^{9, 81, 97–99}

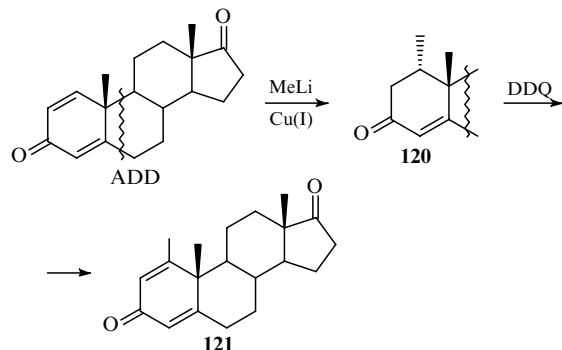
Thus, the majority of 4-substituted AD described above represent highly active irreversible AI with K_i ranging from 30 to 200 nM.¹⁰⁰

3. 1-Substituted androstanes

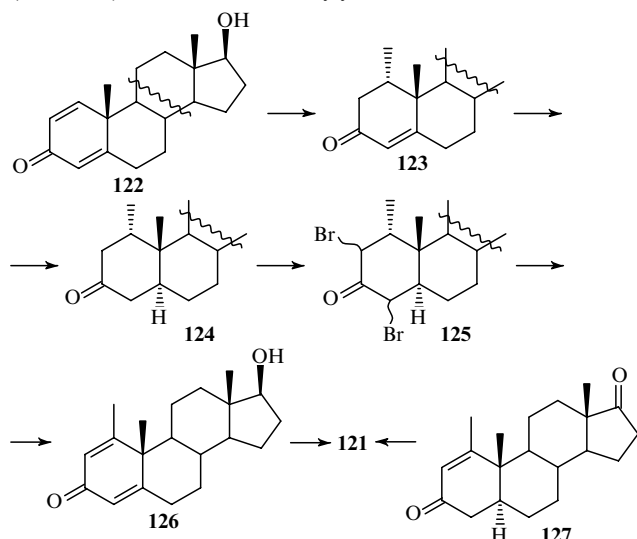
1-Methylandrosta-1,4-diene-3,17-dione (**121**) is the most valuable and perhaps the only steroid AI of this series. It was synthesised in 1983¹⁰² and patented under the trade name atamestane in more than a dozen countries. Atamestane is an irreversible inhibitor of estrogen biosynthesis *in vitro* and *in vivo*.^{102–105}

Androsta-1,4-diene-3,17-dione (ADD) is the starting compound in the synthesis of atamestane **121**. This synthesis required two principal problems to be solved, *viz.*, introduction of a methyl group into position 1 of the steroid skeleton and regeneration of

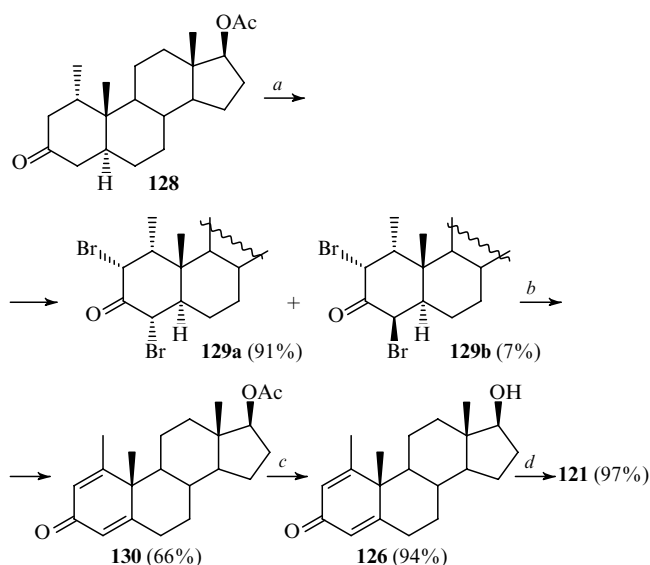
the 1,2-double bond in the resulting 1 α -methyl- Δ^4 -3-oxo derivative **120**. The first problem can be solved through selective 1,4-addition of organometallic compounds (*e.g.*, methyl lithium cuprates) to ADD.¹⁰⁶ However, the high cost of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) employed in 1,2-dehydrogenation of Δ^4 -4-ketosteroid **120** and the formation of a 4,6-dehydro derivative as a side product are the limiting factors.^{107, 108}



Early patents applied by the 'Schering AG' company dealt with the synthesis of atamestane **121** by oxidation of its 17 β -hydroxy derivative **126**¹⁰² or by microbiological dehydrogenation of the 1-methyl- Δ^1 -5 α -derivative **127** in up to 65% yields.^{109, 110} Compounds **126** and **127** were prepared in a multistep procedure (see below) and in unsatisfactory yields.



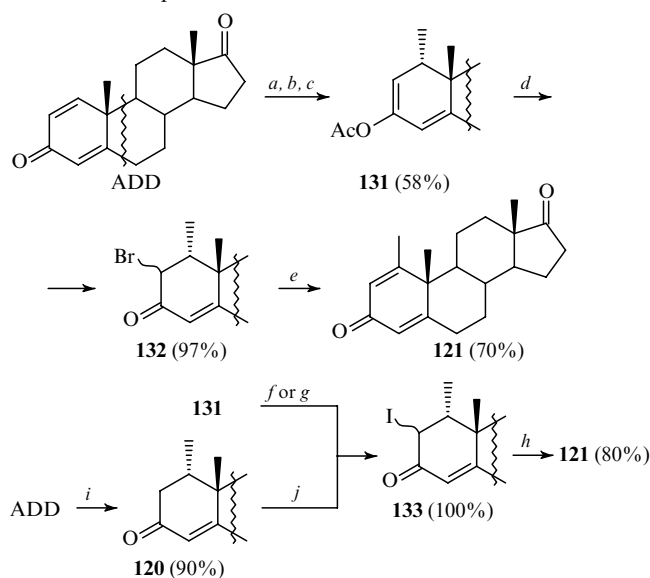
Thus the 4,5-double bond in the 1 α -methyl derivative **123** obtained from the dienone **122**¹⁰⁶ was reduced and the resulting compound **124** was brominated to give the 2,4-dibromosteroid **125**. Elimination of two HBr molecules from the dibromide **125** gave the dienone **126**.^{111, 112} Oxidation of the 17 β -hydroxy group in compound **126** gave the target product **121**. The characteristic feature of this synthetic scheme is that the 4,5-double bond in the intermediate compounds is first reduced and then recovered together with the formation of the 1,2-double bond. Obvious disadvantages of this scheme consist in the formation of an undesirable side product, *viz.*, 17 β -hydroxy-1 α -methylandrosterane-4,6-dien-3-one, and the necessity of tedious chromatographic purification following dehydrobromination. Nevertheless, this scheme has recently been applied¹¹³ in the synthesis of atamestane **121** from 1 α -methyl dihydrotestosterone acetate (**128**)¹¹⁴ with satisfactory yields at all steps.



(a) 2 equiv. Br₂, 4N HBr, AcOH, THF, 50 °C, 0.5 h; (b) LiBr, Li₂CO₃, DMF, 80 °C, 18 h; (c) MeOH, NaOH, Δ , 1.5 h; (d) TPAP–NMO, CH₂Cl₂, 20 °C.

Dibromination has led to the epimeric dibromides **129a,b** isolated in the individual state, and their configuration was established by ¹H NMR. However, dehydrobromination of compounds **129a,b** with lithium carbonate and lithium bromide occurred in only 66% yields. No formation of side products has been reported. The alcohol **126** prepared by deacetylation of the 17 β -acetoxy derivative **130** was oxidised into atamestane **121** using a tetrapropylammonium perruthenate–*N*-methylmorpholine *N*-oxide system in quantitative yield. The overall yield was 60%.¹¹³

A shorter and more efficient method for the synthesis of atamestane **121** which does not require chromatographic procedures has been patented.¹¹⁵



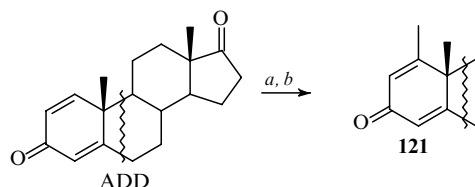
(a) MeLi, CuI, Cl(CH₂)₂Cl, –30 to 0 °C; (b) Ac₂O, Cl(CH₂)₂Cl, 20 °C; (c) NH₄Cl, H₂O, 20 °C; (d) 1,3-bromo-5,5-dimethylimidazolidin-2-one (dibromantin), dioxane, H₂O, 20 °C; (e) MgO, DMF, 110 °C, 2 h; (f) NaOAc, ICl, Me₂CO, –10 °C, 99% (2 β -I-isomer); (g) (CH₂CO)₂Ni, abs. MeOH, N₂, 20 °C, 55% (2 α -I-isomer); (h) Li₂CO₃, DMF, 130 °C, 1.5 h; (i) Me₃Al, 1 mol.% – 5 mol.% CuBr, Me₃SiCl, THF–PhMe, 20 °C; (j) I₂, CuO, glacial AcOH, N₂, 60 °C, 24 h.

The intermediate 1 α -methylenolate formed upon 1,4-addition of dimethylolithium cuprate to ADD in the presence of acetic anhydride is converted into the crystalline dienol acetate **131**. Bromination of the latter in aqueous dioxane gave a mixture of epimeric 2 ξ -bromo-1 α -methylandrosta-4-en-17-ones (**132**) in which the 2 β -isomer was predominant. Dehydrobromination of the bromo ketone **132** with magnesium oxide resulted in the target product **121** in 70% yield.

Dehydroiodination of the 2-iodo derivative **133** is a modification of the above-described procedure.¹¹⁶ This compound is formed from dienol acetate **131** and monochloroiodine in acetone in quantitative yield. When *N*-iodosuccinimide was used, the yield of the iodide **133** dropped to 55%. The 2-iodosteroid **131** was also obtained by iodination of 1 α -methyl- Δ^4 -3-ketone **120** with elementary iodine in glacial acetic acid. Dehydroiodination proceeded smoothly on boiling of the iodo derivative **131** with lithium carbonate in DMF.

Yet another method for obtaining the intermediate **120** for the synthesis of atamestane **121** was the use of trimethylaluminium in the presence of catalytic amounts (1 mol.% – 5 mol.%) of monovalent copper salts for the introduction of the 1 α -methyl group into ADD.¹¹⁷ Various modifications of this approach, in particular, the use of Lewis acids for acceleration of the reaction and suppression of competitive 1,2-addition and the mechanism of these reactions are discussed in detail with steroid 1,4-dien-3-ones and 1-en-3-ones as examples.¹¹⁴ It was shown that selective 1,4-addition of trimethylaluminium to ADD occurs in the presence of equimolar amounts of chlorotrimethylsilane and catalytic amounts of copper(I) bromide, the yield of 1 α -methylandrosta-4-en-3,17-dione **120** being 90%.

Finally, a single-step procedure for the synthesis of atamestane **121** from ADD has been patented.¹¹⁸ This method consists in successive treatment of ADD with trimethylaluminium in hexane with a stoichiometric amount of sterically hindered di-*tert*-butylphenol in the presence of catalytic amounts of nickel(II) acetylacetonate. The yield of steroid **121** was 42%.



(a) Me₃Al, *n*-C₆H₁₄; (b) 3,5-(Bu^t)₂C₆H₃OH, EtOAc, Ni(acac)₂, 58 °C, 2 h.

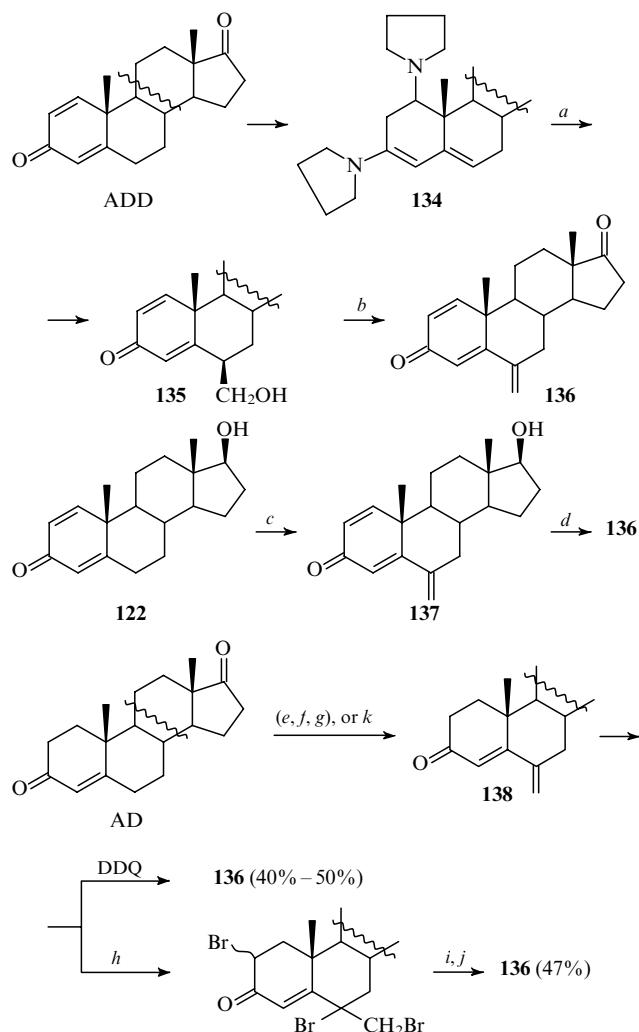
Syntheses of 15 α -alkyl atamestane analogues^{107, 119, 120} and 1 β ,2 β -cyclopropano-4-OHA have been patented.¹²¹

4. 6-Substituted androstanes

6-Methyleneandrost-1,4-diene-3,17-dione (**136**) synthesised in the late 80's as an anticancer drug known under the trade name 'exemestane' is the most well-known aromatase inhibitor of the 6-substituted androstane series. It represents an orally active irreversible selective AI.^{9, 122–124} Exemestane **137** is shown to be 2.5 times more active than formestane **91**.¹²⁴

Exemestane can be synthesised from both AD and ADD (Scheme 6). The key stage in this synthesis is methylenation of a steroid at position 6. When AD is used as the starting compound, the methylene group at position 6 is introduced by direct methylenation of 3-oxo-4,5-dehydrosteroid using the method of Annen *et al.*¹²⁵ The yields in this stage do not exceed 45%; the penultimate stage consists in 1,2-dehydrogenation of 6-methylene-AD **138** by boiling either with DDQ in anhydrous dioxane or with selenium dioxide in *tert*-butyl alcohol. The yields in the second stage are 40% – 50%.¹¹⁷ Thus, the overall yield of exemestane was as low as 20% – 25%. This scheme involves tedious chromatographic purification of reaction products in both stages and the use of an expensive reagent (DDQ). An

Scheme 6



(a) HCHO, PhH, EtOH, 90%; (b) MeOH, HCl, 20 °C, 5 h (80%); (c) HCHO, Me₂NH·HCl, AmⁱOH, 131 °C (31%); (d) CrO₃, H₂SO₄ (79%); (e) HC(OEt)₃, *p*-TsOH, THF – EtOH, 40 °C, 2 h; (f) PhNHMe, HCHO, 40 °C, 2 h; (g) conc. HCl, 1 h (73%); (h) Br₂, Et₂O, HBr, AcOH, 2–3 °C (84%); (i) NaI, Me₂CO, Δ , 15 min; (j) Li₂CO₃, LiCl, DMF, 120 °C, 2.5 h; (k) H₂C(OR)₂, POCl₃, CHCl₃, NaOAc, Δ (40% – 50%).

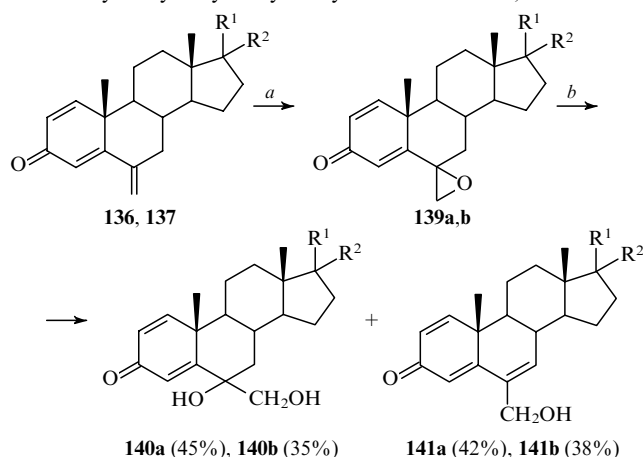
improved procedure for the synthesis of the steroid **136** has been patented. Although this requires a larger number of steps, it yields only crystalline intermediates and is suitable for large-scale syntheses. It includes the Mannich aminomethylation of a 3,5-dien-3-ol ester prepared from AD (see Scheme 6). The 6-methylene steroid **138** is obtained in > 70% yield. Compound **138** is then brominated with bromine in acetic acid. Dehydrobromination of the tribromide thus formed is carried out in two steps. At first, the 6-methylene group is regenerated by treatment of the tribromide with sodium iodide in acetone. The resulting 2-bromo-6-methylene steroid (not shown in Scheme 6) is further dehydrobrominated without purification by boiling with lithium salts in DMF to give exemestane **136** in 47% yield for the last two stages.¹²⁶

Two approaches for the synthesis of exemestane **136** from 3-oxo-1,4-didehydrosteroids are shown in Scheme 6. Direct γ -methylenation, which is applicable for a wide range of substrates,¹²⁵ has failed in the case of ADD. However, the 17 β -hydroxy derivative **122**, which is an accessible industrial raw material, can participate in the Mannich reaction. The resulting product **137** formed in 31% yield is oxidised to exemestane **136**.¹²⁷ And, finally, ADD was used directly as the starting material for introducing the 6-methylene group *via* the 1,3-bispyrrolidino derivative **134** which was converted into 6 β -hydroxymethyl ste-

roid **135** by standard procedures.¹²⁸ Dehydration of the latter gave exemestane **136** in 80% yield.¹²⁹

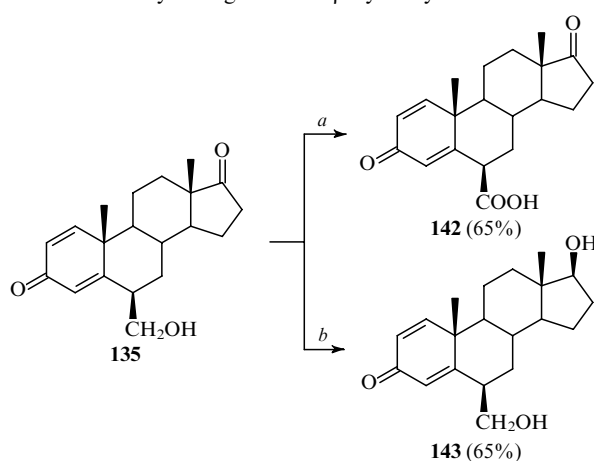
A series of exemestane analogues modified at position 6 and its 17 β -hydroxy derivatives have been synthesised in order to investigate the structure–activity relationships.¹²⁴ The reason for these studies was the experimental evidence about a wide set of exemestane metabolites. The design of its analogues was based on the hypothesis according to which exemestane metabolism results in modification of not only the carbonyl group at C(17) but also the exocyclic double bond.¹²⁴

Synthesis of exemestane **136** analogues is considered below. Epoxidation of exemestane **136** or its 17 β -hydroxy derivative **137** with a peroxy acid gave epimeric mixtures of spirooxiranes **139a,b**, respectively. Their subsequent hydrolysis with aqueous perchloric acid gave 6-hydroxymethyl-1,4,6-trienes **141a,b** along with epimeric 6-hydroxy-6-hydroxymethyl derivatives **140a,b**.¹²⁴



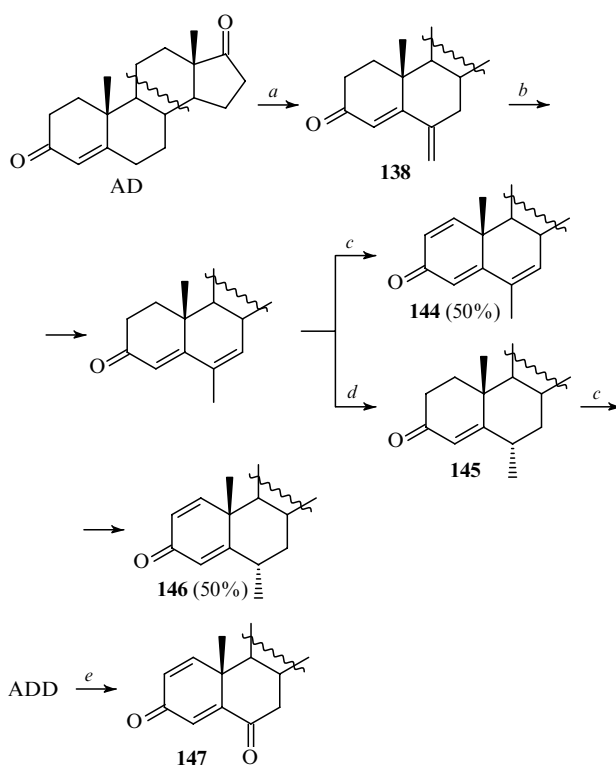
$R^1, R^2 = \text{O}$ (**136**, **139a–141a**); $R^1 = \beta\text{-OH}$, $R^2 = \text{H}$ (**137**, **139b–141b**);
(a) MCPBA, CH_2Cl_2 , 20 °C, 48 h (80%); (b) HClO_4 , THF, 20 °C, 3 h.

The Jones oxidation of 6 β -hydroxymethyl-AD **135** gave 6 β -carboxy-AD **142**, while selective reduction of the diketone **135** with sodium borohydride gave the 17 β -hydroxy derivative **143**.¹²⁴



(a) CrO_3 , H_2SO_4 ; (b) NaBH_4 , MeOH.

A series of 6-methyl-substituted AD and ADD have been synthesised. Thus 6-methylene-AD **138** was isomerised over Pd/C into a 4,6-didehydro-6-methyl analogue. Its dehydrogenation with DDQ gave 1,4,6-triene **144** in 50% yield, while reduction over Pd/C in the presence of cyclohexene as a hydrogen donor yielded 6 α -methyl-AD **145**. The latter was further dehydrogenated into 6 α -methyl-1,4-diene steroid **146**. Finally, oxidation of ADD with oxygen in the presence of alkali gave androsta-1,4-diene-3,6,17-trione **147**.¹²⁴ Preparation of the 2-fluoro derivative of exemestane is patented.¹³⁰

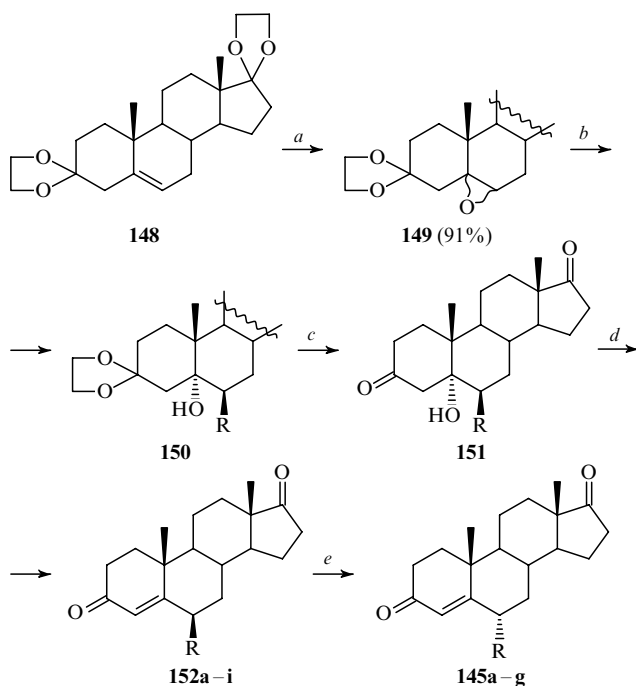


(a) $\text{CH}_2(\text{OEt})_2$, POCl_3 , CHCl_3 (60%); (b) 5% Pd/C, EtOH, Δ , PhCH_2OH (90%); (c) DDQ, dioxane, Δ , 15 h; (d) Pd/C, cyclohexene (60%); (e) O_2 , KOBu^t , Bu^tOH (15%).

Exemestane **136** is a highly selective irreversible AI. The irreversibility of its inhibitory action is assigned to the presence of a 1,2-double bond in the molecule;¹²³ the corresponding 1,2-hydrogenated analogues represent reversible AI. It is these properties rather than pharmacokinetic ones that account for the prolonged action of exemestane on the organism.¹²³

None of the synthetic exemestane analogues displays *in vitro* activity which would be equal or greater than that of exemestane itself. Thus the 17 β -hydroxy derivative **137** is active *in vitro*, but its activity is 2.6-fold less than that of compound **136**. According to their inhibitory activity, exemestane analogues modified at C(6) and having a 17-keto group can be arranged in the following order: 6-methylene (**136**) > 6-spirooxirane (**139a**) > 6 β -hydroxymethyl (**135**) > 6-hydroxy-6-hydroxymethyl (**140a**) > 6 β -carboxy derivative (**142**). 17 β -Hydroxy analogues of some of these compounds, e.g., **139b**, **140b** and **143**, manifest 3–8-fold lower activity than the corresponding 17-oxo compounds. Isomerisation or reduction of the double bond (leading to compounds **144** and **146**) decreases their inhibitory activity threefold in comparison with exemestane itself.¹²⁴

A series of 6-alkyl- and 6-aryl-substituted AD has been described and their inhibitory activity has been studied with the view of determining the topography of the hydrophobic binding pocket in the active site of the enzyme.^{131–134} The key compound in this synthesis was a mixture of isomers of 5,6-epoxide **149** obtained by epoxidation of androst-5-ene-3,17-dione diketal **148**. The opening of the oxirane ring with Grignard reagents gave 5 α -hydroxy-6 β -substituted androstanes **150**. Treatment of the latter with HClO_4 in THF gave the corresponding 3,17-diketones **151** in high yields. Dehydration of these hydroxy diketones with thionyl chloride in pyridine has led to a series of 6 β -substituted AD **152a–i**. Epimerisation of the 6 β -centre in 6 β -substituted Δ^4 -3-ketones **152** into thermodynamically more stable 6 α -isomers **145a–g** occurred in 16%–56% yields.^{131,132}



R = Me (a), Et (b), Prⁿ (c), Bu (d), Prⁱ (e), Ph (f), CH₂Ph (g),
CH=CH₂ (h), C≡CH (i).

(a) MCPBA, CH₂Cl₂, 20 °C, 4 h (a mixture of isomers ~ 1 : 1);
(b) RMgBr, THF, Δ (86%–98%); (c) 3M HClO₄, THF, 20 °C, 3 h;
(d) SOCl₂, Py, 0 °C, 3 min; (e) 1M HCl, EtOH, Δ (16%–56%).

Biochemical assessment of both 6 α -(**145**) and 6 β -(**152**) substituted AD has been carried out (Table 3). These compounds appeared to be competitive aromatase inhibitors with K_i ranging from 1.4 to 63 nM. Introduction of a methyl group into 6 α - and 6 β -positions of AD increases its affinity for aromatase. Introduction of an additional methylene group into position 6 of the steroid molecule changes its inhibitory properties. Thus 6 β -ethyl-AD **152b** had the highest K_i value (1.4 nM) in this series of compounds. Further elongation of the chain does not result in any significant alteration in the inhibitory activity. 6 α -Benzyl-AD **145g** and 6 β -vinyl-AD **152h** also manifest high activity. Bulky substituents, such as 6-isopropyl (**152e** and **145e**) or polar substituents, like 6 β -ethynyl-(**152i**), decrease the inhibitory activity (K_i = 21–63 nM). The activity of 6 β -substituted AD decreases in the following order: Et > Pr > CH=CH₂ > Bu > Me > Prⁱ > Ph > C≡CH > CH₂Ph, while that of 6 α -substituted AD decreases in the order: Et > Me > Prⁿ > CH₂Ph > Bu > Ph > Prⁱ. The stereochemistry of the C(6) atom affects the inhibitory activity. Thus 6 β -alkyl isomers possess greater affinity for the enzyme than the corresponding 6 α -isomers with the exception of 6 α - and 6 β -methyl analogues **145a** and **152a**. Exchange of the 6 β -ethyl substituent by the 6 β -vinyl substituent decreases the affinity of compound **152h** compared to that of compound **152b**. It was shown that there is a hydrophobic binding pocket in the active site of the enzyme in the β -region of position 6 of the steroid substrate. Judging by the data on the crystal structure of cytochrome P-450 and the inhibitory activity of steroid substrates of this series, the following sizes for the pocket have been proposed: length 6.27 Å, width 5.25 Å, height 7.74 Å.¹³¹ In 1995, Numazawa and Oshibe¹³¹ synthesised and assayed 6 α - and 6 β -alkyl-substituted AD with 5–7 methylene groups in the side chains. Their K_i values varied from 2.8 to 80 nM. The earlier structure–activity regularities were also confirmed for compounds of this series. Thus 6 β -pentyl-AD manifested the highest activity; further elongation of the chain sharply decreased the affinity.¹³³

The analysis of effects of the chain length and configuration of the alkyl substituent at position 6 of ADD analogues¹³⁵ on their inhibitory activity is an extension of earlier studies.^{131, 133}

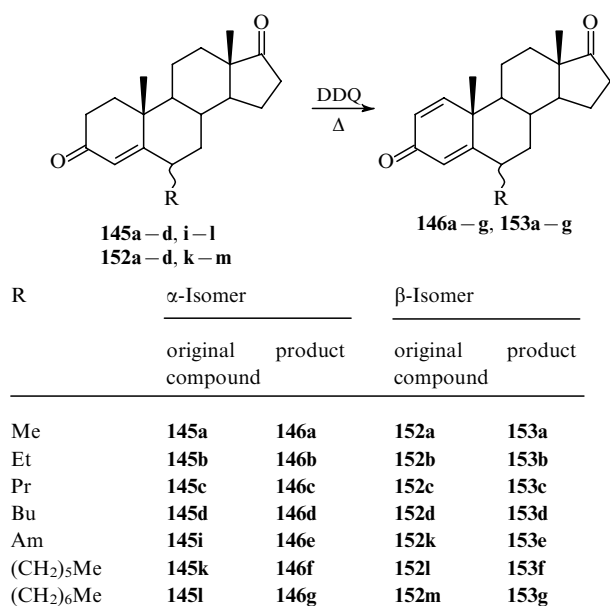
Table 3. Data on *in vitro* inhibition of aromatase from human placenta by 6-substituted androstanes.

R	The position of double bond ^a		K_i /nM	IC ₅₀ /nM	Ref.
	Δ^1	Δ^6			
α -Me (145a)	—	—	5.6	350	131
β -Me (152a)	—	—	11	720	131
α -Et (145b)	—	—	4.7	260	131
β -Et (152b)	—	—	1.4	140	131
α -Pr ⁿ (145c)	—	—	6.7	390	131
β -Pr ⁿ (152c)	—	—	4.6	240	131
α -Bu ⁿ (145d)	—	—	12	790	131
β -Bu ⁿ (152d)	—	—	8.8	510	131
α -Pr ⁱ (145e)	—	—	31	1400	131
β -Pr ⁱ (152e)	—	—	22	1100	131
α -Ph (145f)	—	—	21	1100	131
β -Ph (152f)	—	—	37	1700	131
α -CH ₂ Ph (145g)	—	—	10	660	131
β -CH ₂ Ph (152g)	—	—	63	4000	131
β -CH=CH ₂ (152h)	—	—	5.1	320	131
β -C≡CH (152i)	—	—	62	1900	131
Pr ⁱ	—	—	4.9		131
α -Br	—	—	3.4		173
β -Br	—	—	800		173
=O (147)	+	—		268	124
=CH ₂ (136)	+	—	26–27	42.5	9, 97, 124
α -Me (146a)	+	—	54		135
β -Me (153a)	+	—	43		135
α -Et (146b)	+	—	19		135
β -Et (153b)	+	—	4.7		135
α -Pr ⁿ (146c)	+	—	22		135
β -Pr ⁿ (153c)	+	—	7.0		135
α -Bu ⁿ (146d)	+	—	16		135
β -Bu ⁿ (153d)	+	—	14		135
α -(CH ₂) ₄ Me (146e)	+	—	11		135
β -(CH ₂) ₄ Me (153e)	+	—	5.0		135
α -(CH ₂) ₅ Me (146f)	+	—	25		135
β -(CH ₂) ₅ Me (153f)	+	—	8.0		135
α -(CH ₂) ₆ Me (146g)	+	—	20		135
β -(CH ₂) ₆ Me (153g)	+	—	7.8		135
Me (144)	+	+		91	124

^a Symbols + and — denote the presence and absence of the double bond in this position, respectively.

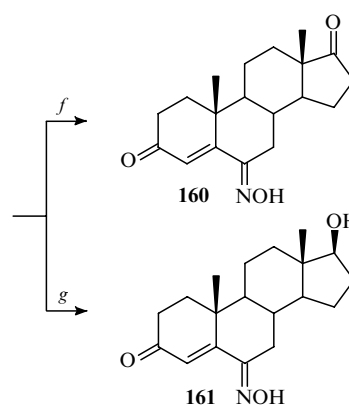
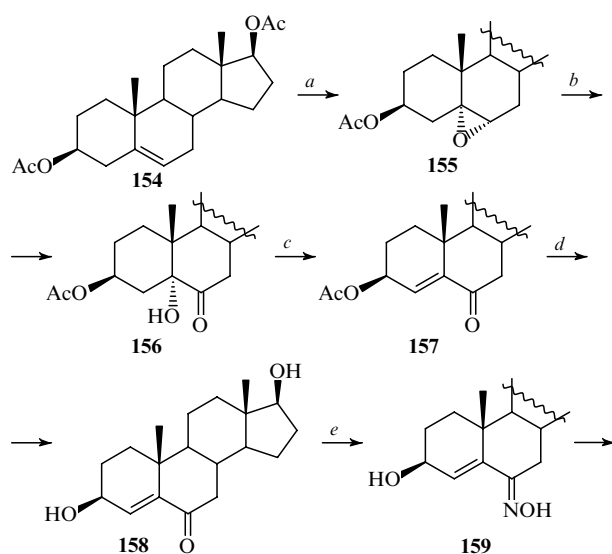
The 6 α - and 6 β -alkyl-substituted ADD **146a–g** and **153a–g** were obtained by dehydrogenation of their Δ^4 -3-keto precursors.

Compounds **146a–g** and **153a–g** appeared to be competitive AI with K_i ranging from 4.7 to 54 nM (see Table 3). Among those, only 6 α -ethyl-ADD **146b** is the suicide AI. 6 β -Isomers manifest greater activity than 6 α -analogues. However, there was no correlation between the length of the alkyl chain and the affinity for the enzyme. The ability of 6 β -alkyl isomers to inhibit aromatase decreases in the following order: Et > (CH₂)₄Me > Pr > (CH₂)₆Me > (CH₂)₅Me > Bu > Me, which is consistent with the results obtained for 6 β -alkyl derivatives of AD.¹³³ The activity of 6 α -isomers of alkyl-substituted ADD **146a–g**



decreases in the order: (CH₂)₄Me > Bu > Et > (CH₂)₆Me > Pr > (CH₂)₅Me > Me, which does not match that for 6 α -alkyl-AD.¹³³ Based on the experimental data and the results of molecular modelling studies, Numazawa *et al.*¹³⁵ assumed that at least 6 β -alkyl-ADD **153** can bind with the same hydrophobic pocket in the active centre of aromatase as does the corresponding 6 β -alkyl-AD **152**.

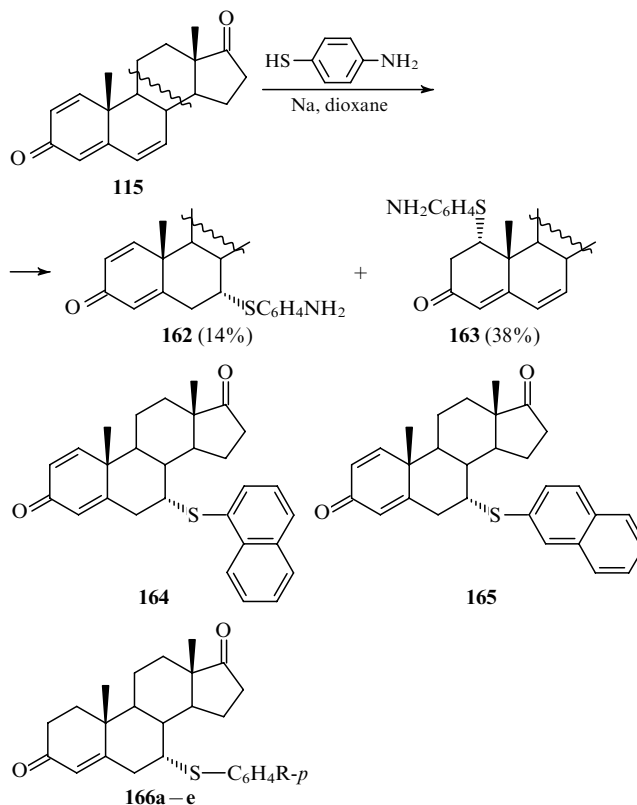
6-Hydroxyimino-AD **160** and its 17 β -hydroxy analogue **161** are competitive AI.¹³⁶ The key derivative **158** was obtained by standard methods from 3,17-diacetate **154** via 5 α ,6 α -epoxide **155** with its subsequent oxidative conversion into 5 α -hydroxy-6-ketone **156** with chromic anhydride. Dehydration of the latter and hydrolysis of 3,17-acetoxy groups in Δ^4 -6-ketone **157** gave the dihydroxy derivative **158** in high yield. Treatment of the latter with hydroxylamine hydrochloride resulted in the (*E*)-oxime **159**; its oxidation with chromic anhydride in pyridine gave 6-hydroxyimino-AD **160** in 70% yield. Oxidation of oxime **159** with manganese dioxide under mild conditions resulted in the testosterone derivative **161**.



(a) MCPBA, CH₂Cl₂; (b) CrO₃, H₂O; (c) SOCl₂, Py (90%); (d) KOH, MeOH (82%); (e) NH₂OH·HCl (75%); (f) CrO₃–Py (70%); (g) MnO₂, CHCl₃, 20 °C (45%).

5. 7-Substituted and 6,7-disubstituted androstanes

The key stage in the synthesis of 7-substituted androstanes is 1,6-conjugate addition of the corresponding reagents to 6-dehydro derivatives of AD and ADD. Thus 7 α -thio-substituted ADD **162**, one of the first highly active 7 α -substituted androstanes, was obtained in 14% yield by addition of *p*-aminothiophenol to 6-dehydro-ADD **115**.¹³⁷



R = H (a), NH₂ (b), I (c), OMe (d), N₃ (e).

This is accompanied by the formation of its inactive 2 α -isomer **163** (yield ~ 40%). The attempts to improve the regioselectivity and to increase the yield of 7 α -substituted compound **162** by changing the reaction conditions (solvent, temperature and reagent ratio) failed.¹³⁷

Further transformations of 7 α -(*p*-aminophenylthio)-ADD **162** have led to its analogues with bromine or iodine atoms in the *para*-position of the aryl substituent. 7 α -Naphthalene derivatives **164** and **165** are also described.¹³⁸ All these steroids are irreversible suicide AI (*K*_i = 12–27 nM).¹³⁸ According to the patent,¹³⁹

7 α -alkyl(acyl)thio- and 7 α -mercapto-ADD are highly active preparations for *in vivo* treatment of mammary tumours.

7 α -Arylthio-substituted AD **166a–e** were obtained by analogous addition of substituted thiophenols to 6-dehydro-AD.²⁴ The activity of the steroid **166b** was twice as low as that of its ADD analogue **162**. The steroid **166e** (K_i = 1 nM) was the most efficient in this series (Table 4).^{25, 140}

The compounds described above contain an aryl substituent which is linked to the steroid skeleton by the C–S bond. It was found, however, that the presence of a sulfur atom and the stereochemistry of the C(7) atom are not essential for the manifestation of activity, since 7 α - and 7 β -substituted AD **170a,b**, **171a,b** and **173a,b** with one or several methylene groups between the steroid skeleton and the phenyl substituent appear to be efficient AI.¹⁴¹

These androgens with arylaliphatic substituents were obtained by the same approach as that used for 7 α -thio-substituted compounds described above. The silylated testosterone derivative **167** was used as the starting compound. Introduction of a phenylethyl or a phenylpropyl substituent was carried out by addition of the cuprate reagent prepared from the corresponding lithium reagent and 1 equiv. of copper(I) tetrakis(tributylphosphine) iodide. Subsequent addition of 0.2 equiv. of the steroid **167** and deprotection gave the desired 1,6-addition products as mixtures of α,β -diastereomers **168a** and **169a** (71%, $\alpha:\beta$ = 2 : 1) or **168b** and **169b** (50%, $\alpha:\beta$ = 1 : 1) isolated in the individual state by chromatography. The structure of the 7 α -isomer **168a** was additionally confirmed by X-ray analysis. Oxidation of 17 β -alcohols **168a**, **169a**, **168b** and **169b** gave 17-ketones **170a**, **171a** and **171b**, respectively. 7 α - And 7 β -benzyl derivatives **172** and **173** were obtained in a similar way.

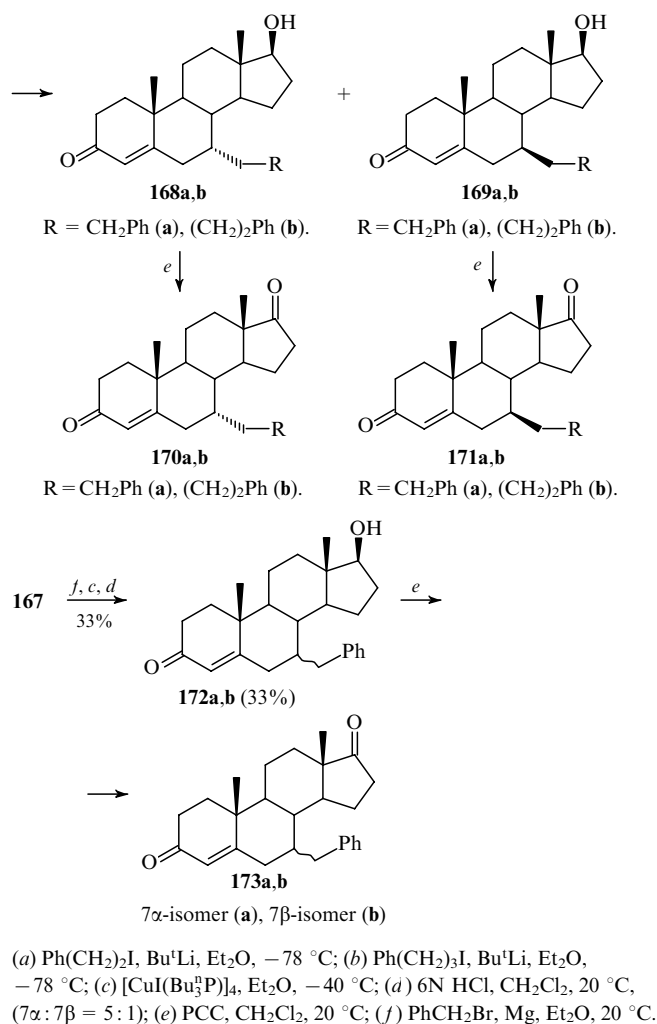
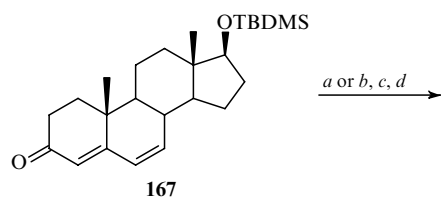
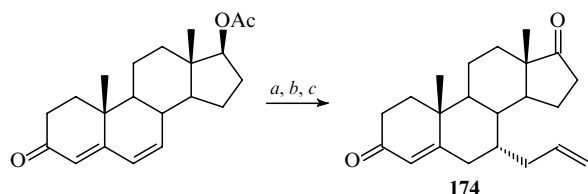


Table 4. Data on *in vitro* inhibition of aromatase from human placenta by 7-substituted and 6,7-disubstituted androstanes.

Compound	R ¹	R ²	R ³	X	Y	The presence of a Δ^1 double bond	K_i /nM	IC ₅₀ /nM	Ref.
166a	H	H	α -SPh	O	O	–	212	650	80
166b	H	H	α -SC ₆ H ₄ NH ₂	O	O	–	18		25, 141
166c	H	H	α -SC ₆ H ₄ I	O	O	–	12		25, 15
166d	H	H	α -SC ₆ H ₄ OMe	O	O	–	31		25
166e	H	H	α -SC ₆ H ₄ N ₃	O	O	–	1		25
173a	H	H	α -CH ₂ Ph	O	O	–	18.9		141
173b	H	H	β -CH ₂ Ph	O	O	–	44.5		141
170a	H	H	α -(CH ₂) ₂ Ph	O	O	–	13.1		141
170a	H	H	β -(CH ₂) ₂ Ph	O	O	–	40.2		141
170b	H	H	α -(CH ₂) ₃ Ph	O	O	–	16.5		141
172	H	H	α -CH ₂ Ph	O	β -OH	–	39.5		141
168a	H	H	α -(CH ₂) ₂ Ph	O	β -OH	–	36.0		141
162	H	H	α -SC ₆ H ₄ NH ₂	O	O	+	9.9		25
179	OPh	H	α -SPh	O	O	–	472	1650	80
187	H	α -CF ₂		O	O	–	50		145
189	H	α -CH ₂		H ₂	O	–	5.0		145
190	H	α -CH ₂		H ₂	β -OH	–	120		145

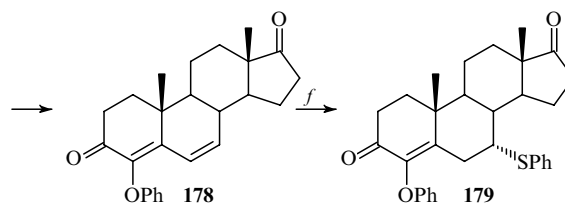
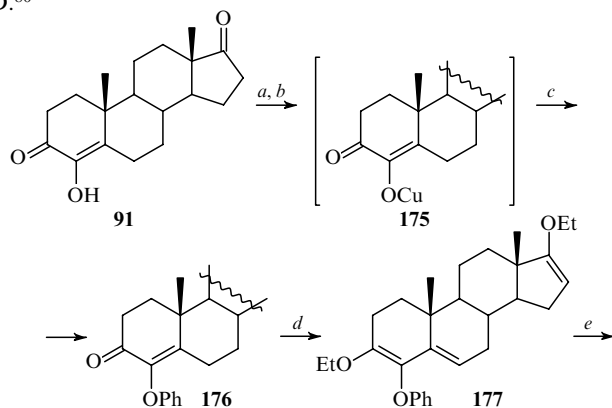
7 α -Substituted AD **170a,b** and **173a** are efficient competitive AI with K_i 13–19 nM. The corresponding 17 β -alcohols **168a,b** and **172** as well as 7 β -substituted AD **171a,b** and **173b** are less active (K_i = 36–44 nM). Thus, introduction of bulky aryl-aliphatic substituents into position 7 of AD favours high inhibitory activity. It was found that the length of the carbon chain between the steroid and the aryl group does not significantly affect the activity, thus indicating the presence of a bulky pocket in the active site of the enzyme near position 7 of the steroid substrate.

According to patent data,¹⁴² 7 α -allyl-AD **174** synthesised from the corresponding 17 β -acetoxy-androsta-4,6-dien-3-one is a rather active AI.



(a) $\text{H}_2\text{C}=\text{CHCH}_2\text{SiMe}_3$, TiCl_4 , CH_2Cl_2 , -70°C ; (b) HC/MeOH ; (c) PCC.

Disubstituted 4-phenoxy-7 α -phenylthio-AD **179** has been synthesised in order to explore the nature of the binding site of aromatase in the vicinity of the C(4), C(6) and C(7) atoms of AD.⁸⁰



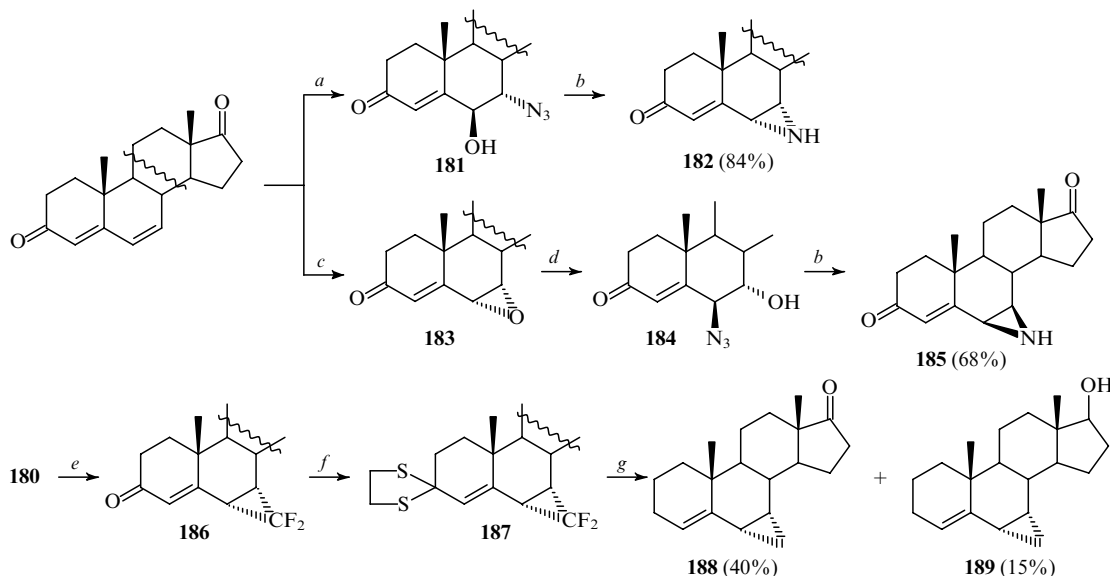
(a) CuI , Bu_2S , MeLi , Et_2O , -78 to 20°C ; (b) Et_2O , THF , Py , -78°C ; (c) PhI , Δ (55%); (d) $\text{CH}(\text{OEt})_3$, $p\text{-TsOH}$, 20°C , 24 h; (e) DDQ (5%) aqueous Me_2CO , 20°C , 3 min (50%); (f) PhSH , Na , dioxane, 60°C , 8 h (40%).

The starting compound in this synthesis, 4-OHA **91**, was converted into the 4-phenoxy derivative **176** via the intermediate copper enolate **175** (yield > 50%).⁸¹ The formation of the necessary 6,7-double bond was achieved by treating the ether **177** with an equimolar amount of DDQ in aqueous acetone. Addition of thiophenol to $\Delta^{4,6}$ -4-phenoxy-AD formed completes the synthesis of the 4-phenoxy-7-phenylthio-substituted compound **179**. However, its inhibitory activity was much lower than that of the monosubstituted analogues, viz., 4-phenylthio- (**98d**) and 7 α -phenylthio-AD **166a**. These results together with molecular modelling data for all the three compounds have led Liu *et al.*^{80,81} to infer the existence of a single hydrophobic pocket in the active site of aromatase in the vicinity of the C(4) and C(7) atoms of the steroid substrate.

In conclusion, it is appropriate to mention the synthesis of 6,7-disubstituted androstanes. Thus 6,7-epimino-AD¹⁴³ represent a practically novel class of derivatives. The key compounds in this synthesis are 7 α -azido-6 β -hydroxy- (**181**) and 6 β -azido-7 α -hydroxy-AD **184** (Scheme 7). Treatment of 4,6-dienedione **180** with sodium azide and chromic anhydride in acetic acid gives the azido alcohol **181**, which was converted into 6 α ,7 α -aziridine **182** in 80% yield upon heating with 2 equiv. of triphenylphosphine in toluene. Epoxidation of 6-dehydro-AD **180** with *m*-chloroperbenzoic acid in boiling chloroform gave the 6 α ,7 α -oxide **183**; its diaxial opening in 6 β -azido-7 α -hydroxy-AD **184** occurred in high yield and was performed by treatment of an equimolar mixture of sodium azide and concentrated sulfuric acid in DMSO. Reaction of the azide **184** with triphenylphosphine in toluene gives 6 β ,7 β -epimino-AD **185**.

The β -configuration of its three-membered ring was confirmed by ^1H NMR spectral data and by independent synthesis,

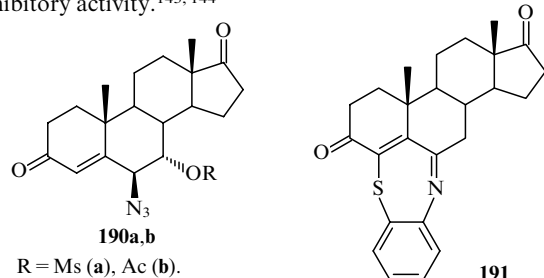
Scheme 7



(a) NaN_3 , CrO_3 , AcOH , 20°C (42%); (b) Ph_3P , PhMe , Δ , 3 h; (c) MCPBA, Δ , 3 h (57%); (d) NaN_3 , conc. H_2SO_4 , DMSO , 20°C (84%); (e) $\text{ClF}_2\text{CCO}_2\text{Na}$, diglyme Δ , 5 h; (f) $(\text{CH}_2)_2\text{SH}$, $p\text{-TsOH}$, AcOH , 20°C , 24 h (77%); (g) $\text{Na}-\text{NH}_3$, THF , 0.5 h (40%).

viz., by reduction of 7-mesylate **190a** with lithium aluminium hydride. The stereochemical aspect of the formation of steroids **182** and **185** deserves mention: in each case, the corresponding azido alcohol yields only one isomer with the aziridine ring configuration identical with that of the azido group.

The compounds obtained appeared to be weak aromatase inhibitors; only 6 β -azido-7 α -acetate **190b** manifested moderate inhibitory activity.^{143, 144}



This section is finished with a description of a series of 6 α ,7 α -cyclopropaandrost-4-en-17-ones.^{145, 146} Addition of difluorocarbene generated from sodium difluorochloroacetate to 6-dehydro-AD **180** gave 6 α ,7 α -difluorocyclopropane-AD **186**. Reduction of its 3-ethylenedithio derivative **187** with lithium in ammonia gave a mixture of 3-deoxy-6 α ,7 α -cyclopropaandrost-4-en-17-one **188** and its 17 β -hydroxy derivative **189**. These compounds proved to be efficient competitive AI,¹⁴⁵ the cyclopropane derivative **188** ($K_i = 5$ nM) being the most active one. However, introduction of a 6 α ,7 α -difluorocyclopropane group into the AD molecule (compound **186**) did not affect considerably its affinity for the enzyme. This suggests that it is the keto group at position 17 of AD that plays the crucial role in the binding of the steroid with aromatase.

A recent study¹⁴⁷ devoted to the synthesis and biochemical assay of compound **191**, yet another representative of substituted androstanes obtained by the base-catalysed Michael addition of 2-aminothiophenol to 3,17-diacetoxyandrost-4-en-6-one with subsequent cyclisation, is also worth mentioning. Compound **191** manifested weak inhibitory activity of a competitive type ($K_i = 42$ 300 nM).

IV. Structure–activity relationships in substituted androstanes as aromatase inhibitors

The data considered in Section III and those listed in Tables 1–4 allow one to make certain conclusions about the structural requirements for steroid substrates to act as aromatase inhibitors. Although the substituted androstanes described above are rather diverse in nature and mechanisms of their inhibitory action have hitherto been studied relatively little, one may note some general regularities concerning the relationships between their structure and inhibitory activity judging mainly by the affinity for the enzyme and inhibitory properties of a series of similarly substituted androstanes. According to Cole and Robinson,¹⁵ efficient AI have two domains which play an important role in binding of the steroid substrate with the enzyme, namely, an iron-coordinating domain and a hydrophobic domain. The structural requirements for the latter are considered to be a crucial factor, although chemical details of its specificity are unknown.

The introduction into, or removal from, certain positions of the AD molecule of definite substituents and/or additional double bonds affect the inhibitory activity as indicated by arrows in Fig. 1.

The steroid molecule must contain at least one keto group, specifically at position 17 to manifest aromatase-inhibiting activity. All substituted androstanes sharply decrease their activity as AI upon reduction of the 17-keto group to the hydroxy group and especially following its esterification. Evidently, in some cases the carbonyl function at position 3 is not strictly required as a structural element, because, as has been shown in the preceding

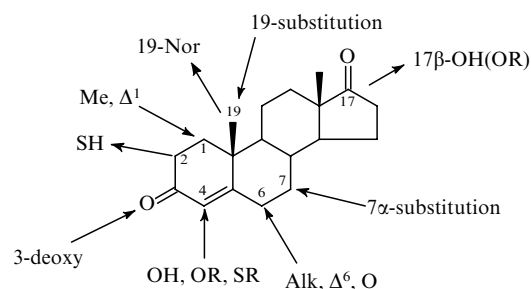


Figure 1. The functional groups affecting the inhibitory activity and their position in the AD molecule. The arrows directed towards a specific position denote enhancement of activity, those directed from this position denote decrease in activity.

section, some 3-deoxy analogues retain high inhibitory activity.^{14, 33, 35, 36, 145} Moreover, replacement of the 3-keto group in AD or in 19-substituted AD by a 3-methylene group (or a halogenomethylene group) affords compounds possessing high competitive inhibitory activity.^{148, 149} The study of inhibitory activity of androst-4-ene-3,6,17-trione and its 3-hydroxy analogue revealed that both of them can irreversibly bind with aromatase.^{150, 151}

An important role in manifestation of biological activity is played by the conformation of the ring A. For example, androst-2-ene-3,17-dione binds with aromatase very weakly, whereas its 4-dehydro isomer is an efficient AI with $K_i = 37$ nM.^{15, 145, 152} The presence of a substituent at position 10 of the steroid skeleton of AD is indispensable for activity. As has been shown in Section III, this substituent plays an essential role in the oxidation of the steroid substrate by the enzyme. Thus 19-nor-4-hydroxyandrost-4-ene-3,17-dione binds with aromatase but is devoid of inhibitory activity.^{15, 64}

Introduction of additional double bonds into the molecule of AD and its substituted analogues enhances their inhibitory activity. It is particularly true for 1,2- and 6,7-double bonds. It is assumed¹²³ that the presence of a 1,2-double bond in a steroid molecule is responsible for the irreversible type of inhibition and, correspondingly, for the long-lasting effect of AI *in vivo*.

Introduction of various substituents into the rings A and B (positions 1, 4, 6, 7 and 19) as well as alkylation or arylation of 4-amino-, -mercapto- or -hydroxy-androstanes are the most common structural modifications. High affinity for the enzyme has been noted for steroid AI with small substituents at C(1), C(4) and C(19) and with bulky substituents at C(7). Introduction of hydrophobic substituents is a general trend in the design of efficient AI, although the optimal volume and position of functional groups are often difficult to predict.

2 α -Substitution and involvement of the C(6) and C(7) atoms in the formation of a three-membered heterocycle have a negative effect.^{14, 19}

Thus, studies of structure–activity relationships of steroid AI and their interactions with the active site of aromatase provides valuable information about the nature of the enzyme and allows one to gain better insight into the mechanism of action of this enzyme. Investigation of this mechanism is far beyond the scope of the present review; it is evident, however, that the synthesis and analysis of activity of various series of steroid AI represent a step on the way to its elucidation.

V. *In vivo* activities and applications of major steroid aromatase inhibitors

As can be seen from Tables 1–4, highly efficient AI usually have similar K_i which are close to the lower limits of sensitivity (0.5–1.0 nM). The possibility of their practical application will further be determined by their biological properties *in vivo*, pharmacological and pharmacokinetic characteristics, the pres-

ence or absence of side hormonal effects typical of some steroids of the androstane series, and, naturally, by the methods of their synthesis and the possibility of scaling.

This section considers pharmacological activities and clinical applications of several major substituted androstanes the properties of which have been studied in sufficiently great detail. Owing to their antitumour activity, some of these steroid compounds, *viz.*, 4-hydroxy-AD **91**, 1-methyl-ADD **121** and 6-methylene-ADD **136**, have found wide use in the clinical practice. The former known under the trade name formestane is already used in the therapeutic practice, while the other two are undergoing clinical trials. Besides, there is ample literature evidence concerning the pharmacological activity of another two AI. The first of them, 19-ethynyl-AD **1** (promestane), manifests high activity in inhibiting ovarian aromatase on oral administration and efficiently reduces mammary and ovarian tumours in both experimental models and the clinic.^{15, 36, 37} The synthetic 'Organon' product, 19-ethyldithio-AD, possesses very weak androgenic activity but very efficiently inhibits estrogen biosynthesis *in vivo*.^{43, 44} Antitumour activities of these AI have been surveyed recently.^{21, 153, 154}

4-Hydroxy-AD (**91**, formestane) was designed in 1984 by the 'Ciba-Geigy' company for treatment of post-menopausal mammary tumours in women and is now commercially available in Great Britain, Germany, Austria and some other countries.⁷¹ Some patents issued by the 'Schering AG' company deal with their application in the therapy of benign prostatic hyperplasia.^{65, 155}

Studies of formestane effects on human placenta aromatase revealed its high inhibitory activity.^{62, 64} Formestane produced a significant antitumour effect in rats with experimental mammary tumours.^{36, 70, 87} This inhibition is highly selective.⁶³ However, there is evidence that formestane also inhibits 5 α -reductase.^{69, 156}

One main disadvantage of formestane reported by some authors^{48, 67, 88, 98, 157} is its low bioavailability and short-term effect. Since this drug is highly active on subcutaneous administration,⁹ it is normally used in the form of injections. The results of clinical trials of this drug in patients with mammary tumours (500–1000 mg weekly, *i.m.*) testify to its high efficiency.^{157–160} According to the experimental protocol elaborated for IIInd phase of clinical trials, formestane injected once or twice a week causes partial or complete remission of the tumour.^{66, 68, 158, 159} This drug is generally well tolerated and produces only nonspecific side effects. One should mention in this connection that replacement hydrocortisone therapy was necessary for patients receiving formestane for a prolonged period, since this drug inhibits pregnenolone biosynthesis and, as a consequence, biosynthesis of corticosteroids.^{67, 161}

According to the literature data, atamestane and exemestane have no such shortcomings. Comparative characteristics of *in vivo* activities of formestane, atamestane and exemestane and analysis of mechanisms of their action in animals have been documented.^{9, 69}

1-Methyl-ADD or atamestane was designed by the 'Schering AG' company in 1983¹⁰² and patented in more than 30 countries. The main objective of its clinical trials initiated in 1986 in Europe and Japan was to estimate its efficiency in the treatment of mammary tumours and endometriosis in women and of benign prostatic hyperplasia in men. As mentioned above, atamestane is a selective irreversible inhibitor of estrogen biosynthesis *in vitro* and *in vivo*. Studies in rats revealed that its activity exceeds that of formestane almost 1.5-fold;^{102, 162} according to other data, its effect is weaker than those of formestane and exemestane.⁹ DMBA-induced mammary tumours in rats reduced appreciably after subcutaneous administration of atamestane (30 or 150 mg per kg per day).¹⁰³ Neither atamestane nor its main metabolites, *viz.*, 5 β - and 17 β -reduced compounds, manifest any affinity for steroid receptors, which correlates with the endocrine-pharmacological profile of this drug.¹⁰⁴ *In vivo* studies failed to detect estrogen, anti-estrogen, androgen, progestane or antigonadotropic activities in atamestane.¹⁰⁵ As the affinity of atamestane for enzymes responsible for steroid biosynthesis in adrenal glands

is negligibly small in comparison with its affinity for aromatase, it does not exert any appreciable influence on these glands even when used in high doses and upon prolonged administration. This finding has been confirmed experimentally.¹⁰⁵

As has been mentioned above, atamestane has been recommended for treatment of benign prostatic hyperplasia.^{154, 163} Along with other factors, estrogens play an important role in the etiology of this disease. Apart from the finding that the incidence of this disease correlates with a shift of the androgens/estrogens ratio towards estrogens upon ageing in males, the presence of the estrogen receptor meeting the classical criteria has also been demonstrated by Habenicht *et al.*^{164, 165} The role of estrogens in the pathogenesis of this disease revealed in animals has been confirmed by clinical tests.¹⁶⁴ The results of successful clinical trials of atamestane administered in an oral dose of 200 mg 3 times daily for 3 months in the endocrine therapy of benign prostatic hyperplasia were published several years ago.¹⁶⁶ The use of atamestane in the form of tablets for increasing testosterone content in the organism has been patented.¹⁶²

Exemestane **136** has also been recommended for clinical use. This preparation was designed in 1988 by the Italian company 'Farmitalia Carlo Erba' and tested in many countries of the world as an independent therapeutic agent for treating estrogen-dependent tumours, especially post-menopausal mammary tumours in women. The choice of exemestane is based on its pharmacological properties which characterise this drug as a highly active (on oral administration) selective AI.^{9, 97} Studies in animals revealed long-term inhibition of ovarian aromatase on subcutaneous and oral administration.^{9, 97, 167} The activity of exemestane exceeds that of formestane twofold on subcutaneous administration and 27-fold on oral administration.¹²³ This drug does not manifest any affinity for the majority of steroid receptors with the exception of its weak binding with the androgenic receptor; the androgenic activity of exemestane was as low as 10% of the testosterone activity.^{98, 123} The results of endocrinological clinical trials of small doses of exemestane published in 1995 testify to a long-term selective decrease in estrogen levels and good tolerance of this drug.^{168, 169} The antitumour effect of exemestane has been studied in a model of DMBA-induced rat mammary tumours.¹⁶⁷ Subcutaneous or oral administration of exemestane caused partial or complete remission of the tumour.^{123, 124} Exemestane has a specific action on women: it does not influence the levels of hydrocortisone, aldosterone, 17-hydroxyprogesterone and luteinising and follicle-stimulating hormones even when used in very high doses.¹²³ The composition of tablets containing exemestane¹⁷⁰ and designed for the treatment of mammary tumours and the use of this AI as a component of a combined preparation for prophylaxis and treatment of benign prostatic hyperplasia have been patented.¹⁵⁵

VI. Conclusion

Thus, substituted androstanes are aromatase inhibitors in their pharmacological effect and antitumour agents in the mode of action. They may compete successfully with other drugs and are sometimes indispensable in the treatment of hormone-dependent tumours. Special mention should be made of the relative simplicity of synthesis of these preparations from industrially available steroid sources.

Analysis of methods used for the synthesis of AI together with detailed studies of their activity *in vitro* and *in vivo* give a strong impetus to the design of new efficient drugs and the development of methods for their synthesis and offers a possibility to choose the most efficient drug in each concrete case.

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Catalytic antibodies: prospects for the use in organic synthesis

N K Kochetkov

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Abstract. Data on catalytic antibodies as a new generation of biocatalysts are reviewed. The principles used in the design, and the methods for the preparation of all presently known classes of catalytic antibodies, which catalyse particular conversions of organic compounds, are discussed. Data on the efficiency, regio- and stereospecificity and mechanisms of action of catalytic antibodies are presented and their possible applications in fine organic synthesis are considered. The bibliography includes 124 references.

I. Introduction

Elaboration of an immense variety of methods designed for the formation of the carbon skeleton and its directed functionalisation makes it possible currently to obtain organic compounds of virtually any degree of complexity. Usually, the synthesis of structurally complex compounds is accomplished in several steps. The efficiency and unambiguity of each of these steps are the two crucial factors that determine the success of the synthesis. The efficiency of the reaction is characterised by its rate and the product yield, while its unambiguity is characterised by its regio- and stereospecificity. This enables one to achieve the maximum degree of purity of the target compound and to avoid tedious isolation and purification procedures. The progress in fine organic synthesis and the access to more and more complex structures necessitates enhancement in reaction efficiency and specificity. However, the use of purely chemical approaches in multistep syntheses is often insufficient. Recent trends are towards the use of enzymic reactions for the formation of the carbon skeleton and its functionalisation at particular stages of the synthesis.

The use of enzymes often makes it possible to carry out the reaction at higher rates and to achieve higher degree of purity of the reaction products due to high regio- and stereoselectivity of

enzymes. Therefore, the methods of enzymic and chemoenzymic synthesis are becoming more and more popular in the routine practice of fine organic synthesis. However, low availability of natural enzymes endowed with the desired activity and specificity is an obstacle for the wide application of biosynthetic procedures. This demands additional tedious work aimed at a search for suitable and accessible enzyme sources, elaboration of methods for isolation and purification of the enzymes and detailed analysis of their specificity. Therefore, the laboratory and industrial use of natural enzymes that catalyse definite chemical conversions is rather limited.

Preparation of artificial enzymes with high efficiency and, which is the most important, with high predetermined selectivity has long been the dream of organic chemists. Such enzymes have to be prepared in a laboratory to be used for accomplishment of a particular reaction. Such artificial enzymes, which are endowed with predetermined specificity (the so-called 'tailor-made enzymes'), would make it possible to enhance considerably the efficiency of organic synthesis and open up new ways to the synthesis of novel classes of organic compounds.

Natural enzymes are high-molecular-weight proteins possessing a unique structure. Their catalytic activity and the selectivity of their action are determined by the strictly specific amino acid sequence of the protein chain. This, in turn, predetermines the conformation of the protein molecule and, ultimately, the formation of the spatial structure of the active site of the enzyme.

Directed synthesis might be considered as the simplest way to obtain an artificial enzyme. However, despite the generally acknowledged progress in synthetic protein chemistry, this approach is fairly inefficient not only because it is labour-consuming but because it requires information about the primary structure of the target enzyme. However, determination of an amino acid sequence is by itself a complicated and labour-consuming task.

The solution of this problem came from the use of a different approach to the preparation of artificial enzymes with predetermined specificity. This is based on the biosynthesis and rests on tremendous potentialities of the cell immunological apparatus, which can produce a great variety of protein molecules.

It is well known that a specific feature of the immune system of animals is its ability to synthesise antibodies, *i.e.*, protective

N K Kochetkov N D Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninskii prosp. 47, 117913 Moscow, Russian Federation. Fax (7-095) 135 53 28. Tel. (7-095) 137 61 48

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proteins that 'neutralise' alien molecules and more complex entities (the so-called antigens) getting into the organism. The immune system generates a protein molecule of an antibody the structure of which relates to the structure of the antigen in such a way that the active site of the antibody appears to be complementary to the specific part of the antigen called the hapten. The antibody forms a rather stable complex with the antigen and thus 'neutralises' its effect. In other words, the biosynthetic apparatus of the immune system provides the synthesis of the protein molecule in which the active site is formed, the structure and spatial configuration of which are predetermined by the structure of the antigen administered to the organism. It is this principle that is being employed in the synthesis of artificial enzymes.

According to the current views, the catalytic effect of a natural enzyme consists primarily in the facilitation of the transition of the reaction substrate from the ground state to the excited transition state. The latter is stabilised in the active site of the enzyme to be further converted to reaction product(s). Therefore, the formation of an active site promoting the generation and stabilisation of the transition state of the substrate is a prerequisite for manifestation of catalytic activity by the protein molecule. Thus, the biosynthesis of the antibody possessing catalytic activity by the immune apparatus requires the use of an antigen the structure of which mimics the transition state formed in the catalytic reaction. It is impossible, however, to obtain a stable molecule corresponding to the transition state, since the latter represents an unstable complex. For this reason, only compounds the molecules of which mimicked the spatial and electronic structure of the transition state were used as antigens generating catalytically active antibodies. Being incorporated into immune cells, such antigens ought to generate antibodies that stabilise the transition state and, hence, manifest catalytic properties like the natural enzymes.

Although this idea was first forwarded long ago,^{1,2} its practical implementation faced serious difficulties because immune cells synthesise a great number of antibodies ('polyclonal antibodies') in response to antigens. Isolation of an antibody manifesting the highest catalytic activity and selectivity from a complex mixture of structurally similar proteins is very problematic, which made this method impracticable.

The situation has changed totally with the discovery and detailed development of the method of synthesis of the so-called 'monoclonal antibodies' that are fewer in number and less diverse.³ The antibodies isolated with recourse to this method did manifest catalytic activity.

Such antibodies, which were named 'catalytic antibodies' (CA) or 'abzymes' (abbreviated from 'antibody enzymes'), were first synthesised about 10 years ago.^{4,5} This area continues to develop rapidly since that time. By now, nearly a hundred CA that accelerate and specifically direct various reactions have been generated and the basic principles underlying the preparation of CA with predetermined specificity have been formulated. Their physicochemical characteristics appeared to be similar to those of the natural enzymes.

In some cases, the activity of CA was close to that of the natural enzymes. As a rule, these CA manifested high specificity and stereoselectivity which might be predetermined. Moreover, several CA were prepared that catalysed reactions (e.g., the Diels–Alder reaction) for which natural enzymes had not been found. What is most remarkable and promising for synthetic chemistry is that CA could be obtained which made it possible to change the direction of a known reaction and to channel it through a route which is energetically forbidden under normal non-catalysed conditions. In other words, it was possible to change chemo-, regio- and stereospecificity of the reaction and to implement conversions unattainable with conventional chemical methods.

Hence, 'catalytic antibodies' represent a new generation of protein biocatalysts, and their preparation is a considerable step forward in theoretical and practical aspects of biocatalysis.

In this review, which encompasses the literature up to 1997, the main attention is given to the chemical aspects of the problem and the prospects of application of CA for the solution of current tasks of synthetic chemistry. As for other aspects, such as enzymic kinetics of CA and some other physicochemical problems, they are reviewed only briefly and where appropriate, e.g., in relation to the specificity of CA, the structure of their active sites and the mechanisms of their catalytic action. The readers who are interested in this problem as well as in the problems of immunochemistry and molecular biology of the catalytic antibodies may be referred to the original literature.

II. The basic principles and techniques used in the synthesis of catalytic antibodies

The essence of action of catalytic antibodies, like that of ordinary enzymes, is facilitation of the formation of the transition state of the substrate molecule to favour its conversion into the reaction products. This is accompanied by a decrease in the energy barrier on the reaction coordinate during the formation of the transition state, so that the reaction rate increases. This is a result of several specific interactions occurring in the active site of the enzyme. The cavity of the latter matches the spatial structure of the substrate. The active site contains active groups in its surface favouring the corresponding conversions of the substrate molecule. The spatial and electronic complementarity of the active site and the substrate favours the 'recognition' of the substrate by the enzyme and the formation of the enzyme–substrate complex, while the active groups enable the conversion of substrate molecules into the reaction products which involves acid–base catalysis, nucleophilic or electrophilic interactions, etc.

As the enzyme–substrate complex is formed, the mobility of the substrate molecule is restricted, and the latter becomes 'fixed' in a conformation which is the most favourable for further conversions. This provides a significant gain in energy and creates the so-called 'entropic trap'. This catalytic effect is especially important for bimolecular reactions, where both interacting molecules are fixed in a reciprocal position favourable for the reaction. Other factors, such as the presence in the active site of hydrophobic zones favouring substrate conversions in non-polar aprotic ('non-aqueous') media, also play a substantial role in the manifestation of the catalytic effect.

In order to obtain an effective catalytic antibody (CA), it is necessary that its active site possesses the properties characteristic of the active site of the enzyme (see above), which ensures the manifestation of the catalytic effect.⁶ This task is accomplished by an antigen, which induces the formation of the active site of a desired structure during the biosynthesis of the protein molecule by the immune apparatus of the cell in response to administration of the antigen.

The antigen used to obtain CA usually consists of two main fragments: a low-molecular-weight hapten and a high-molecular-weight carrier, usually, an available natural protein. It is the hapten that represents the fragment of the antigen molecule which is directly involved in the formation of the active site of CA. Its spatial and electronic structures must correspond to the transition state of this reaction and enable the formation of active groups, hydrophobic zones, etc., in the active site.

The protein fragment of the antigen (the so-called 'immunogen') is a high-molecular-weight carrier that ensures the generation of antibodies by the immune apparatus. Some available natural proteins, such as hemocyanin from the mollusc *Megatura crenulata* (keyhole limpet hemocyanin, KLH) or bovine serum albumin (BSA), are the most popular immunogens.

It is the proper choice of the hapten that is the key factor determining success in the preparation of CA. Naturally, the correct design of a hapten requires knowledge of the structure of the transition state, the pathways of its induction and subsequent decomposition, in short, a knowledge of the reaction mechanism. A number of CA catalysing many reactions which occur by

different mechanisms have been prepared. However, it is impossible to formulate general recommendations concerning the design of a hapten. The reasoning behind the choice of a hapten structure will be given below for each concrete case.

Sometimes, the choice of a hapten is semi-empirical because of the lack of exact knowledge of the reaction mechanism. In such cases, researcher's experience and even intuition come to the foreground. Thus in the early studies, a somewhat simplified concept of the correlation between the spatial and electronic structures of the hapten and the structure of the transition state have played a crucial role. This sufficed to prepare the first efficient CA. Mimicking of the transition state in the hydrolysis of the ester group by phosphoric or phosphonic acid groups provides an example (see Section III).

In addition to the main 'reactive' fragment, which is responsible for the formation of the active site of CA, the hapten must contain fragments providing the 'recognition' of the substrate by the antibody. This is achieved by incorporation into the hapten of groups analogous to those in the substrate. In addition, the hapten must contain a group which enables its immobilisation on the protein, so that the hapten fragment in the antigen is located at some distance from the protein chain. The role of such 'spacer' or 'linker' groups may be played by a short aliphatic chain having a terminal reactive functional group (*e.g.*, a carboxy group). In the immobilisation, the carboxy group of the spacer reacts with the amino group of the lysine residue of a protein and binds the hapten to the protein by a strong amide bond.

Normally, immobilisation of the hapten on the protein is performed under mild conditions that do not affect either the hapten or the immunogenic protein. The number of hapten molecules bound to the protein molecule depends on the immobilisation conditions. As a rule, the antigen synthesis is conducted so as to achieve binding of not less than 10–20 hapten residues per one protein molecule.

The antigen thus prepared is used for immunisation of animals (usually, inbred mice) using standard procedures⁷ which differ from one another in some details for different CA. As a rule, two or three immunisations (as intramuscular injections) are performed in the presence of an adjuvant (most commonly, Freund's adjuvant) followed by one intravenous injection without the adjuvant in order to enhance the immune response. After the lapse of a definite time, spleen cells of the immunised animal are removed to prepare monoclonal antibodies by the classical hybridoma technology.⁸ To this end, the spleen cells are 'fused' with myeloma cells in a polyethylene glycol solution. The hybridomas thus obtained are able to produce monoclonal antibodies against various fragments of the antigen molecule. From the total bulk of monoclonal antibodies, those generated against particular structural fragments of the hapten and able to form complexes with it due to complementarity of their structures are selected using the so-called enzyme-linked immunosorbent assay (ELISA).⁹ The hapten immobilised on BSA is used as a specific reagent. The formation of a hapten–antibody complex points to the complementarity of the structure of the active site of the antibody to that of the hapten (and, correspondingly, to that of the transition state of the substrate which had been mimicked by the given hapten). Such antibodies are likely to manifest catalytic activity. The ability of the selected antibody to catalyse a specific reaction is assayed in direct experiments.

In order to obtain large quantities of CA for further analysis, the appropriate hybridoma selected by the ELISA technique is repeatedly injected into experimental mice after which the target CA is isolated from the ascites fluid where it is present in a high concentration. The CA thus obtained is further purified by conventional methods of protein chemistry (precipitation, chromatography and electrophoresis).

Being a protein, CA completely loses its activity upon thermal treatment (denaturation) or this is changed following treatment with typical protein modifiers (iodoacetamide, diethyl carbonate, tetranitromethane, *etc.*).

Sometimes, the preparation of active CA requires more sophisticated and specific procedures. These may include sequential immunisation of mice with two antigens differing in the hapten structure (the so-called 'heterologous immunisation').¹⁰ This provides the formation of an active site which matches the features of both haptens and thus imparts a required specificity on CA. An alternative approach consists of the use of an antigen whose hapten not only is a stable model of the transition state generated in the course of the substrate conversion but can also interact with the active site of the CA formed in this process, thus reproducing the dynamics of conversion of the substrate molecule in the course of the catalytic reaction (the so-called 'reactive immunisation').¹¹

In their properties and behaviour, CA are typical proteins pertaining to the class of immunoglobulins. Their physico-chemical characteristics are close to those of natural enzymes. Thus the behaviour of CA in a catalytic process follows saturation kinetics and is described by the Michaelis–Menten equation. It thus follows that the catalytic effect of CA is based on the formation of the enzyme–substrate complex, which has been directly confirmed in mass spectrometric studies.¹²

The inhibition of the CA activity by the hapten or its analogues suggests that the cavity in the active site of CA is in fact complementary to the hapten used for its generation. Inhibitory analysis of CA is widely employed in the studies on the structure of the active site of CA and the mechanism of its catalytic effect. Quantitatively, the catalytic effect of CA is estimated by the ratio of the rate constants of the catalytic and non-catalytic (basic) reactions.

An important feature of CA is its specificity, which also includes stereoselectivity. Specificity of CA is established using a traditional approach, *viz.*, in reactions of structural analogues of the substrate, where the rates of their conversions and/or inhibitory effect in catalysis are determined.

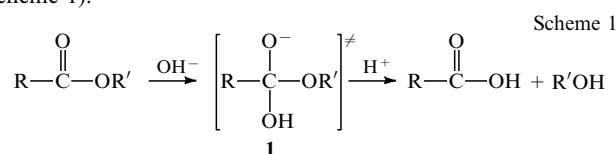
In some cases, the structure of CA or its active site has been studied in more detail using X-ray structural analysis of CA itself or its complex with the substrate. These studies were mainly undertaken in order to elucidate the mechanism of action of CA at the molecular level, to compare the structure and mechanism of action of CA with those of the natural enzyme and to solve other enzymological problems with CA as the models.

In the subsequent sections, we shall consider the procedures used to prepare CA catalysing reactions of various types which are classified according to the principle conventionally employed in organic chemistry and familiar to organic chemists. The chronological order may not be strictly followed.

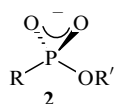
III. Hydrolysis of the ester bond and other transacylation reactions

Hydrolysis of the ester bond is the first example of a chemical conversion for which catalytic antibodies have been specially raised and the principles of selection of haptens, which are the 'active' parts of the artificial antigens used in generation of specific CA by biosynthesis in the immune apparatus of an animal, have been considered.

Success in the synthesis of these CA was achieved primarily due to the correct choice of a group mimicking the transition state **1** formed in the hapten in the cleavage of the ester bond (Scheme 1).

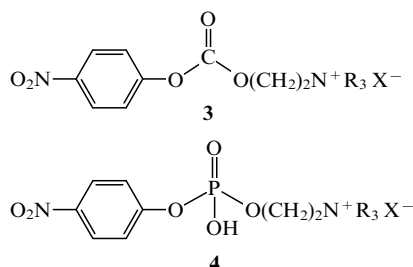


The RP(O)(OR')O group (**2**) in phosphoric or phosphonic acid derivatives, which contains a tetrahedral phosphorus(V) atom and bears a negative charge, mimicked the transition state **1** of the reaction of cleavage of the ester bond containing a tetrahedral carbon atom and bearing a negative charge.^{4,5}



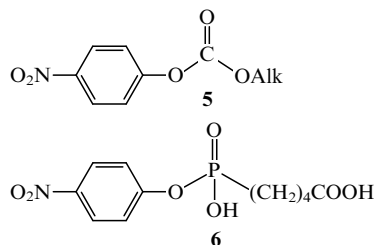
R = Ar, OAlk, OAr.

The idea to use phosphoric or phosphonic acid derivatives came about also from the consideration of the known data on the structure of synthetic inhibitors of natural esterases, particularly of choline esterases.¹³ These inhibitors represent phosphate (or phosphonate) analogues of the corresponding substrates (*e.g.*, acetylcholine) with a phosphorus-containing group in place of the ester bond. They form complexes with choline esterase, which points to the complementarity of the phosphate group to the enzyme active site. It was found that some antibodies raised against such inhibitors manifested catalytic properties, *i.e.*, they enhanced the hydrolysis of the ester bond in the corresponding substrate. This confirmed the presence of the active site favouring hydrolysis. Thus the MOPS 167 antibody raised against the inhibitor of *O*-(4-nitrophenoxy)carbonylcholine (**3**) esterase formed a complex with this inhibitor (4-nitrophenylphosphorylcholine) (**4**) and possessed noticeable catalytic activity, *viz.*, it accelerated manifold the hydrolysis of the choline derivative **3**.⁵



This antibody manifested the features of natural esterases (Michaelis–Menten kinetics, inhibition by compound **4**, characteristic dependence of its activity on pH, *etc.*). Its catalytic effect was regiospecific, *viz.*, the hydrolysis of substrate **3** analogues with an altered structure of the aliphatic chain or devoid of the quaternary nitrogen atom was accelerated in a much lesser degree or not at all. These data suggest that the phosphorus-containing group efficiently mimics the transition state which appears in the hydrolysis of the ester bond and can generate the active site in the CA possessing esterase activity. This circumstance has been widely employed in further preparation of this type of CA.

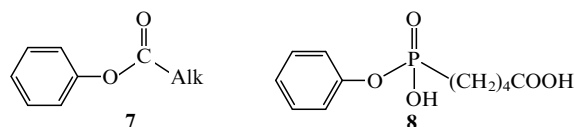
Thus a 4-nitrophenyl phosphonate derivative (**6**) containing a tetramethylene fragment with a carboxy group as a spacer was used as a hapten[†] to raise a CA catalysing the hydrolysis of 4-nitrophenyl carbonate (**5**).¹⁴



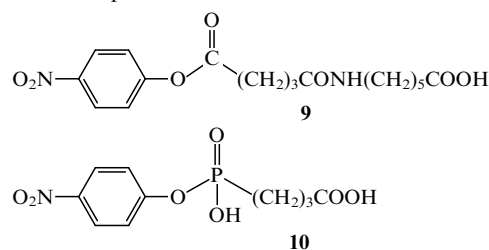
Immobilisation of phosphonate **6** through this carboxy group made it possible to obtain an artificial antigen containing, on the average, 15 hapten residues per one protein molecule. This antigen was used for immunisation, and a CA was isolated which accelerated the hydrolysis of carbonate **5** 800-fold in comparison with the non-catalysed reaction. This CA manifested the properties of an esterase, *viz.*, its hydrolysis followed Michaelis–Menten kinetics, suggesting the formation of an enzyme–substrate com-

plex, and its activity showed a typical pH-dependence. This CA was inhibited by 4-nitrophenyl phosphate, the phosphate analogue of the substrate. Its effect was regiospecific, *viz.*, the rate of hydrolysis of 3-methyl-4-nitrophenyl carbonate was 10-fold smaller in comparison with the original compound, while the hydrolysis of isomeric 2-nitrophenyl carbonate was not catalysed at all.

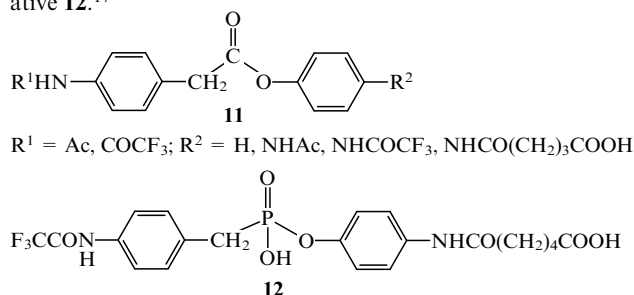
Haptens with similar structures were used to obtain CA catalysing the hydrolysis of phenol esters. Thus the hapten **8** was used to raise CA catalysing the hydrolysis of the simplest *O*-acylphenols of the type **7**.



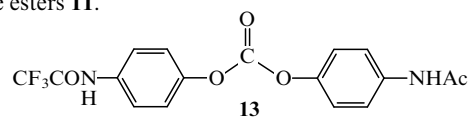
One of the CA prepared accelerated the hydrolysis of acylphenols more than 10⁴-fold.¹⁵ The hydrolysis of the ester bonds in nitrophenols **9** acylated with *N*-carboxyalkyl glutaramide, such as compound **9**, was accelerated 10⁴-fold in the presence of CA raised against the hapten **10**.¹⁶



The hydrolysis of structurally more complex substrates **11** (aminophenol esters with substituted aminophenylacetic acids) would be accelerated in the presence of CA raised against phosphorus-containing haptens, *viz.*, a benzylphosphonate derivative **12**.¹⁷

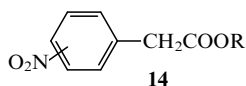


The structural similarity of the benzylphosphonic acid derivative to the acid moiety of the substrate allows more precise mimicking of the transition state of hydrolysis of the esters **11**. Several CA have been isolated from a mixture of antibodies raised against the hapten **12**. The most efficient of them accelerated the hydrolysis of the esters **11** 10⁶-fold and manifested all the features of the enzyme. Thus its activity changed after treatment with specific protein modifiers (diethyl carbonate, tetranitromethane, *etc.*). The activity of this CA strongly depended on the nature of substituents in the aromatic nuclei of the substrate **11**. It was inactive in the hydrolysis of carbonate **13** structurally similar to the esters **11**.



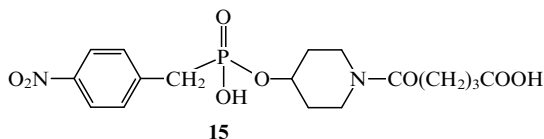
The problem of specificity of the CA of the esterase type is of considerable importance for their practical applications in the solution of synthetic tasks. This problem and the factors determining the specificity have been studied with the hydrolysis of nitrophenylacetates **14** as an example.¹⁸

[†] For the synthesis of this hapten and other compounds mentioned in this review, see the original papers.



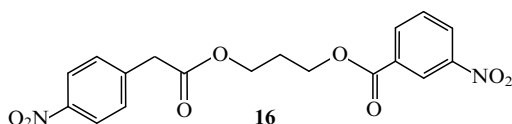
R = Alk, Bn, O₂NC₆H₄CH₂, ClC₆H₄CH₂ etc.

To this end, the hapten **15** containing a 4-hydroxypiperidine residue (enhancing the antigen immunogenicity) and a spacer was synthesised.



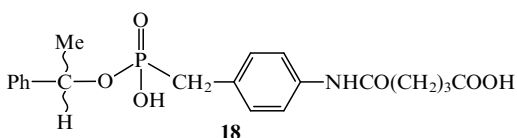
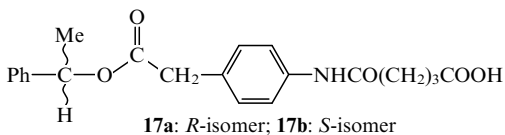
A catalytic antibody raised against the hapten **15** appeared to be highly efficient. It accelerated the hydrolysis of the esters **14** (3×10^4 -fold, on average). The results of the kinetic analysis of hydrolysis of structurally different esters **14** revealed that the catalytic effect of CA was manifested only in the case of 4-nitro-substituted derivatives. The hydrolysis of the corresponding 3-nitro derivatives was not catalysed at all, which confirmed the previously established regularity.[‡]

This specificity allowed the hydrolysis of a mixed ester of 1,3-propylene glycol **16** to occur in a strictly selective manner.



The effect of the nature of the alcoholic component is much less pronounced. Thus CA catalyse the hydrolysis of esters **14** containing residues of various primary alcohols, although the rates of this hydrolysis vary from 10^4 to 10^6 . In contrast, the hydrolysis of the esters **14** containing residues of secondary alcohols is not catalysed at all, with the exception of 1,1,1,3,3,3-hexafluoropropan-2-ol derivatives.

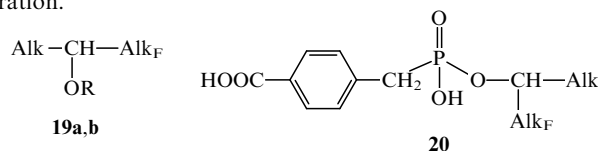
High stereospecificity is one of the most distinguishing and important features of enzymic catalysis. This problem has received much attention in the studies of CA, and the generation of the first highly stereospecific CA has been a considerable achievement. For the first time, this has been studied in the preparation of a CA catalysing the hydrolysis of esters of substituted phenylacetic acid with α -methylbenzyl alcohol (**17**) containing a chiral carbon atom.²⁰ The hapten **18**, which is a phosphonate analogue of the substrate **17** and also contains an asymmetric carbon atom, was used to raise a specific CA.



The ester **18** was used as a racemate. Eleven active CA catalysing the hydrolysis of the esters **17** were obtained. Study of the hydrolysis of pure enantiomers **17a** and **17b** in the presence of these CA showed that nine of them catalysed the hydrolysis of the *R*-isomer, while the other two catalysed the hydrolysis of the *S*-isomer. A detailed analysis revealed that all of these CA manifested the characteristic properties of esterases and high

stereoselectivity. Thus the degree of hydrolysis of the enantiomer which corresponds to the specificity of the CA is 98%, while that of the other enantiomer is only 2%. The catalytic activity of stereospecific CA catalysing the hydrolysis of the *R*- and *S*-isomers is different. The catalytic antibody, which catalyses the cleavage of the *R*-isomer, accelerates the reaction 8×10^4 -fold (vs. 1.6×10^3 -fold increase in the case of the CA specific toward the *S*-isomer). Thus, the racemic hapten **18** generates CA manifesting two different stereospecificities and each of the enantiomers of **18** 'forges' the active site of CA with the complementary spatial structure. As has been mentioned above, the number of antibodies raised against each enantiomer of the hapten **18** is different due to the peculiarities of the protein chain biosynthesis in the immune apparatus.

Catalytic antibodies of different stereospecificities can be isolated in the individual state or be specifically generated using the corresponding optically pure hapten enantiomers. Such CA manifest high stereoselectivity and are used successfully in the synthetic practice, e.g., for kinetic resolution of mixtures of stereoisomeric alcohols by selective hydrolysis of their esters. For example, racemates of the fluorine-containing alcohols **19a** were resolved by hydrolysis of the corresponding phenylacetates **19b**.²¹ CA with predetermined stereoselectivity were generated using enantiomers of the hapten **20** having an *R*- or *S*-configuration.



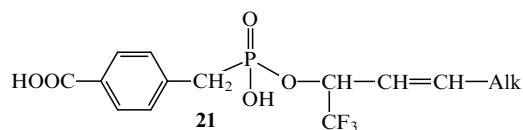
R = H (**a**), COBn (**b**);

Alk = C₆H₁₃, C₇H₁₅, C₈H₁₇;

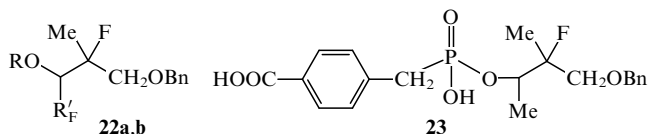
Alk_F = CHF₂, CF₃.

The hydrolysis of the racemic phenylacetates **19b** in the presence of these CA yielded the *R*- and *S*-isomers of the alcohols **19a** with optical purity 98%. It is noteworthy that the stereoselectivity of the resolution did not depend on the length of the aliphatic chain.

Kinetic resolution of the stereoisomeric alcohols **19a** containing the allylic group (Alk = CH=CHC₆H₁₃) was carried out in a similar way. With the use of CA against the enantiomers of the hapten **21** it was possible to isolate all the four isomers of the corresponding alcohols **19a** of high optical purity from a mixture of phenylacetates **19b** (Alk = CH=CHC₆H₁₃, Alk_F = CF₃).



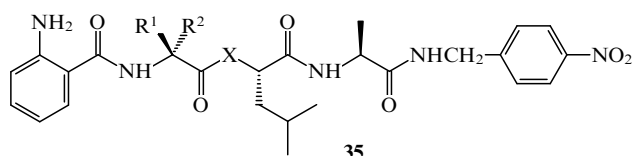
The diastereomeric alcohols **22a** were resolved by the hydrolysis of their phenylacetates **22b** catalysed by the catalytic antibodies raised against the haptens **23** having *syn*- and *anti*-configurations.²²



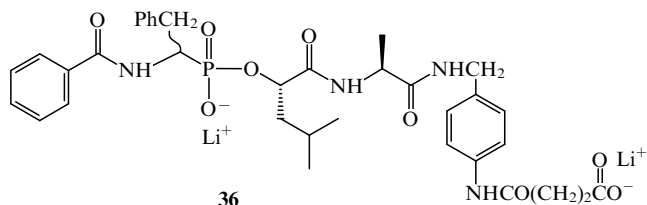
R = H (**a**), COBn (**b**).

The catalytic antibody against the *syn*-isomer of **23** hydrolysed the *syn*-isomer of **22b** to yield the alcohol with optical purity 99% (the degree of hydrolysis was 49%), while CA against the *anti*-isomer of **23** hydrolysed the *anti*-isomer of **22b** with the same high degree of purity. The resolution of the alcohols HOCH(R_F)C(F)(Alk)CH₂OBn, which differed from compounds **22a** in the length of the aliphatic chain (Et, Pr and Bu substituents instead of the methyl substituent), occurred in a similar way. After

[‡] The specificity of antibodies against nitro-substituted substrates was established by Landsteiner¹⁹ at the dawn of development of immunochemistry.



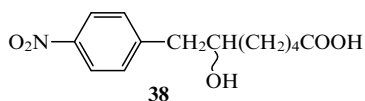
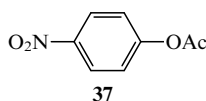
X = O, NH; R¹, R² = H, Bn.



This CA hydrolysed only the ester bond (X = O) without affecting the peptide bond (X = NH) (chemoselectivity). It is noteworthy that this antibody exclusively catalysed the hydrolysis of the depsipeptide **35** containing the D-phenylalanine residue, whereas the depsipeptide containing the L-isomer was hydrolysed by no more than 0.5% (stereoselectivity). Evidence for the high regiospecificity of this CA followed from its inability to catalyse the hydrolysis of the depsipeptide **35** analogues in which leucine or tryptophan was substituted for the phenylalanine residue.[§]

All the above examples of preparation of CA are based on the use of substrate analogues as the haptens in which the ester bond was replaced by a residue of phosphoric or phosphonic acid and which mimic the transition state of ester hydrolysis. Catalytic antibodies against these haptens manifested chemo-, regio- and stereoselectivity. Haptens of this type are used in the synthetic practice most often and most successfully.

However, haptens of a different structure, among which haptens containing secondary alcoholic groups instead of the ester group in the substrate molecule are the most popular, can also be used for the preparation of CA possessing esterase activity.[¶] Although the mechanism of action of such haptens is not clearly understood, several active CA were raised against them. For the first time, a hapten of this type was designed by analogy with pepstatin, a well-known inhibitor of pepsin.²⁸ Thus preparation of CA catalysing the hydrolysis of 4-nitrophenyl carbonate **5** or the corresponding acetate **37** was based on the use of 7-(4-nitrophenyl)-6-hydroxyheptanoic acid (**38**) as a hapten.



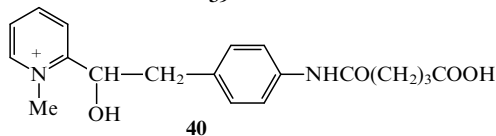
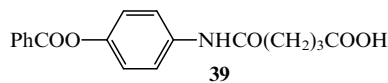
The acid **38** contains the structural elements of the substrates **5** and **37**; its structure resembles that of the phosphorus-containing hapten **6** used to obtain CA with the same character of action (see p. 1002).

The catalytic antibody against the acid **38** accelerated the hydrolysis of the esters **5** and **37** 930- and 1225-fold, respectively. This CA displayed all the typical features of esterases, although its activity was much lower than that of CA generated against the phosphorus-containing hapten **6**. Nevertheless, this finding confirmed the possibility of using the secondary alcoholic group for mimicking the transition state of the hydrolytic reaction.

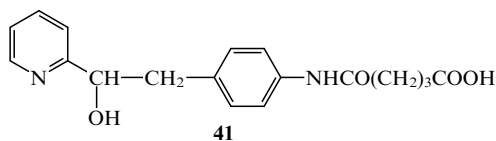
§ For the preparation of CA catalysing the hydrolysis of carbamates, see D van Vranken, D Panomitros, P G Schulz *Tetrahedron Lett.* **35** 3873 (1994); P Wentworth, A Datta, S Smith, A Marshall, L Partridge, G M Blackburn *J. Am. Chem. Soc.* **119** 2315 (1997).

¶ For attempts to use haptens of a different structure (e.g., containing the isosteric and isoelectronic CF₂ group) for preparing CA of the esterase type, see Ref. 27.

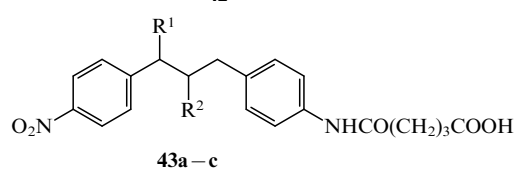
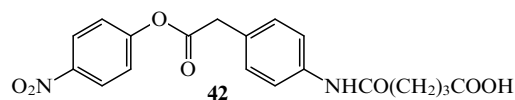
The use of haptens containing a positively charged group together with a secondary alcoholic group appeared to be more successful.²⁹ Thus a CA catalysing the hydrolysis of the ester bond in the benzoate **39** was raised against the hapten **40**.



It was assumed that the positive charge of *N*-methylpyridinium generated an acidic group (presumably, a carboxy group) in the appropriate position of the active site of the antibody, while the tetrahedral carbon atom of the secondary alcoholic group provided the formation of its spatial structure. The catalytic antibody raised against the hapten **40** was found to be highly efficient; it manifested activity close to that of natural esterases and accelerated the hydrolysis of the benzoate **39** 10⁶-fold. This was attributed to the fact that, in addition to the formation of the spatial structure of the active site, the hapten **40** induced the generation of a carboxy group which, in turn, facilitated the conversion of the substrate with the involvement of general acid–base catalysis. Indirect evidence for the presence of a carboxy group in CA and its role in the hydrolysis of the ester bond can be derived from the fact that the hapten **41**, the pyridine analogue of compound **40**, which is deprived of the positive charge, does not generate active CA.



Thus, the preparation of efficient CA requires not only the formation of an active site complementary to the transition state, but also the generation in the active site of groups favouring the very conversion of the transition state into the reaction products, e.g., involving general acid–base catalysis. This view was confirmed³⁰ in studies of the hydrolysis of the ester bond in compound **42** catalysed by CA raised against the haptens **43**. These CA accelerated the ester hydrolysis 3 × 10³-fold.



43a: R¹ = NH₂, R² = OH;

43b: R¹ = N⁺Alk₃, R² = OH;

43c: R¹ = N⁺Alk₃, R² = O—P(=O)(OH)₂.

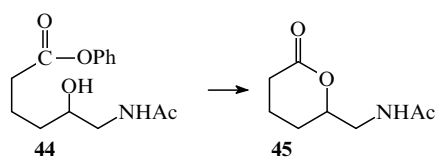
A detailed study of CA generated against the haptens **43a–c** having different substituents using enzymic kinetics and, especially, inhibitory analysis has led to an important conclusion, viz., that the lack of catalytic activity in CA depends not only on insufficient binding of the substrate because of insufficient matching of the active site but, rather, on the arrangement of groups responsible for the dynamics of conversion of the transition state into the reaction products in the active site. Thus the number of active CA raised against the hapten **43a** containing an amino

group (it virtually functions as the H_3N^+ group) exceeds that of CA raised against the hapten **43b** containing a bulkier Alk_3N^+ group, because the access to the positively charged centre of the hapten is hindered, which impedes the formation of the carboxy group in the appropriate position of the active site. The presence of an additional charged phosphorus group in the hapten **43c** also impedes the formation of the active centre, which results in less active CA. Thus the activity of CA against the haptens **43a–c** is believed³⁰ to depend primarily on the reciprocal position of the charged groups in the 1,2-amino-alcohol fragment of the molecule. This circumstance must be taken into consideration in the design of haptens for highly efficient CA.

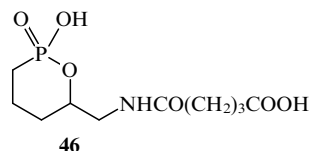
Attempts have been made to introduce certain groups aimed at increasing the efficiency of CA by the methods common for natural enzymes, *viz.*, by chemical modification and site-directed mutagenesis. The incorporation of a covalently bound imidazole residue into the active site of the antibody MOPS 315 possessing esterase activity³¹ is an example of such a modification, which resulted in an increase in the activity of the CA 10^3 -fold in comparison with that observed after mere addition of imidazole to the reaction medium in the same hydrolytic reaction.

All the examples cited above are related to the preparation of CA catalysing the simplest transacylation reaction, *i.e.*, the hydrolysis of esters where the acyl group is transferred to the water molecule present in huge excess. This reaction is of the pseudo-first order. In a wider sense, *O*-transacylation implies the transfer of an acyl residue to any hydroxy-containing compound and occurs according to a more complex mechanism.

The intramolecular transfer of the acyl group in the phenyl ester of the hydroxy acid **44** to the hydroxy group to yield the lactone **45** is the simplest example of the *O*-transacylation reaction.³²



The hapten **46**, which is a phosphate analogue of the lactone **45**, was used to obtain CA catalysing this reaction. Like other haptens used to raise CA of the esterase type, the phosphonate **46** used (in the form of one enantiomer) mimicked the transition state which appears in the lactonisation of the ester **44**. In the presence of a CA obtained, the reaction was accelerated 167-fold in comparison with the non-catalysed process; this occurred with high stereoselectivity and followed the Michaelis–Menten kinetics.

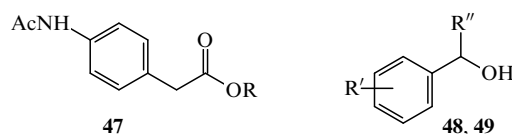


The cyclisation of the racemic ester **44** was terminated after conversion of 50% of the substrate to yield only one of stereoisomers of the lactone **45**, since only one enantiomer of compound **44** underwent conversion. The second enantiomer did not enter into the reaction. Thus, the enantiomer of the hapten **46** used has created the active site of CA complementary to only one of the enantiomers of the substrate. This CA can be regarded simultaneously as an enzyme promoting the formation of a new ester (lactone) bond and as a synthase.

In addition to CA catalysing the intramolecular transfer of an acyl group within the same substrate, some CA of the transferase type have also been obtained. These CA catalysed the intermolecular transfer of acyl groups from one substrate to another. The reactions occurring in aqueous media, *i.e.*, in the presence of large excess of water as the competing acceptor, present special interest.

The preparation and examination of CA catalysing such reactions were performed mostly with the view of investigating the reaction mechanisms, the practical aspect of their use for the solution of problems of organic synthesis was studied relatively little. The complexity of catalysis of two-substrate reactions lies in that they can follow two fundamentally different mechanisms, *viz.*, through the formation of a ternary complex ($\text{CA} + \text{substrate 1} + \text{substrate 2}$) or in a more complex way which involves several steps. Realisation of such reactions in aqueous media implies the formation of an additional active site in CA responsible for 'ejection' of a competing water molecule from the reaction sphere, *e.g.*, due to the presence of hydrophobic groups. This property must be 'preset' in the structure of the hapten mimicking the transition state.

A detailed study of one of such reactions, *viz.*, the selective transfer of 4-acetylaminophenylacetic acid from the esters **47** to substituted benzyl (**48**) and α -methylbenzyl alcohols (**49**) in the water–DMSO system (10 : 1), has been carried out.³³



$\text{R} = \text{Alk, Ar, Bn, CH}_2=\text{CH}.$

48: $\text{R}'' = \text{H}$, **49:** $\text{R}'' = \text{Me}.$

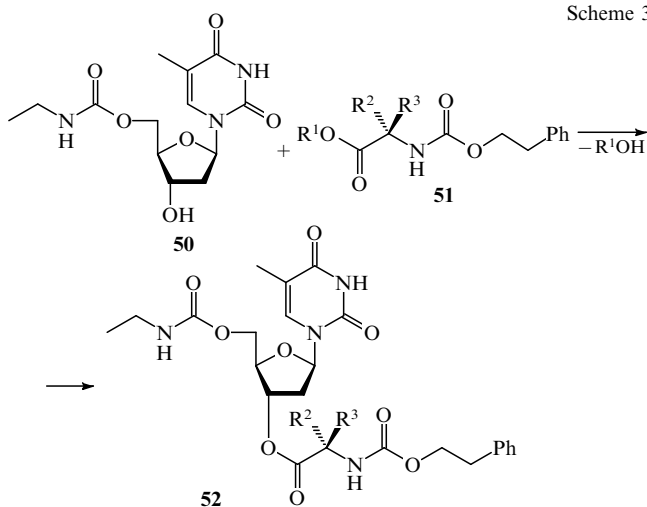
The corresponding CA was raised against the hapten **18**. This CA efficiently catalysed the transfer of the acyl residue not only to the water molecule (hydrolysis) (see p. 1003) but also to alcohols. The latter reaction is selective and unaccompanied by the hydrolysis of the ester **47** despite the presence of a large excess of water. Transacylation in a system of various acyl donors **47** ($\text{R} = \text{Alk, CH}_2=\text{CH, Ar, Bn}$) and acceptors (alcohols **48** and **49**) is highly efficient; the catalysed reaction occurs 10^4 – 10^6 times faster, even in the case of the secondary alcohols **49** the hydroxy group of which is much more sterically hindered than that of water. Interestingly, the vinyl ester **47** as an acyl donor proved to be especially efficient and convenient, since vinyl alcohol produced upon transacylation is isomerised into acetaldehyde and eliminated from the reaction.

Detailed studies of the catalytic effect of CA raised against the hapten **18** using the methods of enzymic kinetics and inhibitory analysis as well as X-ray analysis of several CA complexes with substrates have prompted important conclusions about the mechanisms of two-substrate transacylation reactions which can be briefly summarised as follows.^{34,35} The transfer of the acyl residue from the ester **47** onto the alcohol occurs *via* the intermediate formation of an acyl derivative of the CA. Subsequent transfer of the acyl group onto the acceptor alcohol follows the so-called 'ping-pong' kinetics where the entering of the first substrate (the ester) into the active site of the CA, the removal of the leaving group with the concomitant formation of the acyl derivative of the CA, the entering of the second substrate (the acyl group acceptor) and the liberation of the transacylation product accompanied by the recovery of the catalyst (CA) regularly alternate. The whole sequence of reactions is then repeated. The active site of CA undergoes certain conformational changes in the course of the reaction depending on the structure of the second reaction substrate. For molecular mechanisms of the acyl transfer see Refs 36, 37

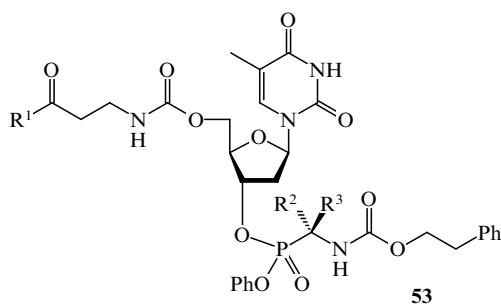
The reactions of the acyl transfer catalysed by natural transferases are widely represented in various biochemical processes occurring in living organisms. In this connection, the preparation of CA catalysing one of the most important reactions of this kind, *viz.*, aminoacylation, which consists in the transfer of the amino acid residue onto a nucleotide residue is of considerable interest. In a cell, this reaction is catalysed by the natural enzyme (aminoacyl-tRNA synthase) and is the key stage in protein biosynthesis.

The transfer of the *N*-acylalanine residue onto the hydroxy group of the thymidine derivative **50** from the ester **51** resulting in the derivative **52** has been studied (Scheme 3).³⁸

Scheme 3



$R^1 = \text{Ph}, 4\text{-FC}_6\text{H}_4, \text{CH}_2\text{CN}$; $R^2, R^3 = \text{H}, \text{Me}$.



$R^2, R^3 = \text{H}, \text{Me}$.

The corresponding CA was raised against the haptin **53**, the phosphate analogue of the aminoacylation product **52**.

This haptin structure enables the formation of the active site of CA which ensures the mutually advantageous arrangement of the reaction substrates and gives a considerable gain in entropy in the formation of the transition state of this bimolecular reaction. The tetrahedral structure of the phosphonate group differs from the trigonal structure of the reaction product, which prevents the inhibition of the aminoacylation reaction by the reaction products.

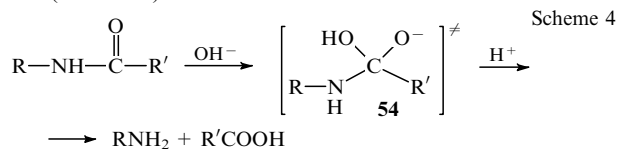
The aminoacylation of thymidine **50** took place in the case of phenyl ($R^1 = \text{C}_6\text{H}_5$), 4-fluorophenyl ($R^1 = 4\text{-FC}_6\text{H}_4$) and cyanomethyl ($R^1 = \text{CH}_2\text{CN}$) esters **51**, but not for the ethyl ($R^1 = \text{C}_2\text{H}_5$) esters **51**. Four of the CA raised against the haptin **53** catalysed the transesterification of L-alanine esters and three CA catalysed the transesterification of D-alanine esters. The most active of these CA accelerated the aminoacylation reaction more than 10^8 -fold. A kinetic analysis showed that these CA only weakly recognised the alcoholic component but were more selective with respect to substrate stereochemistry, *i.e.*, the reaction was highly stereospecific.

IV. Hydrolysis and formation of the amide bond

The search for CA endowed with the ability to catalyse hydrolytic cleavage of the amide bond in a way similar to that of natural proteolytic enzymes is of considerable importance, because it opens up new ways to selective hydrolysis of a polypeptide chain of the protein molecule, which represents one of the basic challenges to bioorganic chemistry. This problem is much more difficult than hydrolysis of the ester bond, and achievements in this area are far more modest. Since the hydrolysis of the $\text{NH}-\text{CO}$ bond is a more energy-consuming process and occurs according to a more complex mechanism, a more accurate choice

of a haptin that would initiate the biosynthesis of highly specific CA able to lower the energy barrier of this reaction is required. Only CA efficiently catalysing the hydrolysis of only the simplest amides have been obtained so far.

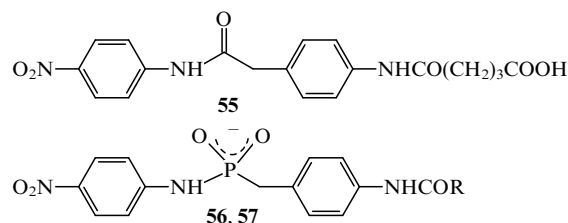
The hydrolysis of the amide bond occurs through the transition state **54** which is further decomposed to give an amine and an acid (Scheme 4).



Scheme 4

The catalytic antibody must stabilise the ionic site in the transition state **54** and induce simultaneously protonation of the nitrogen atom as the amine is split off. Amide analogues in which the carboxamide bond was replaced by the sterically and electronically similar phosphamide bond were used as haptens mimicking the transition state **54** and forming the active site of CA.

For example, the hydrolysis of 4-nitroanilides of phenylacetic acids **55** was catalysed by CA raised against the haptin **56**.

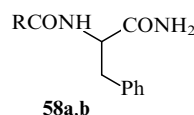


$R = (\text{CH}_2)_2\text{COOH}$ (**56**), Me (**57**).

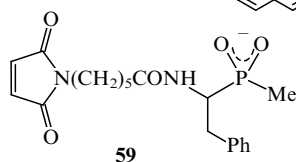
The haptin **56** contained a phosphonamide group as well as functional groups analogous to the corresponding groups of the substrate **55** and essential for its 'recognition' and a spacer.³⁹ The most active of the CA obtained accelerated 2.5×10^5 -fold the hydrolysis of the amide **55** at pH 9.0 compared to the non-catalysed reaction and manifested the features typical of natural amidases (Michaelis–Menten kinetics, inhibition with phosphonamide **57**, which is an analogue of the haptin **56**, *etc.*). The effect of this CA was highly specific, *viz.*, in contrast with 4-nitroanilide **55**, it did not catalyse the hydrolysis of 2- and 3-nitroanilides. Similar specificity was observed for CA of the esterase type (see Section III). The narrow specificity of CA against the acyl fragment of the substrate is the most essential.

Unfortunately, the hydrolysis of 4-nitroanilides of various α -amino acids and some di- and tripeptides was not catalysed by these CA. Therefore, they are not suitable for the catalytic hydrolysis of the peptide bond.

Certain success has been achieved in the synthesis of CA catalysing hydrolysis of the simplest non-substituted amides of *N*-acylated phenylalanines **58**. The corresponding CA was generated using the haptin **59**, which is an analogue of the amides **58**; the carboxamide group in this haptin was replaced by the methylphosphinic acid residue, and the alkyl spacer had a terminal maleimide residue essential for immobilisation.⁴⁰



$R = \text{Me}$ (**a**), $(\text{CH}_2)_5\text{NHSO}_2$ -[maleimide ring]- NMe_2 (**b**)

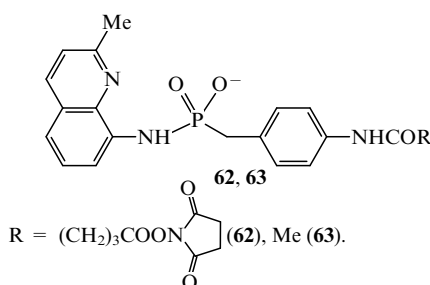
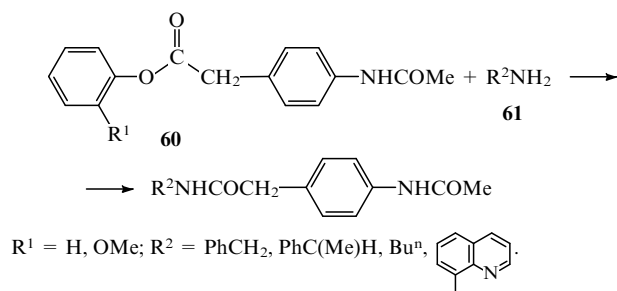


This CA accelerated the hydrolysis of the amide **58b** only 130-fold and catalysed the hydrolysis of D-phenylalanine derivatives only; it did not possess esterase activity. High regiospecificity of this CA was manifested in that it catalysed hydrolysis of only the non-substituted amide group, while the acylamide bond in the amides **58a,b** was unaffected. Although the practical application of this CA is impeded due to its narrow specificity, it turned out to be a useful tool in the study of the mechanism of the acyl transfer reaction (see p. 1006).

An alternative approach has also been used to obtain CA catalysing the cleavage of peptide bonds. Considering that many natural peptidases are metalloenzymes (*i.e.*, their active site contains a metal ion), it was suggested to use an amide complex containing a metal ion with the corresponding ligand as a hapten. It was assumed that this complex hapten will form a cavity in the active site which might accommodate the amide bond of the substrate coordinated with the metal ion. An attempt to obtain CA selectively hydrolysing the peptide bond of glycylphenylalanine is an example.⁴¹ A hapten containing the trien (tri-ethylenetetraamine) complex of cobalt(III) in addition to the substrate residue was used to raise CA. One of them was found to be active and specific with respect to the peptide structure. Unfortunately, this study was not apparently continued and the CA obtained did not find any practical application. However, the fundamental importance of using metal complexes as haptens is indubitable.

The reverse reaction, *i.e.*, the CA-catalysed synthesis of the peptide bond, especially if this is efficient and selective under mild conditions, is no less interesting than the CA-catalysed cleavage of the amide bond. Although a great number of natural enzymes catalysing this reaction are known, interest in the preparation of CA with predetermined specificity is quite justified.

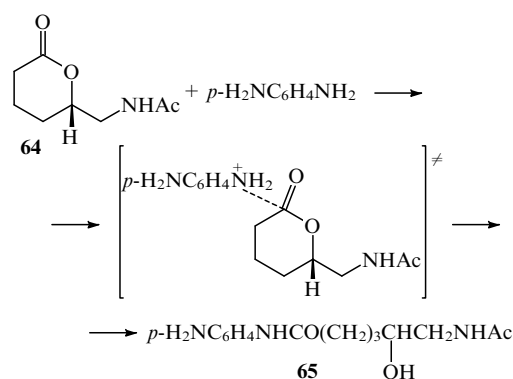
The chemical methods used in the formation of the amide bond are based on aminolysis of certain carboxylic acid derivatives, *i.e.*, the transfer of the acyl residue onto an amine. The specific function of CA consists in the facilitation of this transfer. Actually, the effect of this CA is close to that of CA of the esterase type catalysing the transfer of the acyl group to the water molecule. The essential difference is that in this case the concentration of the amine is commensurable with that of the acyl donor. This is a second-order reaction and occurs according to a more complex mechanism which may involve the formation of the intermediate acyl group carrier, *viz.*, the acylated derivative of CA (*cf.* Section III).^{34–37} This must be taken into consideration in the design of the hapten mimicking the transition state arising in the synthesis of the peptide bond. The simplest aminolysis reaction, *viz.*, direct attack of the nucleophilic nitrogen atom on the ester bond (the transition state of this reaction is analogous to that existing in the hydrolysis of the ester or amide bonds) was used as a model. The transition state was mimicked with a hapten, a substrate analogue, in which the ester bond was replaced by the phosphamide bond. Thus in the preparation of a CA catalysing aminolysis of aryl esters of substituted phenylacetic acids (**60**) with the amines (**61**) (benzylamine, in particular), the 8-aminoquinoline derivative (**62**) containing a phosphonamide group was used as a hapten.⁴²



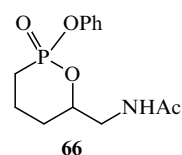
Like natural enzymes, the CA obtained noticeably accelerated the aminolysis which followed Michaelis–Menten kinetics with respect to both reaction components and was inhibited by the hapten analogue (**63**). The effect of CA was specific as regards the amine structure, which has been established in competitive reactions. The ratio of the rates of the CA-catalysed aminolysis with 8-aminoquinoline, benzylamine and butylamine was 30:3.12:1, whereas in the absence of CA the reaction rate was practically independent of the amine structure (the ratio was 0.9:0.7:1). In the presence of CA, the reaction was stereoselective: the rates of aminolysis of the ester **60** with epimers of α -methylbenzylamine were different ($R:S = 2.2:1$).

A CA catalysing aminolysis of the lactone **64** with *p*-phenylenediamine was obtained in a similar way (Scheme 5). This reaction results in the ring opening and the formation of the amino alcohol **65**.⁴³

Scheme 5

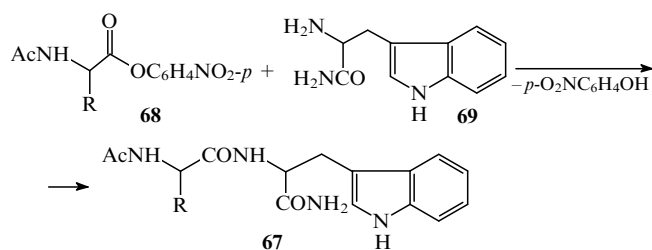


A catalytic antibody raised against the hapten **66**, the phosphonate analogue of lactone **64**, increased the rate of this reaction severalfold and produced a stereospecific effect by catalysing the aminolysis of only the (–)-epimer of the lactone **64**.

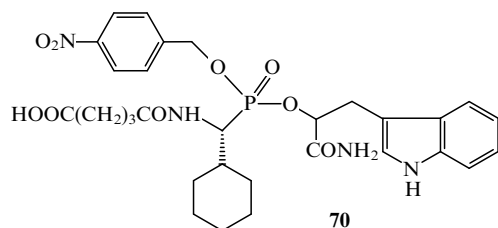


Initially, these studies were important for a comparison of the mechanisms of action of CA in similar reactions of hydrolysis and aminolysis (see Section III)^{34–37} but did not present any interest for synthetic chemistry. However, recently these reactions have again attracted attention of investigators. The reason is that the design of efficient catalysts allowing selective formation of the peptide bond may facilitate the solution of a problem of synthesis of large proteins by directed coupling of peptide blocks that have now become available owing to solid-phase synthesis. The first steps in this direction have already been undertaken aimed at the preparation of CA the effect of which would be similar to that of such natural enzymes as ligases. Using phosphorus-containing compounds as haptens mimicking the transition state, the first representatives of CA catalysing the formation of the peptide bond between amino acids have been obtained. Thus CA efficiently catalysing synthesis of dipeptides **67**⁴⁴ from *p*-nitrophenyl

esters of the corresponding *N*-acetyl amino acids **68** with tryptophan amide (**69**) were raised against the hapten **70**.[†]

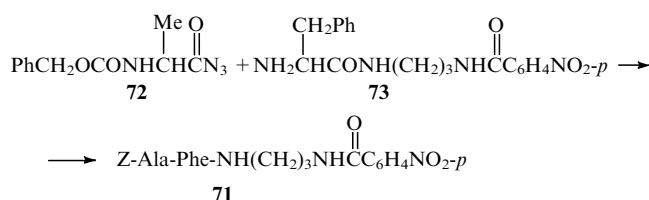


R = Pri, Buⁱ, CH₂Ph.



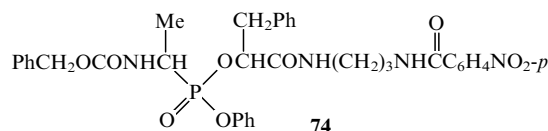
Compound **70** is a phosphonate analogue of the peptides **67** and contains all their characteristic groups. It is assumed⁴⁴ that the *p*-nitrobenzyl residue favours the removal, from the active site of the CA, of *p*-nitrophenol that is split off in the condensation, and the cyclohexyl residue mimics the aliphatic chain of α -amino acids. Two CA of approximately equal efficiency accelerated the synthesis of AcVal-Trp, AcIle-Trp and AcPhe-Trp peptides 220-, 380-, and more than 1000-fold, respectively, in comparison with the non-catalysed reactions. Thus, the CA manifested broad specificity essential for their synthetic application.[‡] Very low racemisation of the original amino acids (0%–4%) (vs. 25% in the non-catalysed reaction) is an important advantage of conducting the condensation in the presence of CA. Interestingly, the configuration of the amino acid has little effect on the efficiency of CA.

A similar approach was used to obtain CA catalysing the formation of a dipeptide (alanylphenylalanine) derivative **71**.⁴⁶



N-Benzyloxycarbonyl-L- or -D-alanine azide (**72**) prepared *in situ* from the corresponding phenyl ester and sodium azide was used as a peptidyl donor in the condensation reaction. The amino group of phenylalanine the C-terminus of which was protected as the amide with *N*-(4-nitrobenzoyl)-1,3-diaminopropane has served as an acceptor.

A phosphonate analogue of the dipeptide **71** to be synthesised containing protective groups of the original amino acids (compound **74**) was used as a hapten.



[†] The hapten **70** with the P–O bond has been employed instead of a less accessible phosphamide analogue.

[‡] One of these CA has been used in the synthesis of tri- and tetrapeptides.⁴⁵

The CA obtained accelerated the condensation of the amino acids **72** and **73** 10⁴-fold in comparison with the non-catalysed reaction. The effect of the CA was stereoselective, *viz.*, the reaction with the L-alanine derivative occurred 7 times faster than that with the D-isomer.

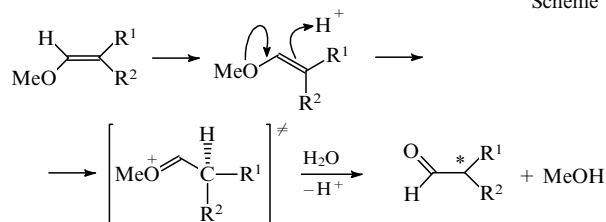
These studies^{44–46} present substantial interest, since they can be regarded as the first steps en route to protein synthesis by coupling peptide fragments.[§]

V. Hydrolytic cleavage of the carbon–oxygen bond in enol ethers and acetals

A great number of papers have been devoted to the synthesis and investigation of CA catalysing the hydrolysis of the C–O bond in enol ethers and acetals to recover the parent carbonyl compounds. These reactions follow similar mechanisms and are involved in many synthetic schemes. Enhancement of the efficiency and selectivity (stereoselectivity, in particular) of these reactions would favour the solution of many synthetic problems.

Hydrolysis of alkyl vinyl ethers with recovery of the corresponding aldehyde or ketone is the simplest example of hydrolysis of enol ethers. This reaction occurs in the presence of an acid catalyst (Scheme 6).

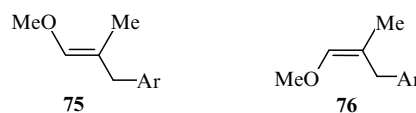
Scheme 6



Protonation of the β -carbon atom of the vinyl group of the ether is the rate-limiting stage. If the β -carbon atom of the vinyl ether is prochiral ($R^1 \neq R^2$), the reaction may yield a mixture of two stereoisomers. The stereochemical outcome of the reaction is important for its synthetic application, in particular, in asymmetric synthesis.

Hydrolysis of *O*-alkylenols normally occurs under relatively drastic conditions with moderate stereoselectivity. Therefore, preparation of CA catalysing this conversion under mild conditions and with satisfactory stereochemical control is of considerable interest. These CA will favour the formation of the oxonium centre in the substrate and the protonation of the β -carbon atom concomitantly with its sp^3 -hybridisation ('pyramidalisation'), while it is the spatial direction of the proton attack that will determine the enantioselectivity of this reaction.

The preparation of CA catalysing the hydrolysis of the vinyl ethers **75** and **76** has been described.⁴⁸



Ar = C₆H₄CONH(CH₂)₃OH

The *N,N*-dialkylpiperidinium derivatives **77** have been used as haptens.

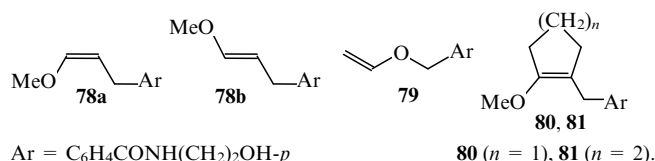


The positive charge on the nitrogen atom in the hapten **77** induces the formation of a negatively charged group in the active site of CA responsible for the formation of the oxonium site and

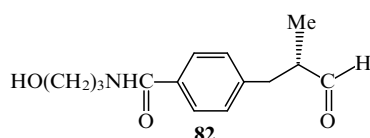
[§] For the preparation of a CA catalysing rearrangement of the peptide bond in aspartylglycine, see Ref. 47.

the protonation of the substrate. In turn, the tetrahedral structure of the nitrogen atom favours the formation of a cavity in the active site facilitating pyramidalisation of the β -carbon atom. The substituent at the C(3) atom of the piperidine ring stabilises the conformation of the ring in the molecule **77** and serves as a linker employed for coupling of the hapten to the protein in the immobilisation.

Several haptens differing in the nature and spatial arrangement of substituents at the nitrogen atom (R^1 and $R^2 = H, Me, CH_2Ar$) have been synthesised to study the relationship between the efficiency and stereoselectivity of the CA action. Active CA have been raised against all of these haptens. One of those, 14D9 raised against the hapten **77** ($R^1 = Me, R^2 = CH_2Ar$) has been selected for a more detailed examination. This CA manifested all the specific features of an enzyme and possessed relatively high efficiency, which strongly depended on the substrate structure. Thus, under comparable reaction conditions (pH 6.0), it accelerated the hydrolysis of the *trans*-isomer **75** 2500-fold and of the *cis*-isomer **76** only 290-fold. Further investigations into this CA revealed⁴⁹ that this antibody manifested broad substrate specificity, although its efficiency was not very high and varied within a very broad range. Thus the hydrolysis of the vinyl ethers **78**, which do not contain alkyl β -substituents, was accelerated 180-fold, while that of the vinyl ether **79** was accelerated only 110-fold. In contrast, this catalytic antibody manifested high activity in the hydrolysis of cyclic vinyl ethers and accelerated the hydrolysis of the methoxycyclopentene derivative (**80**) and methoxycyclohexene derivative (**81**) 12 500- and 370-fold, respectively.

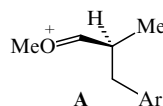


High enantioselectivity is the most essential property of this CA: it catalysed hydrolysis of the vinyl ethers **75** and **76** to yield the same *S*-enantiomer of the aldehyde **82** with very high enantioselectivity (93%–96% *ee*).[†]



The hydrolysis of the cyclic vinyl ether **80** was also highly enantioselective and the cyclic ketone was obtained with 93% *ee* in the presence of this CA. Such a high enantioselectivity, which was comparable with that attainable with the most efficient chemical methods, was rather unexpected and was extensively investigated^{49,50} using numerous substrate analogues and structurally related inhibitors (including deuterated ones) by the enzymic kinetics method. The correlation between the enantioselectivity of the effect of the CA and the spatial structure of the hapten used for its generation as well as the origin of the enantioselective effect of the CA (which is the reason for the *S*- or *R*-configuration of the newly formed chiral centre) are of particular interest. The conformation of the hapten **77** ($R^1 = Me, R^2 = CH_2Ar$), which determines the peculiarities of the cavity formed in the active site of CA in the course of its biosynthesis by the immune apparatus of the cell, was established with the use of inhibitory analysis.⁵⁰ It was shown that the piperidine ring in the molecule **77** has a chair conformation with the *N*-benzyl group in the axial position and

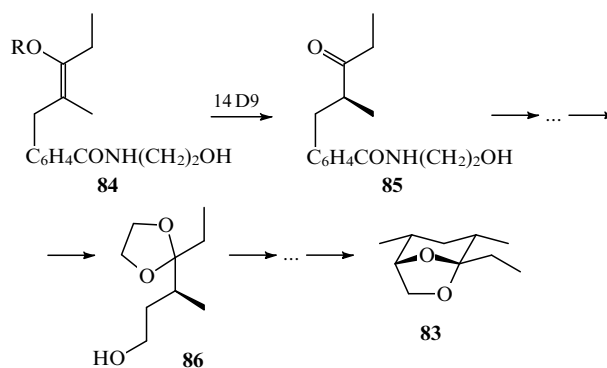
the *N*-methyl group in the equatorial position. The presence of a substituent at the C(3) atom of the piperidine ring, which also occupies the equatorial position, favours this conformation. The substrate molecule (the ether **75**) is arranged in the newly formed active site of CA to 'copy' the conformation of the hapten which had determined the steric configuration of the cavity in the active site of the CA. The position of the benzyl residue of the substrate responsible for its 'recognition' by the active site and fixation in the cavity of the active site of CA is similar to that of the benzyl residue of the hapten **77**. The presence of an anionoid (presumably, carboxy) group in the active site of the substrate induces the formation of a positively charged oxonium site, as a result of which the excited molecule of the substrate accepts the conformation **A**.



It is arranged in the active site as if it mimics the configuration of the hapten, making the β -carbon atom of the substrate accessible for enantioselective protonation on the *r,e*-site and providing the formation of the *S*-aldehyde **82**. Consequently, the enantioselectivity of protonation and the formation of the *S*-aldehyde are predetermined by the configuration of the hapten **77**.

It was emphasised⁵⁰ that the most characteristic feature of the enantioselective formation of the new chiral centre is that the hapten shapes the active site of CA which is complementary to the excited substrate molecule predisposed to the attack by the proton rather than to the neutral substrate molecule. This determines strict spatial directionality of this attack and high enantioselectivity of this process. Thus, the choice of the hapten structure mimicking the excited state of the substrate molecule is considered to be of crucial importance in the design of a CA endowed with high enantioselectivity.^{49,50}

Such catalytic antibodies may acquire great importance in the development of asymmetric synthesis, *i.e.*, the introduction of the first chiral centre with a predetermined absolute configuration into an achiral molecule.⁵¹ The use of CA in the synthesis of the pheromone (–)- α -multistratin (**83**) is an example.



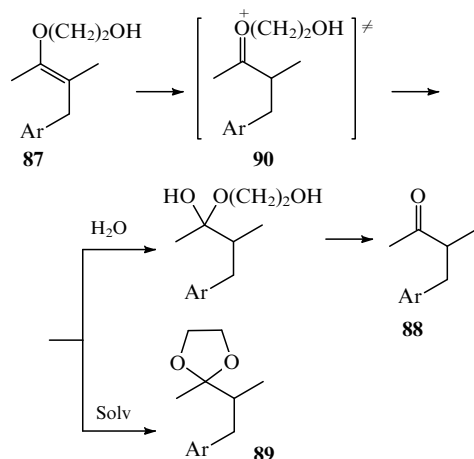
The key stage in this synthesis is the enantioselective introduction of a chiral centre into the molecule of a substrate (the vinyl ether **84**) using CA.⁵² Hydrolytic cleavage of the ether **84** was accelerated 6.5×10^4 -fold by the CA 14D9 and was highly enantioselective (95% *ee*). The ketone **85** obtained in 85% yield was further converted into the ketal **86** and then into (–)- α -multistratin (**83**).

A simple laboratory technique⁵³ specially developed for the synthesis of gram quantities of compounds catalysed by CA consists in the removal of the reaction product by dialysis. Since CA remaining in the dialysis sack are reusable, it is possible to use them in small quantities. A small semi-automatic laboratory unit has been designed for conducting the reaction in the presence of CA.⁵⁴

[†]In order to avoid partial racemisation of the carbonyl compound, which may occur under reaction conditions and obscure the stereochemical result, the CA-catalysed conversion of enol ethers was carried out in the presence of cyanide. The latter converts the carbonyl compound into cyanohydrin and stabilises its configuration.

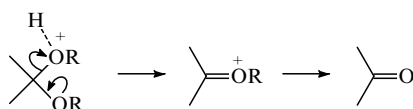
The use of CA in the hydrolysis of vinyl ethers permits one to interfere with the course of the reaction and to perform conversions that are unattainable under ordinary conditions. An amazing result was obtained in the hydrolysis of the vinyl ether **87** in the presence of the CA 14D9 (Scheme 7). This reaction can yield either the ketone **88** or the cyclic ketal **89**.⁵²

Scheme 7



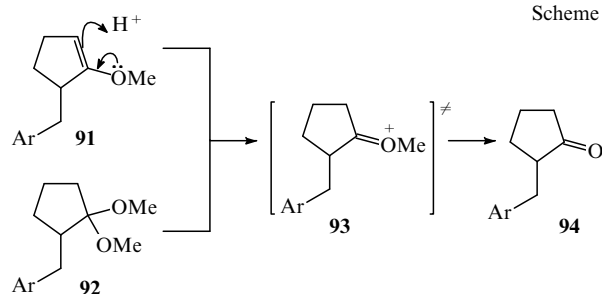
In an aqueous medium (in the absence of the CA 14D9), the acid-catalysed reaction gives only the ketone **88**, because the hydroxy group of the vinyl ether **87** cannot compete with excess water present in the reaction medium. In contrast, the cyclic ketal **89** is formed in organic solvents. However, when the reaction is carried out in an aqueous medium in the presence of CA, 12% of the cyclic ketal **89** is formed in addition to the ketone **88**. The formation of both products obeys the Michaelis–Menten kinetics, they have the *S*-configuration and are formed with very high enantioselectivity (99.5% *ee*), which testifies to the involvement of the active site of CA in their formation *via* the common transition state **90**. Thus, the ketal **89** is formed in a CA-catalysed reaction occurring in aqueous media. The involvement of water is excluded in this reaction because of the hydrophobic environment created in the cavity of the active site of CA where the reaction occurs.

The mechanism of hydrolysis of the acetal bond in the presence of an acidic reagent differs only slightly from that of vinyl ethers. In both cases, the reaction occurs through protonation. However, in contrast with the hydrolysis of vinyl ethers, it is the oxygen atom of the acetal group that undergoes protonation.



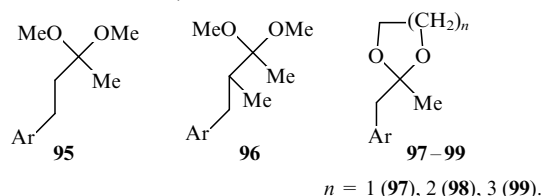
It was found that CA efficiently catalysing hydrolysis of vinyl ethers manifest catalytic activity in the hydrolysis of acetals.⁵⁵ This is apparent from comparative hydrolysis of the vinyl ether **91** and the ketal **92** in the presence of the same CA (Scheme 8).

Scheme 8



Both reactions occur *via* the same transition state **93** and result in the ketone **94**. In an aqueous medium and in the absence of CA,

acid-catalysed hydrolysis of the acetal **92** usually proceeds at a substantially higher rate than that of the ether **91** (the ratio of hydrolysis rates is 0.09 : 1). In the presence of the CA 14D9, the ratio of the reaction rates changes drastically to the opposite (**91** : **92** = 1100 : 1). The dependence of the reactivities of acetals on their structure was studied under conditions of a hydrolytic reaction. It was found that the acyclic ketals **95** and **96**, which are hydrolysed more slowly in the absence of the CA than the cyclic ketal **92** (the rate ratio is **95** : **96** : **92** = 0.23 : 0.38 : 1), demonstrate the opposite reactivities in the presence of the CA (the rate ratio is **95** : **96** : **92** = 90 : 8 : 1).



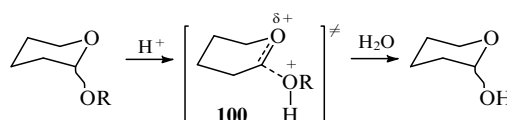
Presumably, the differences in reactivities are due to the fact that the role of steric tensions generated in the cavity of the active site of the CA in the protonation and further decomposition of the acetal is higher in the case of the conformationally more rigid cyclic ketal **92** than in the case of its conformationally flexible acyclic analogues **95** and **96**.

However, this is not the only reason. Recently, the relative effectiveness of the same CA (14D9) has been studied in the hydrolysis of other cyclic ketals (compounds **97–99**) with different ring sizes.⁵⁶ It was found that the effectiveness of the CA decreased with the increase in the ring size (the rate ratio was **97** : **98** : **99** = 1 : 0.37 : 0.04). These data and comparison of the binding constants of these acetals with those of the complementary azaalicyclic analogues in which the ammonium nitrogen atom corresponded to the acetal carbon atom led the authors to conclude that the effectiveness of the CA largely depended primarily on the electrostatic complementarity of its active site with the substrate, while the conformational tension generated during the reaction was of lesser importance.

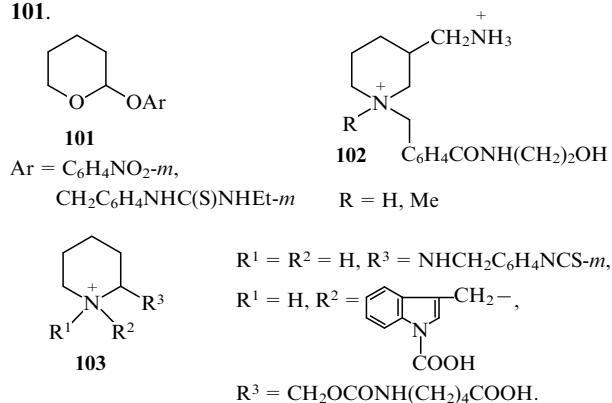
In conclusion, let us dwell briefly on attempts to prepare CA catalysing hydrolysis of mixed acetals (particularly, cleavage of the glycosidic bond).

The hydrolysis of the glycosidic bond under conditions of acid catalysis occurs through the transition state **100** with the oxocarbenium ion in the six-membered ring which has a half-chair conformation (Scheme 9).

Scheme 9



An attempt has been made^{57,58} to obtain CA catalysing the hydrolysis of the simplest model compound, *viz.*, 2-aryloxypyran **101**.



This was achieved using the haptens **102**, analogous to the hapten **77** and containing the CH_2NH_3^+ group at the C(3) atom, and the haptens **103** containing a substituted amino group at the C(2) atom. In both cases, the CA obtained moderately accelerated hydrolysis of the model substrate **101** but were ineffective in hydrolysis of more complex compounds.

These results show that it is possible, in principle, to obtain CA catalysing the hydrolysis of the glycosidic bond. However, the preparation of sufficiently active and selective artificial glycosidases poses the problem of choice of a hapten mimicking the half-chair transition state with a positive charge as well as a polysubstituted, polychiral molecule of a real monosaccharide.

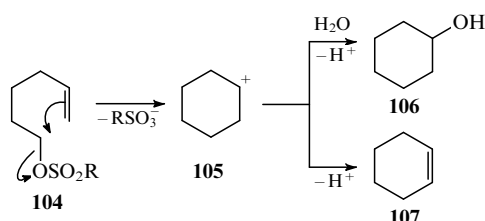
VI. The formation of carbon–carbon bonds

Apparently, preparation of CA that would catalyse the formation of new carbon–carbon bonds making the skeleton of organic molecules is of prime interest in preparative organic synthesis. These include CA that would increase the efficiency of the known reactions and enhances their regio- and stereospecificity and CA able to change the direction of certain reactions in comparison with the non-catalysed processes. This may eventually lead to the discovery of novel reactions that cannot be carried out by conventional chemical methods (the so-called ‘unfavourable transformations’).

Among a great multitude of reactions that result in the formation of the C–C-bond, only very few are known for which the corresponding CA have been obtained. In particular, several CA catalysing cationic cyclisations, sigmatropic rearrangements and pericyclic reactions as well as aldol condensation, which is one of the most common reactions of carbon–carbon bond formation, have been obtained thus far.

1. Cationic cyclisation

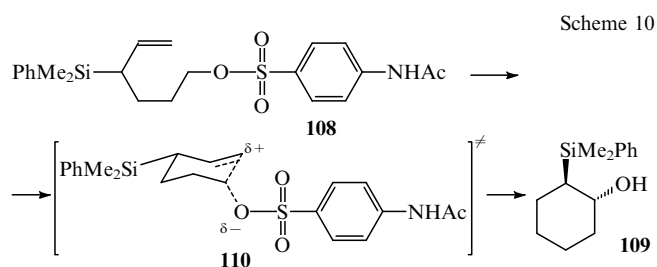
Cationic cyclisation is widely used in the synthesis of carbocyclic systems. Cyclisation of aryl sulfonates of unsaturated alcohols, which occurs in their solvolysis and gives cyclohexane derivatives (the Johnson reaction), has long been known.



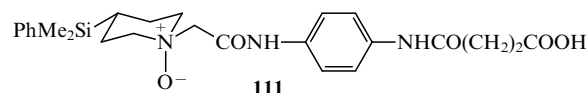
This reaction proceeds through intramolecular electrophilic attack, by the carbocation formed upon solvolysis of the C–O bond, at the double bond of the sulfonate **104**. The resulting cyclic carbocation **105** can be further stabilised either by addition of an external nucleophile to give, *e.g.*, the alcohol **106**, or by elimination of a proton to give the alkene **107**. Under ordinary conditions, this reaction is normally accompanied by the formation of a complex mixture of compounds, which strongly impedes its practical application. Therefore, a search for CA which would not only catalyse the reaction but also enhance its specificity is of considerable interest.

The cyclisation of the sulfonate **108** into the cyclohexanol derivative **109** was studied (Scheme 10).⁵⁹ It was assumed that this reaction occurs *via* the transition state **110** where the original substrate acquires a chair configuration, whereas the C–O bond of the sulfonate becomes polarised, which is accompanied by the appearance of an excess positive charge on the carbon atom. Thus the active site of CA would promote the formation and stabilisation of the carbocation and the formation of a chair conformation of the substrate and thus alleviate sterically the cyclisation.

The piperidine *N*-oxide derivative **111** was used as a hapten aimed at the formation of the active site of a CA which matches



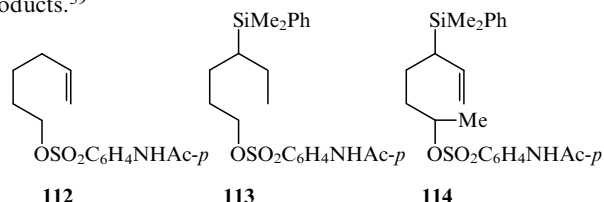
spatially and electronically the transition state. This derivative contains a spacer with a succinic acid residue needed for immobilisation.



In addition to the six-membered ring, which is spatially close to the transition state, compound **111** contains the $^+\text{N}-\text{O}^-$ fragment, which mimics sterically and electronically the formation and cleavage of bonds in the conversion of the sulfonate **108** into the cyclohexane derivative. The dimethylphenylsilyl group was introduced into the substrate **108** and, correspondingly, into the hapten **111** for convenience of monitoring the course of cyclisation. The authors assumed also that the silyl group occupying the quasi-equatorial position favoured the fixation of the chair conformation of the substrate ring in the transition state and the formation of a cyclic carbocation, the primary product of this cyclisation, owing to the β -effect of the silicon atom.

The hapten **111** was used to raise several CA which could catalyse the solvolysis of the sulfonate **108**. One of these, CA 4C6, catalysed the cyclisation of the substrate **108** to give the alcohol **109** and was studied in more detail.⁵⁹ The solvolysis of the sulfonate **108** in a biphasic system (pH 7.0) in the presence of the CA followed Michaelis–Menten kinetics and was accelerated several thousand-fold in comparison with the non-catalysed reaction. However, the most important feature is that this reaction was strictly stereospecific in the presence of the CA. The reaction mixture contained 98% of the *trans*-cyclohexanol **109** and only 2% of the elimination product, *viz.*, the cyclohexene derivative. Other side products were absent. It should be noted that in the absence of the CA the solvolysis of the sulfonate **108** yields a complex mixture of products with less than 30% content of the alcohol **109**.

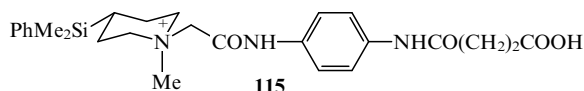
It is noteworthy that the catalytic antibody 4C6 manifests high substrate specificity. The conversions of compounds **112** and **113**, which are analogues of the sulfonate **108**, is not catalysed by this CA, whereas the sulfonate **114**, which has an additional methyl group and produces a secondary carbocation upon solvolysis instead of the primary one, yields a complex mixture of reaction products.⁵⁹



These findings have led the authors to conclude that the CA-catalysed cyclisation reaction occurs by a concerted mechanism: the double bond in the sulfonate **108** anchimerically assists the formation of the carbocation, while the cyclic cation that formed (of the type **105**) undergoes immediately attack by the external nucleophile. Thus, the catalytic antibody 4C6 not only initiates the reaction by generating a carbocation but also promotes its further conversions (cyclisation) due to matching of the active site of the CA to the substrate. Additional evidence in favour of this

hypothesis can be derived from the fact that of all CA against the hapten **111** tested in this study only 4C6 induced the cyclisation, while other CA could merely accelerate the solvolysis of the sulfonate **108**, *i.e.*, they favour the formation of the carbocation without subsequent cyclisation (see below).

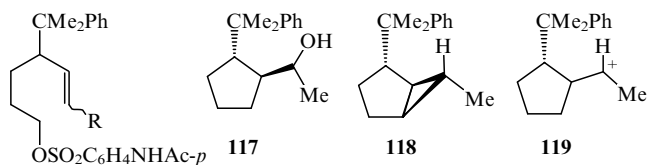
The nature and the ratio of the cyclisation products of unsaturated sulfonates of the type **108** depend also on the nature of CA, *i.e.*, on the structure of the hapten that had induced the CA. Thus it was found that the ratio of the cyclisation products of the sulfonate **108** could be fully reversed when CA 87D7 against the hapten **115**, very close to the analogue of the hapten **111**, was used instead of CA 4C6.



Compound **115** contains the $N^+ - Me$ group instead of the $N \rightarrow O$ group.⁶⁰ The cyclisation of the sulfonate **108** in the presence of this CA gives 90% of the cyclohexene derivative and only 10% of the cyclohexanol **109**. It was shown that the substrate **108** virtually adopts the same conformation in the active sites of both CA (4C6 and 87D7). Therefore, the difference in the ratios of the cyclisation products should be ascribed to the difference in the charge on the nitrogen atom rather than to the conformational effect, since the ammonium group induces a higher negative charge in the active site of CA than does the nitrogen atom of the $N - O$ group.

Replacement of the substrate **108** by its analogue **116a** containing the CMe_2Ph group instead of the silyl group changes the direction of the cyclisation reaction catalysed by the CA 87D7. In this case, the reaction affords the corresponding cyclohexanol in 60% yield.

The direction of cyclisation of the sulfonate **116b** with the propenyl group instead of the vinyl group changes even more significantly.⁶¹

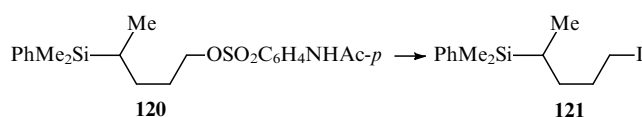


116a,b

R = H (**116a**), Me (**116b**).

In the presence of CA 87D7, solvolysis of the *cis*-isomer of the sulfonate **116b** gives the alcohol **117** in 80% yield, whereas solvolysis of the *trans*-isomer yields the bicyclo[3.1.0]hexane derivative **118** as the main product. This unexpected result can be explained by the fact that the β -effect underlying the stabilisation of the six-membered carbocation is not manifested in the absence of the silyl group. This results in the carbocation **119**, which is further stabilised either by the attack of the external nucleophile to give the alcohol **117** or by the formation of the bicyclic compound **118** upon deprotonation.

As mentioned above, antibodies against the hapten **111** contain those which catalyse solvolysis and favour generation of the carbocation but not cyclisation. One of them, CA 16B5, was used as a convenient tool in elucidation of the mechanism of formation of carbocations in the solvolysis of arylsulfonates.⁶² To this end, the conversion of the sulfonate **120** into the iodide **121** was studied under solvolysis conditions.



The catalytic antibody 16B5 was found to be an efficient catalyst of this reaction and accelerated it more than 500-fold.

Analysis of reaction kinetics and performance of this reaction in the presence of other nucleophiles (NaSCN, NaN₃) revealed that this CA favoured the formation of the carbocationic centre in the transition state. This conclusion was also confirmed by measurements of the secondary isotope effects of α - and β -deuteriated analogues of the sulfonate **120**. Analysis of the CA-catalysed solvolysis of the deuteriated analogues revealed that substitution of the iodine for the sulfonyloxy group occurred with inversion of its configuration, which can be explained by the fact that the carbocation was generated as a tight ion pair in an equilibrium with the covalent sulfonate.

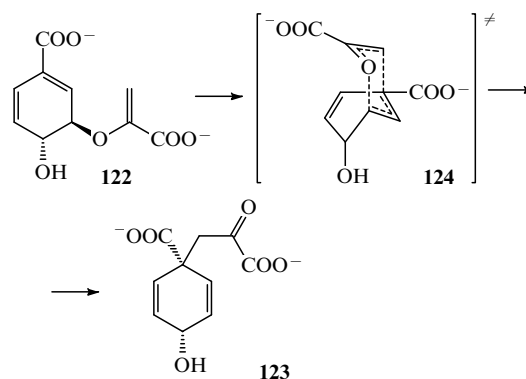
It may be concluded that the direction of the reaction of cationic cyclisation is determined by the peculiarities of both the active site of CA and the structural features of the substrate. These peculiarities affect all the stages of this reaction, such as generation of the carbocation, its stabilisation, the 'positive' charge value, possible ways of carbocation conversions and stabilisation of the secondary carbocation.

The examples of carbocationic cyclisation considered above[†] demonstrate high potentialities of the use of CA in directed synthesis of cyclic compounds and the possibility of their subtle modification by changing the type of the hapten and the structure of the substrate.

2. The Claisen rearrangement of enol ethers

The Claisen rearrangement of enol ethers, which consists in the cleavage of the $O - C$ bond and the transfer of the enol residue and results in the formation of a new carbon-carbon bond, is widely used in the synthesis of complex organic structures, particularly, natural compounds. The possibility of preparing CA that would catalyse this reaction was examined⁶⁴⁻⁶⁶ with the rearrangement of chorismic acid (**122**) into prephenic acid (**123**) as an example. This rearrangement is one key step in the biosynthesis of aromatic amino acids by bacterial or plant cells where this reaction is catalysed by the natural enzyme, *viz.*, chorismate mutase. The preparation of a CA catalysing this reaction was the first case of preparation of an artificial enzyme catalysing the formation of the $C - C$ bond in a pericyclic reaction. The rearrangement of the acid **122** into the acid **123** is a [3,3]-sigmatropic concerted process and occurs *via* the transition state **124**, which is similar to the spatial structure of oxabicyclo[3.3.1]nonene with one six-membered ring in a boat conformation (Scheme 11).

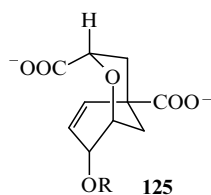
Scheme 11



The bonds corresponding to the structure of the substrate **122** in the transition state **124** are weakened, while the bonds of the future rearrangement product have just been outlined. The hapten derivative of the oxabicyclononene **125** containing a spacer (R) with the active succinimide group needed for its immobilisation on the protein was used to obtain CA the active site of which must promote the generation of a transition state with this spatial

[†]A recent report describes an attempt to obtain a CA catalysing carbanionic cyclisation, one of the versions of the Dieckman reaction.⁶³ Although the catalytic effect was observed in this case, data on the preparation of CA and its characteristics were absent.

structure. It is of note that the dicarboxylic acid **125** ($R = H$) is an inhibitor of the natural enzyme (chorismate mutase).



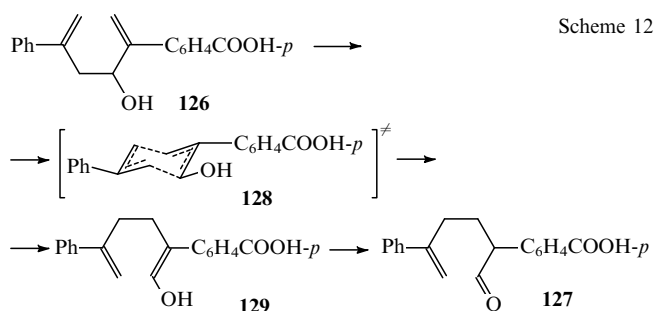
The resulting CA accelerated the conversion of chorismic acid (**122**) into prephenic acid (**123**) $2 \times 10^2 - 10^4$ -fold in comparison with the non-catalysed rearrangement (data from two independent laboratories). This reaction proceeded with high regioselectivity at $10^\circ C$ and pH 7.0 and gave prephenic acid alone. (About 5% of hydroxybenzoic acid was formed in the absence of CA). The stereospecificity of this reaction is also very high. Experiments with (+)- and (–)-isomers of chorismic acid revealed that only the (–)-isomer was a substrate for the reaction. Only 50% of the substrate was consumed in the reaction with racemate. The kinetic measurements establish the enantioselectivity of this reaction in the presence of CA as 90 : 1.

X-Ray structural analysis of a complex of the hapten **125** with the CA ⁶⁷ confirmed the complementarity of the spatial structure of the active site of CA to the structure of the hapten and, correspondingly, to the structure of the transition state **124**. The lack of pH dependence of the Claisen rearrangement in the presence of CA and the absence of ionic groups in the active site testify to the fact that this rearrangement in the presence of the CA represents a pericyclic reaction. The role of the active site amino acid residues has been established in this reaction and the catalytic role of CA in this process has been suggested.⁶⁸ Although the effectiveness of the CA studied is inferior to that of the natural enzyme, the preparation and detailed analysis of this first CA catalysing a pericyclic reaction was a considerable breakthrough en route to artificial enzymes.

3. The Cope rearrangement

The Cope rearrangement is also related to pericyclic reactions and occurs as a [3,3]-sigmatropic rearrangement. No natural enzyme for this reaction has been found thus far.

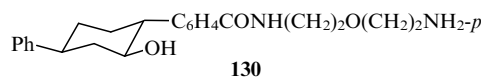
The possibility to obtain CA catalysing this reaction was studied in the example of conversion of a diphenylhexadienol derivative **126** into the unsaturated aldehyde **127** (Scheme 12).⁶⁹



It is suggested that this rearrangement occurs *via* the transition state **128** in which the central six-membered ring has a chair conformation. The enol **129**, which is formed first, is further converted into the aldehyde **127** fixed as an oxime.

With consideration of the accepted reaction mechanism, the diphenylcyclohexanol derivative **130** with a spacer group was used as a hapten. The specific role of this hapten consisted in the formation of the active site of CA and fixation there of the substrate in a conformation most closely matching the transition state. This active site would thus act as an 'entropic trap' (see Section II). The absence of a natural enzyme catalysing the Cope rearrangement made the preparation of this catalytic antibody especially attractive because it provided rationale for the general

principles of design of haptens for the CA catalysing pericyclic reactions.



The most reactive catalytic antibody (AZ-28) raised against the hapten **130** accelerated this rearrangement 5300-fold. Of the two enantiomers of the original alcohol **130**, only the *S*-isomer and not the *R*-isomer entered into the reaction. The kinetic and inhibitory analyses of all the CA catalysing this reaction confirmed that they do generate the transition state **128** in the reaction.

The Fab fragment isolated from the CA AZ-28 was prepared in considerable quantity by genetic engineering methods.⁷⁰ This important experiment illustrates the possibility to use the catalytic antibodies generated in small quantities under laboratory conditions for large-scale productions using the most advanced biotechnological techniques.

An attempt has been made to establish the mechanism of the catalytic action of the CA AZ-28 and its spatial structure by molecular genetics methods and X-ray analysis.

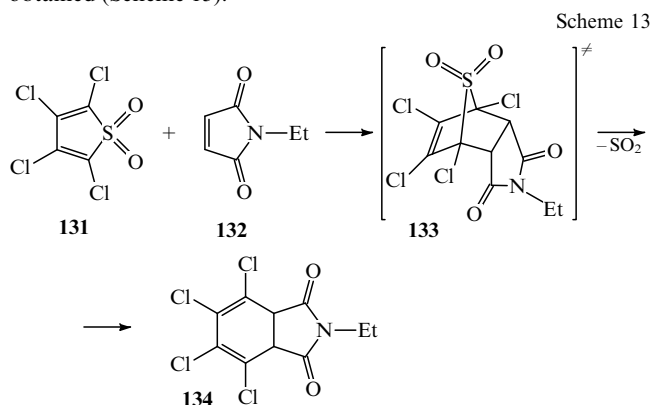
4. The Diels–Alder reaction

The Diels–Alder reaction is the basis for one of the main synthetic procedures used to obtain six-membered alicyclic systems by condensation of a diene with an alkene (dienophile). It represents a $4\pi + 2\pi$ -cycloaddition reaction. The cleavage of particular bonds in the reaction components and the formation of other bonds occur as a single concerted process and conform to the regularities of pericyclic reactions. The success in the condensation depends on the mutual arrangement of the diene and the dienophile, which must be in the appropriate conformation in the transition state enabling the pericyclic process.

No natural enzyme has been found as a catalyst of the Diels–Alder reaction; therefore the preparation of an effective CA is of fundamental interest. Since the Diels–Alder condensation often occurs as a spontaneous exothermic process, the main function of the CA would be to alter its regio- and stereoselectivity rather than to increase the reaction rate.

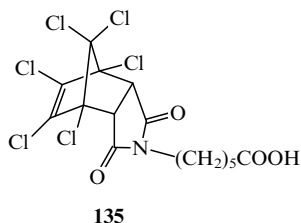
The catalytic effect of the active site of the CA is reduced to the restriction of mobility of the diene and the dienophile and their fixation in the necessary conformation. Thus, the active site of the CA should primarily act as an 'entropic trap' (see Section II), while the presence of reactive groups in this site is less significant. In the design of a hapten for generation of the CA, one had to keep in mind that the CA prepared must not be inhibited by the reaction product. Otherwise, this would reduce the enzyme 'turnover number' and its effectiveness. Therefore, the spatial structure of the active site of the CA must be close to that of the transition state but differ, wherever possible, from the structure of the reaction product.

Several CA catalysing the Diels–Alder reaction have been obtained (Scheme 13).



The first of these CA catalysed the condensation of tetrachlorothiophene dioxide **131** with *N*-ethylmaleimide **132** which occurs *via* intermediate formation of the tricyclic sulfone **133**. Spontaneous elimination of SO₂ results in the dihydrophthalimide derivative **134** (Scheme 13).⁷¹

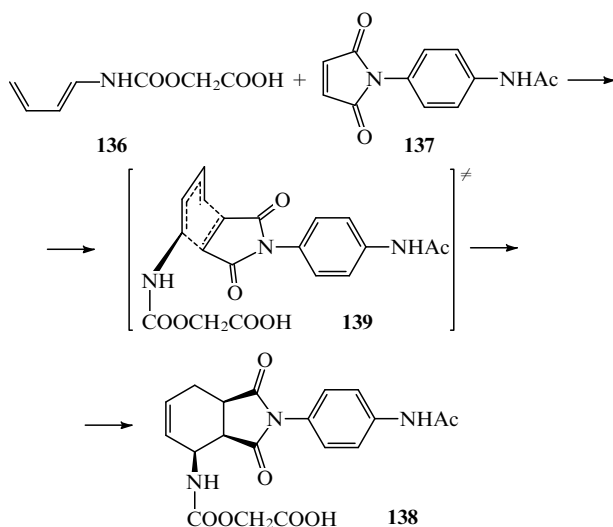
The tricyclic derivative **135** structurally analogous to the intermediate product **133** and containing a hexanoic acid residue essential for immobilisation was used as a hapten. At the same time, the structure of the hapten **135** differs from that of the final product, *viz.*, the imide **134**.



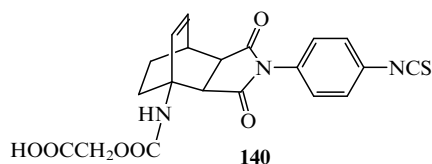
The reaction between the reactive sulfonyl group in the molecule **131** with the amino groups of lysine in CA might irreversibly change its function. To avoid this, the amino groups of lysine were methylated by reaction first with CH₂O followed by reduction with NaBH₃CN. The methylated CA thus obtained was found to be sufficiently active and accelerated the Diels–Alder condensation of the sulfone **131** with the imide **132** manifold. Its effect was substrate-specific. No catalytic effect of CA was manifested when maleimide was used instead of *N*-ethylmaleimide.

Preparation of a CA catalysing the condensation of the acyclic diene **136** with the maleimide derivative **137** is of certain interest. This reaction yields a derivative of *cis*-tetrahydrophthalimide **138**⁷² and proceeds *via* the transition state **139** in which the diene acquires a *cisoid* conformation, while its complex with the dienophile **137** adopts a boat conformation. This favours the pericyclic reaction and ensures *cis*-fusion of the rings in the reaction product **138** (Scheme 14).

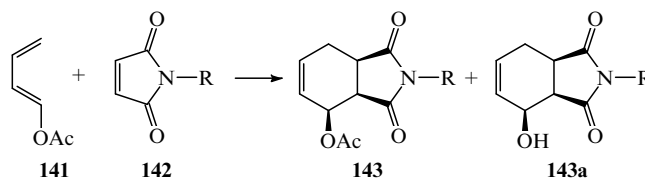
Scheme 14



The hapten **140** containing a cyclohexane ring fixed in a boat conformation by an ethylene bridge and the isothiocyanate group necessary for its immobilisation was chosen for raising CA with the active site mimicking this transition state. The most active CA accelerated the condensation of the diene **136** with the imide **137** approximately 500-fold and followed Michaelis–Menten kinetics. The reaction product **138** was found to bind with the CA ~ 100 times weaker than the original compounds **136** and **137**. Thus, the CA is practically uninhibited by the reaction product.

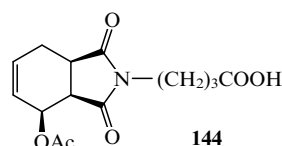


Preparation of a CA catalysing a similar reaction, *viz.*, the condensation of 1-acetoxybutadiene **141** with *N*-methyl- and *N*-benzylmaleimides **142** to give the *N*-substituted tetrahydrophthalimides **143**, is documented.^{73, 74}



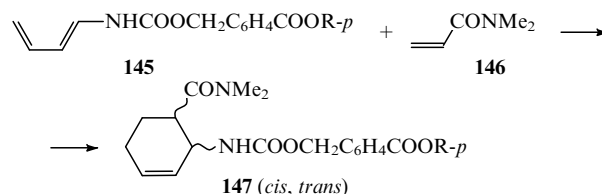
R = Me, Bn.

It was shown^{73, 74} that the CA raised against the hapten **144** accelerated the condensation of the diene **141** with the dienophile **142** more than 1000-fold. It manifested substrate specificity, since it was inactive when more reactive methoxybutadiene or piperylene were used instead of the diene **141**.



It was found also that the activity of this CA depended on pH, which was never observed with other CA catalysing the Diels–Alder reaction. This was rationalised as being due to the fact that this CA also manifested esterase activity and is a unique example of CA possessing dual activity. However, this explanation does not seem to be convincing enough, although the side product of this reaction, *viz.*, alcohol **143a**, has been isolated.

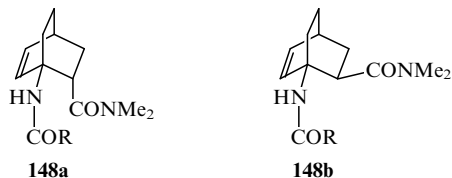
The problem of stereospecificity of the Diels–Alder reaction is the key problem. It was specially studied in the condensation of two acyclic compounds, *viz.*, *trans*-1-*N*-(alkoxycarbonyl)amino-butadiene **145** and *N,N*-dimethylacrylamide **146**, resulting in the cyclohexene derivative **147**.⁷⁵



This reaction may, in principle, yield four compounds, *viz.*, two 1,2-isomers with *cis(endo)*- and *trans(exo)*-configurations and two 1,3-isomers with *cis(endo)* and *trans(exo)* configurations. In the absence of CA, the condensation of compounds **145** and **146** yields only the 1,2-isomers in the *cis*:*trans* ratio 66:34 (thermal condensation) or 85:15 (condensation in a phosphate buffer). Thus, this reaction is not stereospecific. Analysis of molecular models and calculation of the transition states leading to the formation of each of these isomers[‡] revealed that the energy of the transition state for the 1,2 isomers was 2–4 kcal mol^{–1} lower than that for the 1,3-isomers. It is noteworthy that the energy barrier for the 1,2-isomer having the *cis*-configuration is lower than for the *trans*-isomer, *i.e.*, the formation of the *trans*-isomer (an 'unfavourable' reaction) is energetically less favourable.

[‡] The calculation was performed with the use of a simplified model of the diene component of the reaction.

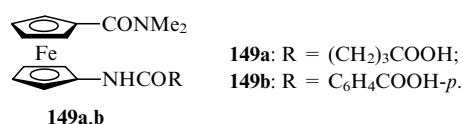
Catalytic antibodies able to selectively direct the condensation of compounds **145** and **146** towards the formation of either *cis*- or *trans*-isomers have been obtained. The haptens **148a** and **148b** with a rigidly fixed ethane bridge where the CONMe₂ and NHCOR groups corresponding to the groups of the reactants ('recognition groups') are in the *cis*- or *trans*-positions relative to each other were used to mimic the transition states.



Two groups of CA were raised against these haptens. One CA, each from both groups, were selected that catalysed the condensation of compounds **145** and **146** in an aqueous medium at pH 7.0 to give the *cis*- (CA 7D4, *endo*-‘Diels–Alder’ase) and *trans*-isomers (CA 22C8, *exo*-‘Diels–Alder’ase). The effectiveness of these CA was not very high: they accelerated the reaction 960- (CA 22C8) and 740-fold (CA 7D4) in comparison with the non-catalysed reaction. It is noteworthy that the *exo*-CA catalysed the ‘unfavourable’ reaction of the *trans*-isomer formation more efficiently than the *endo*-CA. Both CA ensured complete stereoselectivity of the reaction: the isomer **147** was formed in the presence of the CA 7D4, whereas the *trans*-isomer **147** was formed in the presence of the CA 28C8 with the stereoselectivity exceeding 98%. Thus, artificial enzymes (*endo*- and *exo*-‘Diels–Alder’ase’) manifesting high stereoselectivity have been obtained.

A very interesting and a basically new approach to the preparation of stereospecific CA for the Diels–Alder reaction has been recently demonstrated.⁷⁶ In contrast to the above-described, traditional approach based on the use of conformationally rigid haptens, it was suggested to use conformationally flexible haptens. The authors proceeded from the opposite idea that the immune apparatus can produce antibodies against individual conformers of a conformationally flexible hapten including those the ‘frozen’ conformation of which would correspond to the transition state observed in the formation of certain stereoisomers. Thus, biosynthesis can yield a set of antibodies from which CA with the required specificity can be selected.

This idea was examined in the example of condensation of compounds **145** and **146**. The ferrocene derivatives **149a,b** were used as haptens to mimic the transition state of the reaction. They contained the substrate ‘recognition groups’ one of which served as a spacer. This is the first example of the use of organometallic compounds for such a purpose.



It was taken into account that the π -delocalised system and two planar cyclopentadiene rings of ferrocene at a distance 3.3 Å rotating freely around the common axis can form a cavity in the active site of a CA the size and spatial configuration of which would favour the approach and the necessary mutual arrangement of the diene and the dienophile. The rotation of five-membered rings gives the desired steric combinations of the hapten which mimic various transition states that appear in the formation of the stereoisomeric reaction products.

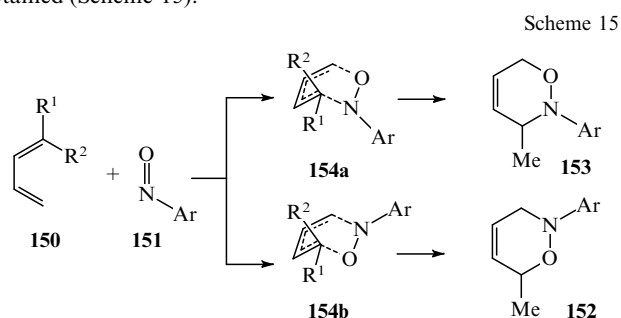
Two most active and stereospecific CA, viz., *endo*-CA (4D5) and *exo*-CA (13G5), were selected from a large group of antibodies raised against compounds **149a** and **149b**. Examination of these CA revealed that they accelerated the condensation only insignificantly and were inferior to the CA raised against ‘rigid’

haptens. However, the specificity of reactions was very high: the condensation of the substrates **145** and **146** catalysed by these CA yielded only the 1,2-isomers: *endo*-CA (4D5) gave the *cis*-isomer **147**, while *exo*-CA (13G5) gave the *trans*-isomer **147** with high diastereoselectivity (98% *de*) and enantioselectivity (95% *ee*). Thus, the concept on the possible use of conformationally flexible haptens that correspond in the geometric and electronic parameters to the transition state of the Diels–Alder reaction for the preparation of stereospecific CA has been fully confirmed.

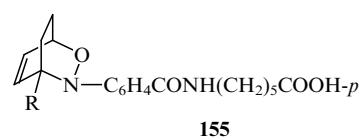
Comparative characteristics of CA raised against ‘rigid’ haptens (e.g., bicyclo[2.2.2]octenes **148**) and conformationally flexible haptens **149** suggest that the ‘antiferrocene’ CA have a bulkier cavity in their active site, since the ferrocene molecule is larger than the bicyclo[2.2.2]octene molecule, and can react therefore with the ‘rigid’ haptens, whereas CA raised against ‘rigid’ haptens does not react with the conformationally flexible haptens.

Although the ‘antiferrocene’ CA are not yet practically valuable, this result is very essential for it offers a fundamentally new approach to the preparation of CA endowed with stereospecific activity through selection of CA from the group of antibodies raised against a conformationally flexible hapten.

In addition to the CA that catalyse the classical Diels–Alder reaction, the first CA catalysing the hetero-Diels–Alder condensation of *cis*-piperylene **150** with 4-nitrosobenzamide derivative **151** to give isomeric dihydro-1,2-oxazines **152** and **153** has been obtained (Scheme 15).⁷⁷



This CA was raised against the ‘rigid’ hapten **155** which mimics the hypothetical transition state **154** with a boat conformation.



This catalytic antibody accelerates the condensation of *cis*-piperylene **150** (R¹ = Me, R² = H) 2600-fold; however, its effectiveness in condensation of *trans*-piperylene (**150**) (R¹ = H, R² = Me) is much lower.⁷⁸ The regioselectivity of this reaction in the presence of the CA is also enhanced: the non-catalysed reaction of the diene **150** with an excess of the nitroso compound **151** gives the oxazines **152** and **153** in the ratio 48:52. In the presence of 10% CA, this ratio alters to 32:68, whereas in the presence of an equimolar amount of CA, 95% of the isomer **153** with high enantioselectivity (82% *ee*) is formed. Apparently, this results from inhibition of the sluggish parallel non-catalysed reaction. The action of the CA is fully inhibited by the hapten analogue **155** in which the *n*-propyl group is used instead of the (CH₂)₅COOH group. This proves that the catalytic reaction occurs in the cavity of the active site of CA.

5. Aldol condensation

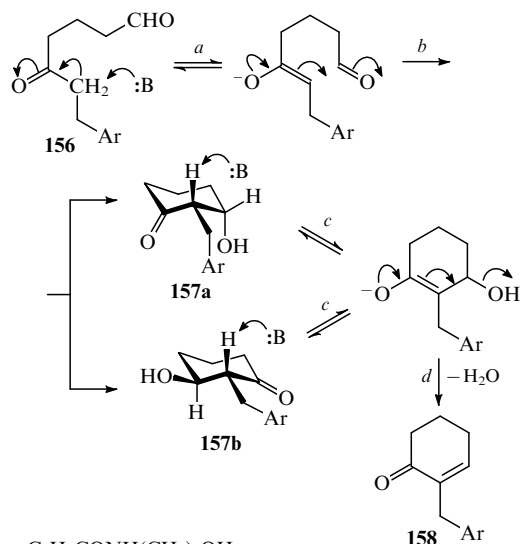
Aldol condensation is one of the most well-studied reactions. It occurs under conditions of acid–base catalysis and results in the formation of a new C–C-bond and a β -hydroxycarbonyl (aldol) system. This reaction occupies a prominent position among the

processes occurring in living cells. Despite numerous multiple modifications and versions allowing for this reaction to be carried out efficiently and in a highly regio- and stereoselective way by purely chemical methods, interest in specific CA with enabling enhanced selectivity is never lost. A great number of natural enzymes (aldolases) catalysing this reaction are presently known; however, all of them manifest relatively narrow specificity which prevents their practical use. The preparation of CA manifesting broader and/or 'predetermined' specificity might be very useful in organic synthesis.

Several approaches are currently used to obtain CA catalysing aldol condensation. One of them is based on general chemical concepts on the mechanism of formation of the β -hydroxycarbonyl system in the condensation of two carbonyl compounds under conditions of acid–base catalysis. Others reproduce, to a certain extent, the catalytic process catalysed by natural enzymes, *viz.*, aldolases.

The first approach can be exemplified by the preparation of a CA catalysing intramolecular cyclisation of the oxo aldehyde **156**, which occurs *via* the formation of two stereoisomeric cyclic aldols **157a** and **157b**. The latter are at equilibrium, and elimination of the water molecule eventually results in the cyclohexenone derivative **158** (Scheme 16).⁷⁹

Scheme 16



$\text{Ar} = \text{C}_6\text{H}_4\text{CONH}(\text{CH}_2)_2\text{OH-p}$

Preparation of a CA catalysing this reaction seems to be a more complicated task than those described above, because this concerns a multistep process. The overall acceleration of the cyclisation of the oxo aldehyde **156** into the enone **158** requires a catalyst which stabilises several transition states by lowering the energetic barrier on the common coordinate of this reaction.

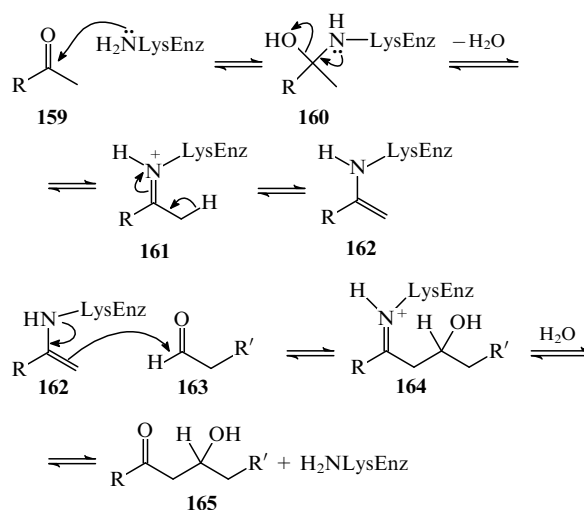
This problem has been solved successfully owing to the fact that all the steps of this reaction occurred under the conditions of acid–base catalysis and the intermediate products (as well as the corresponding transition states) were similar as regards their spatial and electronic structures. This made it possible to raise CA using a single hapten **77** responsible for the formation of the active site of the CA, which exerted a catalytic effect at all the steps of this reaction. The hapten **77** is structurally similar to the cyclic aldols **157a** and **157b** and the final product **158**. The positive charge on the nitrogen atom in the hapten **77** generates a carboxy group in the complementary position of the active site of the CA and thus provides for acid–base catalysis in enolisation (Scheme 16, stage *a*) and elimination (Scheme 16, stages *c* and *d*).

Among other antibodies against the hapten **77**, two CA were catalytically active in the cyclisation of the oxo aldehyde **156**. This reaction followed Michaelis–Menten kinetics and was inhibited by one of the hapten analogues, which testified to its occurrence in the active site of the CA. One of these CA (**78H6**) was studied in

more detail. It was found that general base catalysis takes place and the CA **78H6** is its very potent catalyst. It is of note that the dehydration stages (*c* and *d*) represent energetically less favourable ('adverse') *trans*-elimination reactions in the intermediate aldol **157a** and are regio- and stereospecific. Kinetic studies showed that this reaction was accelerated more than 10^5 -fold in aldolisation (stages *a* and *b*) and more than 10^4 -fold in elimination (stages *c* and *d*) as compared to the reaction carried out under ordinary conditions, *viz.*, in the presence of acetate. This example illustrates the possibility to obtain a unified CA that catalyses a multistage intramolecular process in those cases where the catalytic mechanism and the intermediate products (and, correspondingly, transition states) formed at all stages are sufficiently close.

Another approach to the preparation of a CA the mechanism of action of which is similar to that of natural aldolases seems to be more interesting and versatile.⁸⁰ According to the present concepts of the mechanism of the catalytic action of aldolases, this may be represented by Scheme 17.

Scheme 17

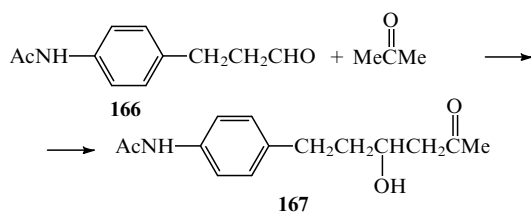


The ϵ -amino group of lysine in the enzyme molecule reacts with the carbonyl group of the aldol donor **159** to yield the hemiaminal **160**, which is further converted into the enamine **162** *via* the immonium ion **161**. It is the enamine **162** that is the genuine aldol donor (the nucleophile) and the key intermediate of the overall reaction. The enamine **162** attacks the aldol acceptor **163** to form a new C–C bond and the immonium ion **164**. Its subsequent hydrolysis gives the aldol **165** and results in the regeneration of the amino group of lysine in the aldolase. Since all the reactions in this chain are reversible, aldolase can also catalyse the reverse reaction, *i.e.*, retroaldol degradation.

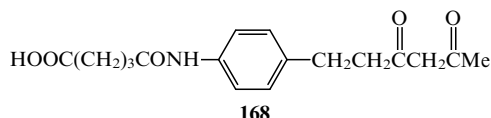
The active site of a CA catalysing this complex chain of reversible reactions must be able to lower the energy barriers in all the stages of this process. It is difficult to imagine the generation of such a CA in a traditional way where a stable and nonreactive hapten does not virtually react with the antibody raised against itself but, rather, merely mimics the transition state.

A fundamentally new approach, which is named 'reactive immunisation', has been proposed. In this case, the hapten reacts with the antibody to form a covalent bond. The active site of the CA that formed acquires the ability to 'perceive' and favour these conversions. Such a hapten not only favours the formation of the transition state of the CA but virtually mimics the reaction itself. Here, structural elements favouring the whole chain of conversions involved in this multistage process are generated in the active site of the CA.

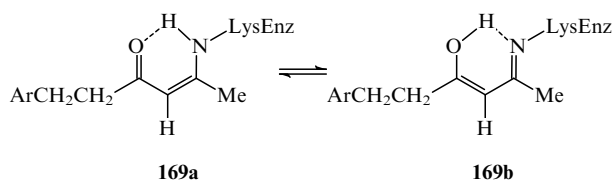
Condensation of 3-(4-acetamidophenyl)propionaldehyde (**166**) with acetone resulting in 4-hydroxy-6-(4-acetamidophenyl)-hexanone (**167**) was used as a model reaction aimed at obtaining CA of the aldolase type.^{80, 81}



A β -diketone derivative **168**, which is structurally similar to compounds **166** and **167** and contains the substrate 'recognition groups' and a spacer, $[\text{CO}(\text{CH}_2)_3\text{COOH}]$, was used as a hapten.



The hapten **168** induced the formation of structural elements that favoured the appearance of a lysine residue in the active site of the CA and the interaction of the NH_2 group of this lysine residue with the substrate to give the key intermediate **169** with an enamine structure.



$\text{Ar} = \text{C}_6\text{H}_4\text{NHCO}(\text{CH}_2)_3\text{COOH}-p$

The stabilisation of the intermediate **169** was achieved owing to the equilibrium $\text{169a} \rightleftharpoons \text{169b}$ and the formation of a conjugated system, *viz.*, carboximide vinyllogue.

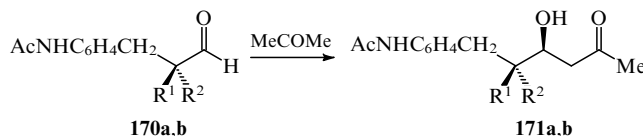
In addition, this hapten favoured the necessary mutual arrangement of the aldehyde **166** and acetone and thus lowered the entropic barrier to the bimolecular reaction. Thus, owing to its conversions in the active site of the CA that is formed, the hapten **168** generated all the elements needed for this reaction to occur. The formation of the enamine, the main driving force of aldol condensation, is crucial for this reaction. It is the formation of the enamine structure of the type **169** that indicated that the reaction of the antigen with the antibody generated against it did occur. This circumstance was taken into consideration in primary monitoring of reactive antibodies by chemical methods [instead of commonly employed monitoring by immunoenzymic methods (see p. 1001)].

The antibodies against the hapten **168** were studied by spectral analysis as complexes with the hapten. It was assumed that all the complexes having absorption bands at 316 nm characteristic of the carboximide vinyllogue **169b** and, correspondingly, capable of forming enamines possessed catalytic properties. The two CA (38C2 and 33F12) thus selected did manifest high activity and catalysed the aldol condensation of the aldehyde **166** with acetone. This catalytic reaction followed Michaelis–Menten kinetics and was inhibited by the hapten analogue or acetylacetone. These and some other data suggest that the CA in fact functions as a natural aldolase. Kinetic measurements showed that these CA accelerate the reaction 10^9 -fold; their activities were close to that of the natural enzyme.

It is essential that both CA manifest broader substrate specificity than the natural aldolase, which catalyses an analogous conversion and thus demonstrates the benefits of the artificial enzyme. Thus the CA 38C2 catalyses the condensation of **166** not only with acetone but also with other ketones (fluoro- and chloroacetone, butan-2-one, pentan-3-one, pentan-2-one, dihydroxyacetone), although its efficiency is lower in this case. The condensation with asymmetrical butan-2-one and pentan-2-one was regioselective, *viz.*, the reaction occurred predominantly at the CH_2 group of the ketone to give branched aldols. The catalytic effect of the CA in the reaction of the aldehyde **166** was manifested

only towards ketones, the reaction with acetaldehyde was not accelerated. However, the CA 38C2 catalysed reactions of acetone with branched analogues of the aldehyde **166** (e.g., with 3-aryl-2-methylpropionaldehyde derivative **170**) with even higher efficiency.

The action of the CA was highly stereoselective. Thus the addition of acetone to the stereoisomeric aldehydes **170** occurred with high diastereoselectivity: the *S*-isomer yielded the 4*S*,5*S*-isomer of the aldol (**171a**) (*de* > 95%), while the *R*-isomer gave the 4*S*,5*R*-aldol **171b** (*de* > 83%).

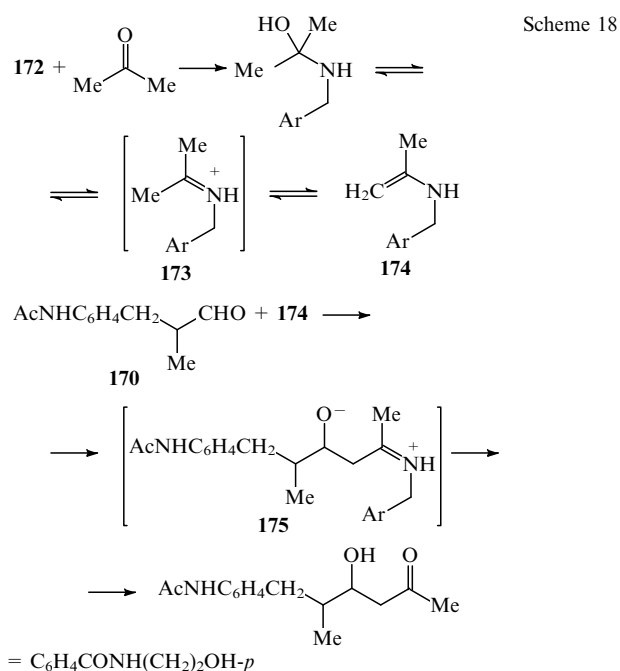


a: $\text{R}^1 = \text{Me}$, $\text{R}^2 = \text{H}$; **b:** $\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$.

It is noteworthy that in both cases the addition of the acetone molecule occurs from the *re*-side irrespective of the configuration of the chiral centre in the aldehyde **170**. The rate of this addition is the same for the both isomers **170**. Therefore it cannot be used for kinetic resolution of the racemate of the aldehyde **170**.

Yet another possibility of catalysis of aldol condensation with CA has been studied.⁸² Since the catalytic effect of aldolases is based on the acceleration of the reaction of the carbonyl group of an aldol donor with the amino group of the lysine residue with subsequent formation of a nucleophilic enamine, it was decided to carry out aldol condensation in the presence of a CA against the hapten of the type **77** using an amine with the appropriate pK_a as a cofactor. This amine would react with the CA in its active site to yield a 'modified' CA the mechanism of action of which would be then typical of that of the natural aldolase.

This possibility has been examined in the condensation of 3-aryl-2-methylpropionaldehyde **170** with acetone in the presence of a CA against the hapten **77** and a benzylamine derivative *p*- $\text{H}_2\text{NCH}_2\text{C}_6\text{H}_4\text{CONH}(\text{CH}_2)_2\text{OH} **172** as a cofactor. This amine is structurally similar to the hapten **77** and has the corresponding value of pK_a (8.5). It may therefore be assumed that it will react with CA against this hapten and modify it in the appropriate way; the reaction of aldol condensation will occur *via* the formation of the immonium ion **173**, the enamine **174** and the product of its condensation with the aldol acceptor **175** (Scheme 18).$



$\text{Ar} = \text{C}_6\text{H}_4\text{CONH}(\text{CH}_2)_2\text{OH}-p$

Indeed, the condensation of the aldehyde **170** with acetone in the presence of the CA 72D4 and a cofactor (amine **172**) at

pH 7–9 occurs with high efficiency and follows Michaelis–Menten kinetics with respect to each component. Evidence was obtained that this reaction involves the formation of the intermediates **173** and **175**. The use of the tertiary amine as a cofactor does not result in a catalytic effect.

This reaction is stereoselective: the racemate of the aldehyde **170** gives *S,S*- and *R,S*-diastereomers of the aldol **171** with *de* 95% and 65%, respectively in 1 : 2.8 ratio.[§]

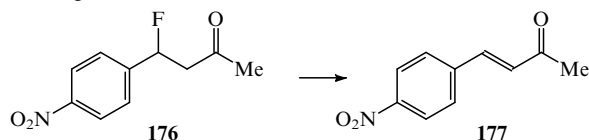
The aforementioned examples of the preparation of artificial aldolases possessing high stereoselectivity and a broader specificity than natural enzymes illustrate one of the most remarkable achievement in the design of a new generation of biocatalysts.

VII. 1,2-Elimination reactions (β -elimination)

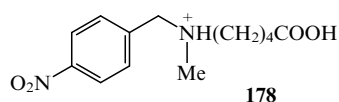
Reactions of 1,2-elimination (dehydrohalogenation, dehydration, *etc.*) underlie many synthetic procedures that are used for introduction of multiple bonds into the carbon skeleton of a molecule. Catalytic antibodies which catalyse these conversions are mostly of interest because they can alter the stereochemical result of some reactions resulting in alkene isomers that are inaccessible in energetically forbidden reactions of non-catalysed elimination. Most frequently, elimination of hydrogen halide, water and other small molecules from the vicinal carbon atoms with the formation of a multiple bond occurs as a concerted process.

Several examples of preparation of CA catalysing 1,2-elimination are presently known. The action of these CA is based on promotion of the reaction by introduction, into the active site of CA, of a group favouring removal of either a proton or a substituent (*e.g.*, the OH group in the dehydration), thereby initiating a concerted elimination process.

The preparation of a CA catalysing elimination of HF from the fluoroketone **176** to give the benzylideneacetone derivative **177** is an example.^{84, 85}



The design of a hapten aimed at generation of the active site of CA was based on an assumption that facilitation of α -deprotonation would accelerate the reaction. Therefore, compound **178** was selected as a hapten, which contained the groups similar to those in the ketone **176**. The CH₂ group in this ketone was replaced by the ammonium group. It was assumed that the latter would generate a group (presumably, a carboxy group) in the complementary position of the active site of CA which would facilitate deprotonation of the CH₂ group of the substrate **176**.



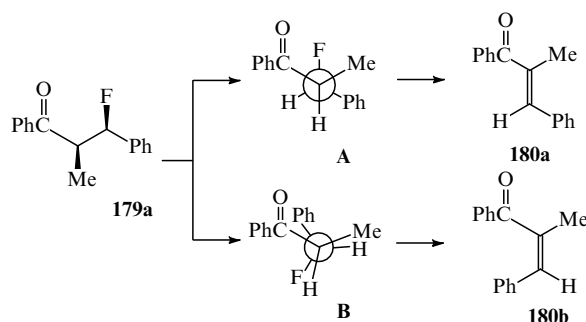
Indeed, compound **178** immobilised on the protein through a (CH₂)₄COOH spacer group generated a CA that accelerated the elimination of HF from the fluoro ketone **176** 10⁴-fold. This reaction followed Michaelis–Menten kinetics and was inhibited by the hapten and its analogues. Modification of the CA with chemical reagents and the character of the pH dependence of the CA activity confirmed the presence of a carboxy group (in the form of aspartate or glutamate) in the active site of the CA. This was confirmed by isolation of the corresponding peptide upon hydrolysis with trypsin of a CA modified with diazoacetamide. The effect of CA was substrate-specific, *viz.*, the elimination from

the *meta*-isomer of the ketone **176** was activated less strongly than from the *para*-isomer. It was found that the racemate of the substrate **176** yielded a mixture of *cis*- and *trans*-isomers of the unsaturated ketone **177**.

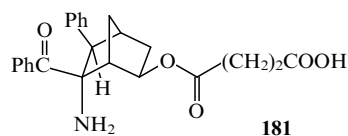
The stereochemical outcome of the elimination reaction is of particular interest. The reactions of all four diastereomers of the ketone **176** containing one deuterium atom in the CH₂ group were studied. Because of free rotation around the CHF–CH₂ bond in the molecule of the ketone **176**, the stereochemistry of β -elimination could be judged from the ratio and the structure of the *cis*- and *trans*-isomers of the unsaturated ketone **177** formed. The experimental results suggest that β -elimination takes place when the fluoro ketone molecule **176** is in the staggered conformation, *i.e.*, when the F and H (or, correspondingly, D) atoms are in the *anti*-periplanar position (*anti*-elimination). It thus follows that the active site of the CA favours *anti*-elimination without discriminating considerably between the *R*- and *S*-isomers of the substrate. This suggests that the carboxy group in the active site of the CA is conformationally flexible and can approach that particular proton the splitting of which is most favourable for the elimination from the *anti*-periplanar position.

In this context, the preparation of CA catalysing elimination of two 'eclipsed' atoms (or groups), *i.e.*, promoting '*syn*-elimination', is of special interest.⁸⁶ In the absence of a catalyst, this reaction is impeded, since the 'eclipsed' conformation is energetically most unfavourable because of the strong steric and/or electronic interaction of the neighbouring groups. Thus *syn*-elimination leading to a *cis*-alkene is an example of the so-called 'unfavourable' reaction and can hardly be realised by purely chemical methods. In order to perform this energetically unfavourable (or even forbidden) reaction, the active site of the CA must fix the substrate molecule in an unfavourable, 'eclipsed' conformation. Then the group facilitating deprotonation (*e.g.*, the carboxy group) present in the active site of the CA must be fixed in a position close to the proton to be eliminated from the substrate.

This idea has been successfully materialised in the preparation of a CA catalysing *syn*-elimination of HF from the ketone **179a** to yield the *cis*-isomer. In the absence of CA, this reaction cannot be performed, since the molecule **179a** adopts the staggered conformation **A**, as a result of which the H and F atoms in the *anti*-periplanar position are eliminated to give the *trans*-alkene **180a**.



A CA raised against the hapten **181** with a rigid bicycloheptane skeleton was used to direct the reaction towards the formation of the *cis*-alkene **180b**.



The hapten **181** forms such a cavity in the active site of the CA, where the PhCO and Ph groups of **179a** are fixed in an 'eclipsed' position relative to the central C–C bond (the conformation **B**). This determines their *cis*-position in the elimination product.

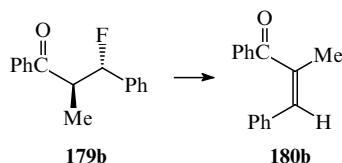
The position of the NH₂ group in the hapten **181** corresponds to the eclipsed position of the proton in the molecule **179a** relative to the fluorine atom that is eliminated. The NH₂ group, which is

[§]This reaction is reversible; the aldol formed can undergo retroaldol degradation or be converted into an unsaturated ketone. For the effect of spatial structure of the aldol on its further conversions, see Ref. 83.

converted into the NH_3^+ group in the CA biosynthesis, generates a carboxy group ensuring the catalysis in a strictly specific position of the active site of the CA.

The catalytic antibody against the hapten **181** catalyses the elimination of HF from the ketone **179a** to give only the *cis*-alkene **180b**, i.e., ensures 'syn-elimination' with high stereospecificity and fully changes the stereochemical result of this reaction in comparison with the non-catalysed process. The catalytic reaction follows Michaelis – Menten kinetics and is inhibited by the hapten **181** and its structural analogues which points to its occurrence in the active site of the CA. Thus, conditions exist which compensate for the consumption of additional energy ($\sim 5 \text{ kcal mol}^{-1}$) needed for the 'unfavourable' *syn*-elimination reaction to take place.

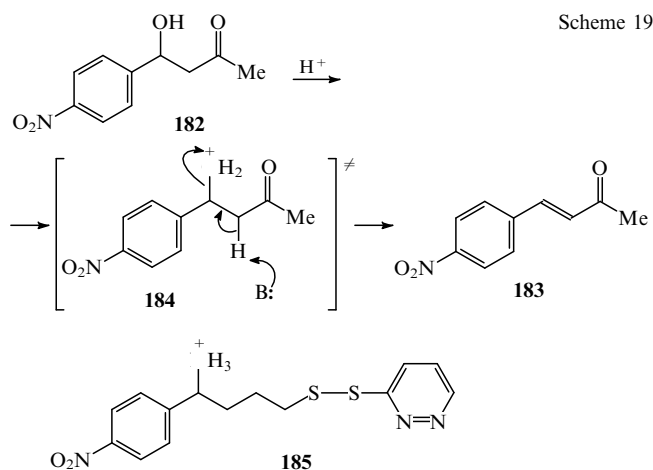
It is of note that this CA catalyses the conversion of the ketone **179a** into the *cis*-alkene **180b** more effectively than the conversion of the diastereomeric ketone **179b**.



The conversion **179b** $\rightarrow$ **180b** occurs as the *anti*-elimination, which suggests that the active site of the CA binds specifically with the conformer where the PhCO and Ph groups (and, correspondingly, the H and F atoms) are 'eclipsed' and is less suitable for the fixation of the conformers with the *anti*-periplanar position of these substituents.

The reaction of 1,2-dehydration is yet another type of β -elimination. One plausible mechanism of dehydration of hydroxy ketones involves protonation of the hydroxy group, the formation of an oxonium intermediate in the transition state and subsequent elimination of the substituent as the water molecule, which is energetically more favourable.

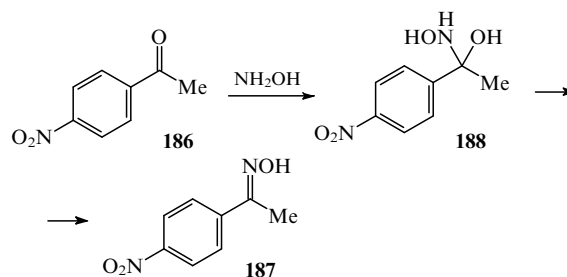
The possibility to obtain a CA catalysing this reaction was studied using the dehydration of the β -hydroxy ketone **182** into the unsaturated ketone **183** as an example (Scheme 19).⁸⁷



The hapten **185** used to obtain such a CA contained the ammonium group instead of the hydroxy group in the ketone **182**. The ammonium group would induce the formation, in the complementary position of the active site, of a group responsible for the protonation of the hydroxy group in the molecule **182** and stabilisation of the transition state **184**. The disulfide group was used in a spacer to provide binding of the hapten **185** with the protein.

This CA accelerated the elimination more than 1000-fold. It is specific to the substrate structure, since it does not catalyse the dehydration of the *meta*-isomer of the ketone **182**. The nature of the group in the active site of CA that stabilises the oxonium centre in the transition state remains obscure.

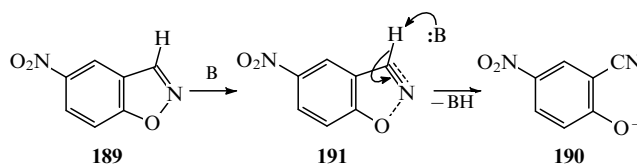
It is of note that the same CA catalyses stereoselective transformation of 4-nitroacetophenone **186** into the oxime **187**, which occurs as a consecutive addition and dehydration.⁸⁸



The dehydration of the intermediate **188** in the absence of the CA is not stereochemically unambiguous and yields a mixture of *syn*- and *anti*-oximes **187** in a 3 : 1 ratio. The reaction conducted under identical conditions but in the presence of the CA is accelerated 10⁴-fold and gives predominantly the *syn*-oxime (the *syn* : *anti* ratio is 9 : 1). It is remarkable that the same CA induces the elimination of small molecules not only from the C – C bond, but also from the C – N bond, if the substrate molecules are structurally close to each other.

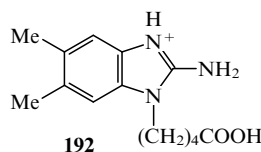
Transformation of benzoisoxazole **189** into the *o*-cyano-phenol derivative **190** is another example of dehydration for which a highly effective CA has been obtained.⁸⁹

This reaction is initiated by deprotonation to give a partially delocalised transition state **191**. This reaction occurs as a concerted *E2*-elimination.



In order to initiate this reaction, the active site of a CA must contain a group favouring deprotonation. Obviously, a carboxy group with appropriate acidity ($\text{pK}_a = 7.8$) matching the proton to be split off meets this demand.

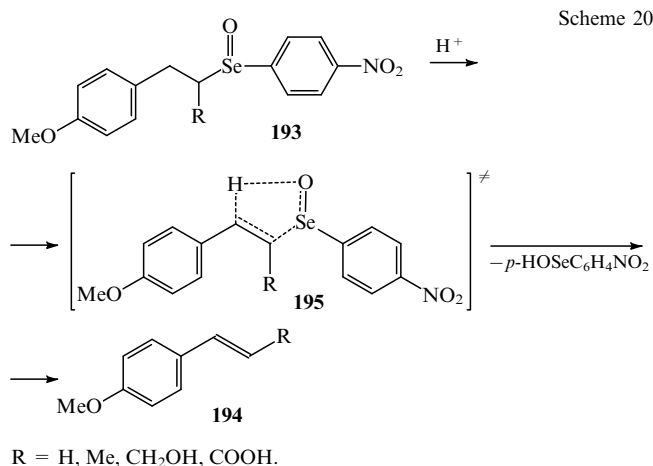
The benzimidazole derivative **192**, which is planar like benzoisoxazole and bears a spacer providing its immobilisation on the protein, was used as a hapten. The N(3) atom in the hapten **192** is protonated and is positively charged, which induces the formation of the carboxylate ion in the active site of a CA.



The most active CA raised against the hapten **192** accelerated the reaction $\sim 10^8$ -fold compared to the reaction catalysed by the acetate ion. Such efficiency is one of the highest attained with CA so far.

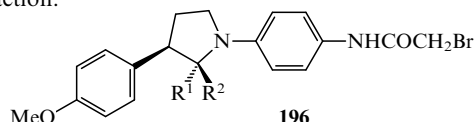
The results of kinetic and inhibitory analyses and the character of pH dependence of the CA effectiveness suggest that initially the CA forms a complex with the substrate. It is followed by deprotonation under the action of the carboxylate ion in the cavity of the active site, resulting in the ring opening. Such a high catalytic effect is attributed⁸⁹ to the correct choice of the hapten stimulating the formation of a carboxy group of proper acidity and at the necessary place of the active site of the CA.

A recent study⁹⁰ describes the preparation of CA catalysing β -elimination of *p*-nitrobenzeneselenenic acid from the selenoxide **193** to yield the unsaturated derivative **194** (Scheme 20).



This reaction, which has recently attracted considerable attention of synthetic chemists, occurs as a [2,3]-sigmatropic process. It is believed that the planar five-membered pericyclic transition state **195**, which is less polar than the original molecule **193**, is formed in the first stage.

The proline derivative **196**, which was deemed to form a relatively low-polar medium in the active site of a CA,⁹⁰ was used as a hapten. Such a medium favours the pericyclic reaction; the carboxy group and the benzene rings form a cavity in which the substrate is fixed in a conformation favourable for the reaction.



$\text{R}^1, \text{R}^2 = \text{H, COOH.}$

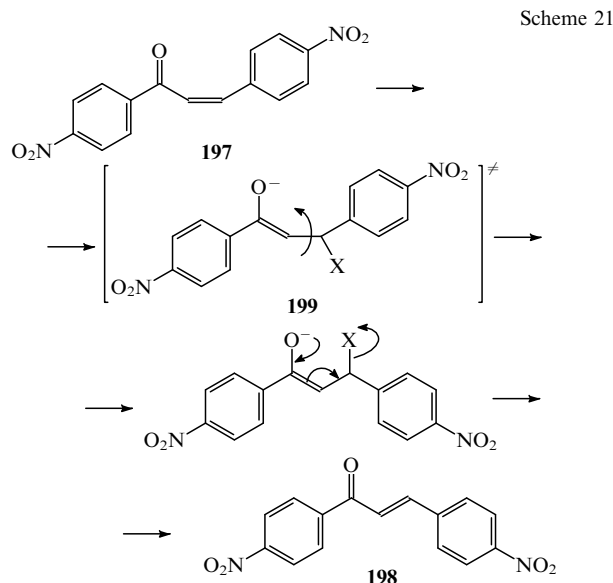
Two CA against the *cis*-isomer of the hapten **196** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{COOH}$) and one CA against its *trans*-isomer ($\text{R}^1 = \text{COOH}$, $\text{R}^2 = \text{H}$) have been obtained. All of them accelerated the elimination reaction several hundred times (2000-fold in case of the most active CA). The reaction rate increased with a decrease in the size of the substituent R in the molecule of the original selenoxide **193** ($\text{COOH} < \text{CH}_2\text{OH} < \text{Me} < \text{H}$).

Of particular interest is the stereochemical result of this reaction, which opens up new opportunities for its application in organic synthesis. The non-catalysed elimination of selenenic acid from the selenoxide **193** results in *trans*-alkenes for steric reasons. If the reaction is performed in the presence of a CA raised against the *trans*-hapten **196** ($\text{R}^1 = \text{COOH}$, $\text{R}^2 = \text{H}$), the racemic selenoxide is converted into the *trans*-alkene **194** (90%), while the *cis*-isomer is formed in insignificant amounts (10%).

On the contrary, in the presence of catalytic antibodies against the *cis*-hapten ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{COOH}$) only a half of the racemate **193** (*i.e.*, one stereoisomer) undergoes conversion. It is noteworthy that whereas one CA gives exclusively *trans*-alkenes, while the other yields both *cis*- and *trans*-isomers **194** in the 45:55 ratio. This unusual result was rationalised as being due to the fact that the cavity of the active site of this CA was split into two parts, so that the CA could interact with both stereoisomers. Detailed analysis of the reaction kinetics revealed strong effects of the medium polarity and solvation on the catalytic activity of the CA.

There is a single study⁹¹ devoted to the preparation of CA which catalyse *cis*–*trans*-isomerisation of a double bond. These CA effect the conversion of the *cis*-isomer of the α,β -unsaturated ketone **197** into the *trans*-isomer **198** (Scheme 21).⁹¹

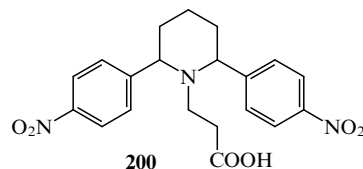
It is believed that the isomerisation occurs by addition of a basic (or a nucleophilic) group to the double bond to give the transition state **199**. After rotation around the ordinary bond that



formed, the substrate acquires a more favourable *transoid* conformation, while elimination of X^- gives the *trans*-isomer **198**.

Such an isomerisation could take place provided that the active site of the CA contained a group X that could add to the double bond and the spatial configuration of the cavity in the active site of the CA favoured subsequent conformational transition.

The hapten **200** was used to obtain a CA in which the nitrogen atom of the piperidine ring generated a carboxy group (a carboxylate ion) in the active site of the CA, while the benzene rings in the molecule **200** form a cavity favouring the conformational transition of the substrate by lowering the energy barrier to this reaction.



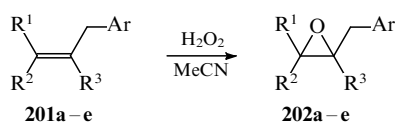
The catalytic antibody against the hapten **200** accelerated the isomerisation of the alkene **197** into the alkene **198** 1.5×10^4 -fold. This reaction was inhibited by the *trans*-isomer of the hapten **200** but not by its *cis*-isomer. The presence of a carboxy group in the active site of the CA was confirmed by chemical modification of this CA. Thus, the CA plays the role of an ordinary acid which lowers the energy barrier to isomerisation.

VIII. Formation and opening of the oxirane ring

Several papers^{92–97} devoted to the preparation of CA catalysing the formation and opening of the oxirane ring present special interest for synthetic chemists.

Thus a CA catalysing synthesis of oxiranes by epoxidation of a non-activated double bond of alkenes under the action of oxidants has been prepared.⁹² This study was focussed mainly not on the acceleration of this well-known reaction but on the possibility of its stereochemical control, *i.e.*, an increase in its enantioselectivity. The catalytic effect of the CA was studied with the conversion of alkenes of the type **201** into the oxiranes **202** as an example.⁹²

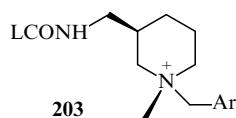
Hydrogen peroxide in acetonitrile was found to be the most suitable oxidant; in this case, the real oxidant is peroxyacetimidic acid $\text{CH}_3\text{C}(=\text{NH})\text{OOH}$. It is essential that the effectiveness of this oxidant is combined with its mild action; it did not destroy the protein.



Ar = C₆H₄CONH(CH₂)₂OH-*p*

Compound	R ¹	R ²	R ³
a	Me	H	Me
b	H	–(CH ₂) ₃ –	
c	H	Me	Me
d	H	H	Me
e	Me	Me	Me

The catalytic antibody must favour the pyramidalisation of carbon atoms, *i.e.*, their transition from *sp*²- to *sp*³-hybridisation. The active site of the CA was formed under the action of the hapten **203** with a positively charged tetrahedral nitrogen atom, which ensured the formation of a negatively charged group that facilitated acid catalysis.



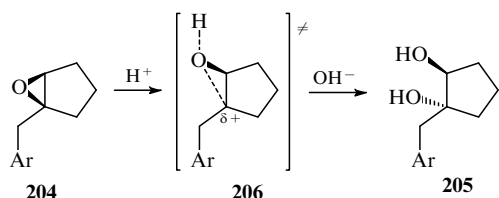
L = spacer; Ar = C₆H₄CONH(CH₂)₂OH-*p*.

One of the catalytic antibodies raised against this hapten was relatively effective in the conversion of the alkenes **201** into the oxiranes **202**. It was found that epoxidation of trisubstituted alkenes (**201a–c**) was accelerated 40–125-fold, epoxidation of the disubstituted alkene **201d** and the tetrasubstituted alkene **201e** was accelerated 60- and 15-fold, respectively. High enantioselectivity of this oxidation presents substantial interest, although it depends on the alkene structure. The alkenes **201b** and **201c** yielded the corresponding oxiranes **202** with optical purity 98% (with allowance made for the reaction product formed in the parallel non-catalysed reaction). Enantioselectivity of the oxidation of the alkene **201a** was 67%, which can probably be ascribed to the ability of this alkene to react in two different conformations.

Catalytic epoxidation of styrene in the presence of a CA raised against a metalloporphyrin derivative with iodosobenzene as an oxygen source has been described.⁹³ This study was undertaken with the view of elucidating the mechanism of action of natural oxidases of the cytochrome type.

Studies aimed at the synthesis of CA that accelerate the opening of the oxirane ring are of considerable interest. Such CA enable a control over the regioselectivity and enantioselectivity of this reaction.

A catalytic antibody of this type was used⁹⁴ to catalyse the hydrolytic opening of the oxirane ring in the alicyclic oxirane **204** (Scheme 22).



Scheme 22

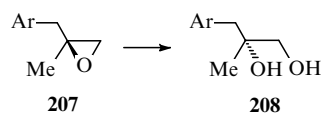
Ar = C₆H₄CONH(CH₂)₂COOH.

This acid-catalysed reaction occurs *via* the transition state **206** in which the tertiary carbon atom bears an excess positive charge and is subject to a nucleophilic attack, in this case, by the OH[–] ion. The catalytic function of the active site of the CA is reduced to the promotion and stabilisation of this positively charged centre and facilitation of ‘pyramidalisation’ of the corresponding carbon atom.

The hapten **203** was used to generate the CA. This hapten is thought⁹⁴ to form a cavity in the CA complementary to the transition state and the positive charge on the nitrogen atom favours the formation of a negatively charged group stabilising the excess positive charge of the transition state.

This antibody accelerated the conversion of the oxirane **204** into the 1,2-diol **205** 440-fold in comparison with the reaction carried out under identical conditions but in the absence of the CA and, which is especially important, with high enantioselectivity: the racemate of the epoxide **204** yields only the *R,S*-diol **205** (*ee* 87%). This reaction obeys Michaelis–Menten kinetics and is inhibited by an analogue of the hapten **203**, which confirms its localisation in the active site of the CA.

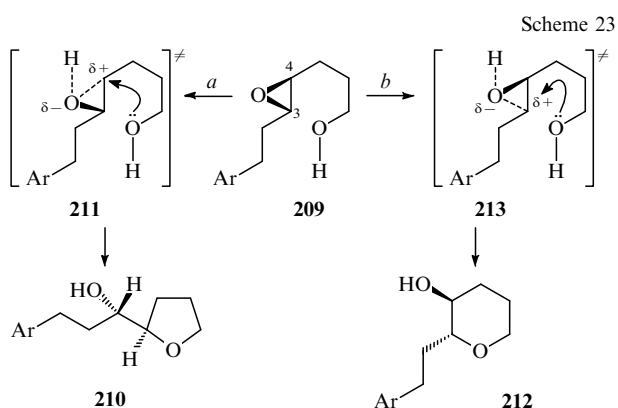
The catalytic antibody raised against the hapten **203** manifests broad substrate specificity and accelerates 100-fold the ring opening in simple epoxides of the aliphatic series, for example, the conversion of the epoxide **207** into the diol **208**. However, in this case the reaction is devoid of enantioselectivity, *viz.*, the *R*- and *S*-isomers of **207** are hydrolysed at the same rate, while hydrolysis of the corresponding racemate does not yield an excess of the *R*- or the *S*-enantiomer.



The difference in the behaviour of the oxiranes **204** and **207** is ascribed to the presence of an additional five-membered ring in the molecule **204**. In this case, the substrate and the active site of the CA created against the cyclic hapten are in a tighter contact.

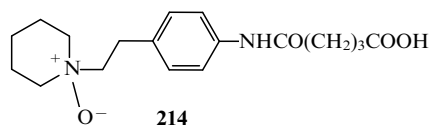
Of particular interest is the use of CA in the catalysis of intramolecular opening of the oxirane ring in epoxy alcohols where a CA can change the regioselectivity of the reaction. The opening of the oxirane ring in the epoxy alcohol **209**, which culminates in the formation of a heterocyclic system, is an example.

This reaction may proceed by two different routes. In the absence of CA, it proceeds only by a route (*a*) as the nucleophilic attack at the C(4) atom of the epoxide ring and gives the tetrahydrofuran derivative **210** in accordance with the so-called ‘Baldwin rule’.⁹⁶ Apparently, the reaction occurs *via* the transition state **211** with a partial positive charge on C(4) (Scheme 23).



Ar = C₆H₄NHAc-*p*, C₆H₄OMe-*p*.

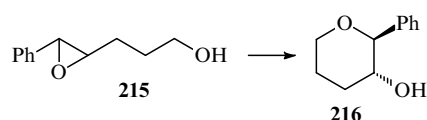
It was found that this reaction can be fully reversed in the presence of the corresponding CA and channeled through the energetically less favourable route (*b*) to give the tetrahydropyran **212**, which requires special conditions, that would direct the reaction *via* the transition state **213**. This demand was met with the use of a CA the active site of which corresponded to the transition state **213** different from the transition state **211**. The piperidine *N*-oxide derivative **214** the geometry of which is close to that of the transition state **213** was used as a hapten.



The haptin **214** has the $N^+ - O^-$ group which matches the carbon and oxygen atoms bearing excess charges in the transition state **213**. All this promoted the formation of groups stabilising this transition state in the active site of the CA.

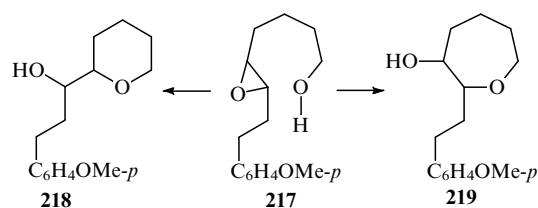
Indeed, one of the CA obtained (26D9) favoured the strictly regiospecific opening of the oxirane ring to give the tetrahydropyran **212** alone. The action of this CA was also highly stereoselective: only the *S,S*-isomer of the epoxy alcohol **209** was converted into the *S,R*-isomer **212**. This alteration in the reaction course in the presence of the CA was due to the formation of a complex between the transition state **213** and the complementary active site of the CA, which decreased the free energy of the transition state **213** and lowered the energy barrier to this reaction. Route (b) proved to be energetically more favourable than route (a).

An analogous CA-induced change in the regiospecificity of the reaction of intramolecular opening of the epoxy alcohol **215** has been reported.⁵⁴ Under conditions of ordinary acid catalysis, only a tetrahydrofuran derivative is formed, whereas in the presence of the CA tetrahydropyran **216** is exclusively formed.⁵⁴



This reaction is highly stereoselective: the racemate **215** gives the *S,R*-isomer **216**, while the *R,R*-isomer of the epoxy alcohol **215** does not enter into the reaction.

Further experiments showed that such changes in regiospecificity are common for the cyclisation of epoxy alcohols. Thus it was found unexpectedly that the cyclisation of the epoxy alcohol **217**, which under normal conditions is converted into the tetrahydropyran derivative **218** in accordance with the Baldwin rule, yields exclusively the oxepane **219** in the presence of the same CA (26D9).



Thus, in this case, too, the CA channels the reaction through an energetically 'unfavourable' route.⁹⁷ Since the geometry of the haptin involved in the formation of the active site of the CA corresponded to the transition state with a six-membered ring, the formation of the oxepane **219** is unexpected at first glance. The authors interpret this phenomenon by the fact that the role of the CA consists primarily in the formation of a group in the appropriate position of the active site which facilitates the strictly specific opening of the oxirane ring. The size of the heterocyclic ring formed in the process depends on the length and conformation of the aliphatic chain (tether) in the epoxy alcohol **217**.

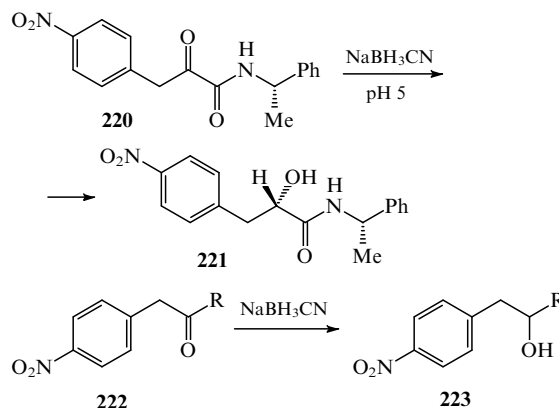
The above examples demonstrate various applications of CA in directed organic synthesis and elaboration of new synthetic procedures.

IX. Redox reactions

Studies aimed at the search for CA catalysing redox reactions have been neither extensive, nor systematic, apparently because of the existence of numerous chemical and biochemical methods for

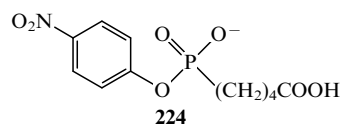
their efficient realisation. Nevertheless, several CA catalysing the reduction of carbonyl groups have been prepared. The use of artificial CA pursued the objective to make reduction more selective.

Some CA catalysed the reduction of the α -oxo amide **220** into the α -hydroxy amide **221**⁹⁸ and the reduction of the ketones **222** into the corresponding alcohols **223** with NaBH_3CN .⁹⁹



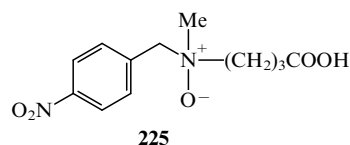
R = Et, Prⁱ, Bn.

In the former case, the corresponding phosphonic acid derivative **224** was used as a haptin.



The phosphorus atom in the haptin **224** is in the same position as the oxo group in the substrate **220** to be reduced. The haptin **224** ensured the formation of a group, in the active site of CA, responsible for the polarisation of the oxo group and the tetrahedral structure of the phosphorus atom provided the stereoselectivity of the nucleophilic attack on the carbon carbonyl atom by the hydride ion in the transition state. The resulting CA accelerated the reduction of the oxo amide **220** 300-fold in comparison with the non-catalysed reaction. High stereoselectivity is the main merit of this reduction, because the alcohol **221** with the *S*-configuration formed in the presence of the CA was of 99% purity, whereas the *R*- and *S*-isomers were formed in approximately equal amounts in the absence of the CA.

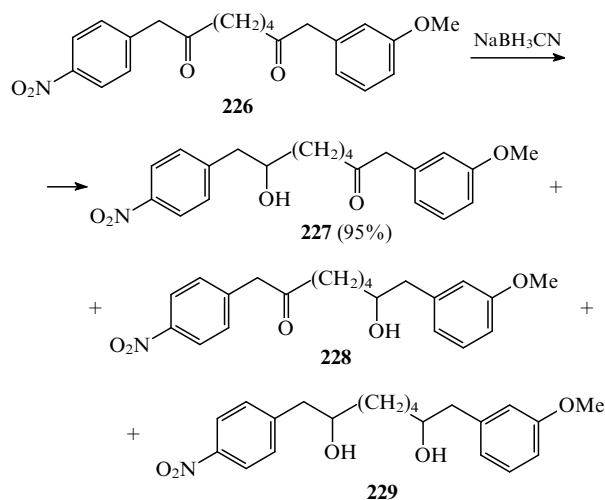
Since the oxo group in the ketone **222** is less reactive than that in the oxo amide **220**, a more effective CA raised against the haptin **225** was used to catalyse this reaction.



The $N^+ - O^-$ group in the molecule **225** ensured the formation of the CA. Its active site ensured both the stabilisation of the tetrahedral transition state and enhancement of the substrate polarisation, which are essential for the nucleophilic attack of the reducing agent.

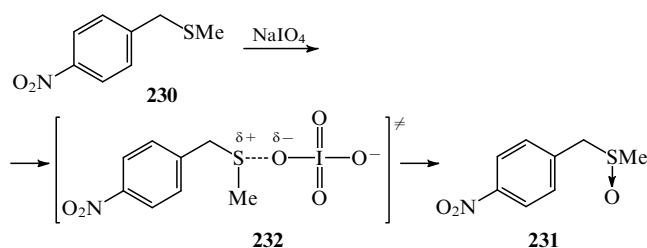
This CA accelerated the reduction of the oxo group in the ketones **222** approximately 100-fold; the alcohols **223** having the *S*-configuration were formed with high stereoselectivity (88%–95% *ee*) irrespective of the size of the alkyl substituent. The effect of CA was also highly regiospecific. The reduction of the unsymmetrical diketone **226** in the presence of this CA afforded the *S*-enantiomer of the hydroxy ketone **227** in 95% yield, whereas other probable reaction products (compounds **228** and **229**) were formed in insignificant amounts. The regiospeci-

ficity of the CA is determined by the structure of the initiating hapten **225**, viz., by the presence of the NO₂ group.



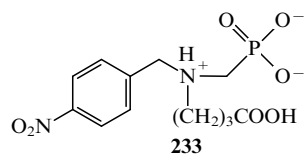
Among oxidation reactions for which effective CA have been obtained, special mention should be made of the oxidation of the sulfide **230** into the sulfoxide **231** (Scheme 24).

Scheme 24



It is believed that this reaction involves the attack at the sulfur atom of the sulfide **230** with the oxygen of the periodate ion which occurs *via* the transition state **232**.

Based on these concepts, the hapten **233**, a benzylaminophosphonic acid derivative, the amino group of which was transformed into the ammonium group under conditions of the CA biosynthesis, was used to generate the CA. The ammonium group favoured the formation of a negatively charged group stabilising the positive charge on the sulfur atom in the transition state, whereas the phosphonic acid residue formed a cavity binding the periodate ion in the active site of the CA.¹⁰⁰



One of the CA raised against this hapten accelerated the oxidation of the sulfide **230** 2×10^5 -fold; its effectiveness was close to that of natural oxidases, although it differed from the latter by low enantioselectivity ($\sim 15\%$ ee). This CA was practically inert with respect to periodate. The mechanism of its catalytic action and the structure of its active site were established by X-ray analysis of a CA-hapten complex.¹⁰¹

It can also be noted that CA catalysing redox reactions have been used to solve some problems of biochemistry and enzymic catalysis, e.g., for determining the reduction potential of flavin¹⁰² and for estimating the contribution of two fluorescein fragments to the free energy of binding in the active site of CA.¹⁰³

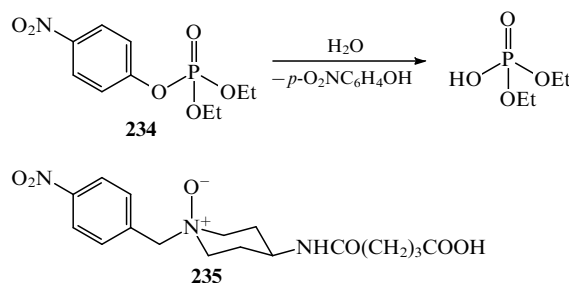
X. Miscellaneous reactions

The catalytic antibodies described below have not found general use; yet they present certain interest since they demonstrate not only the broad range of conversions for which active CA can be obtained but also the high potentialities of these artificial enzymes.

1. Hydrolysis of phosphotriesters

The interest in the synthesis of CA catalysing hydrolysis of phosphotriesters¹⁰⁴ arose in connection with medicinal and environmental problems, since phosphotriesters and their derivatives are the basis for many pesticides and war gases and intermediate products for large-tonnage chemical industry. Preparation of CA providing mild hydrolysis of these toxic compounds and their practical application might become useful in curing poisoning with pesticides, war gases, etc.

Thus the preparation of a CA catalysing hydrolysis of a well-known pesticide paraoxon (**234**), which occurs with the elimination of 4-nitrophenol, was undertaken with compound (**235**) as a hapten.



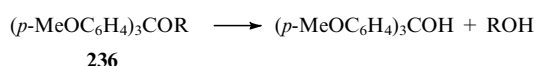
The charges on the N⁺—O[−] group of the molecule **235** generate specific groups in the cavity of the active site of the CA, which favour protonation and/or stabilisation of the negative charge on the oxygen atom of the phosphate group, whereas the spatial structure of the hapten forms a cavity which corresponds to the optimum structure of the transition state.

The CA obtained accelerated hydrolysis of the phosphate **234** ~ 1000 -fold. The linear dependence of the reaction rate on the concentration of the hydroxide ion suggests¹⁰⁴ that the catalytic effect of this CA is most probably associated with the stabilisation of the transition state. The CA possessed rather narrow substrate specificity. Hydrolysis of phosphate **234** analogues with a methoxy or an acetamino group in the benzene ring and of cyclic phosphates was practically not accelerated by this CA.

2. Cleavage of triphenylmethyl ethers

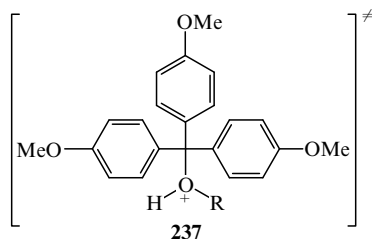
Selective splitting of the triphenylmethyl (trityl) group presents certain practical interest, since this group is widely employed in synthetic practice for temporary protection of the hydroxy group, especially in the synthesis of nucleosides and carbohydrates. Detritylation is usually performed under rather drastic conditions of acid hydrolysis. Preparation of CA which would permit one to perform detritylation under neutral conditions and with required selectivity presents substantial interest.

Detritylation of the ether **236** served as an example.¹⁰⁵

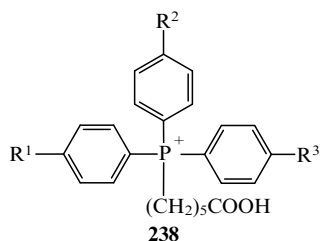


R = (CH₂)₂O(CH₂)₂O(CH₂)₂OH.

The protonation of the oxygen atom possessing enhanced nucleophilicity is the rate-determining step in the detritylation of tris(4-methoxyphenyl)methyl ether **236**. The resulting transition state **237** is further decomposed to give tris(4-methoxyphenyl)methanol.



The triphenylphosphonium derivative **238** containing a spacer was used to obtain the CA catalysing this reaction.



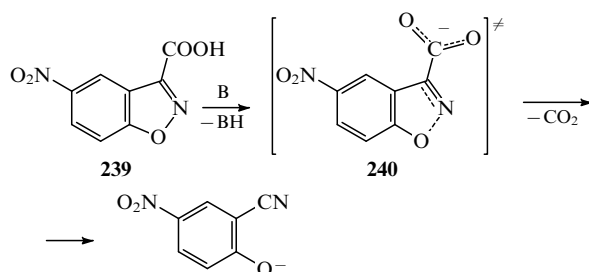
This hapten was structurally similar to the substrate **236**. The positive charge on the phosphorus atom of this hapten favoured the formation of a negatively charged group in the CA.

The CA obtained accelerated the hydrolysis of the ether **236** 270-fold in comparison with the non-catalysed reaction at pH 6.0 and manifested broad specificity as it was active in detritylation of analogues of the ether **236**, *e.g.*, such compounds as $(p\text{-MeOC}_6\text{H}_4)_2\text{C(Ph)O(CH}_2)_5\text{COOH}$ and $(p\text{-MeOC}_6\text{H}_4)\text{-C(Ph)}_2\text{O(CH}_2)_5\text{COOH}$, by accelerating their hydrolysis 200- and 230-fold, respectively. It is of note that hydrolysis of the thio analogue of the ether **236** was also accelerated 70-fold by this CA, whereas that of the amine Ar_3CNHR was not catalysed.

The effect of pH on the detritylation of compound **236** in the presence of the CA suggested¹⁰⁵ that its catalytic action was not owing to the direct effect of the carboxy group but rather due to electrostatic stabilisation of the oxonium centre of the transition state **237** in the cavity of the active site of the CA. This study on the preparation of a CA catalysing detritylation, was not explored further but it gave an impetus to the preparation of CA for other reactions associated with the cleavage of oxygen–carbon bonds (see Section V).

3. Decarboxylation reactions

Preparation of CA catalysing one specific reaction, *viz.*, the decarboxylation of 5-nitrobenzo[d]isoxazole-3-carboxylic acid **239** resulting in 4-nitro-2-cyanophenol, has been described (Scheme 25).¹⁰⁶



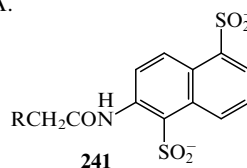
Scheme 25

This first-order reaction[¶] occurs as a concerted process. It is known that it is not associated with acid–base catalysis but its rate depends critically on the reaction medium. This reaction is accelerated by several orders of magnitude in aprotic solvents, in micelles and in the presence of organic polymers. Presumably, it

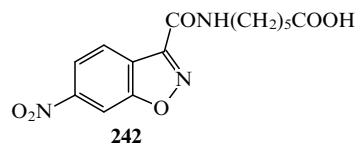
[¶] For an analogous CA-catalysed conversion of nitrobenzoxazole into a cyano phenol derivative, see Section VII.

proceeds *via* the transition state **240** in which the bonds are partially delocalised. A CA catalysing this reaction must contain a hydrophobic active site with polar groups favouring the splitting of CO_2 .

The hapten **241** with a spacer group (R) was used to generate CA.



It was suggested¹⁰⁶ that the naphthalene nucleus of the hapten provides the formation of a cavity complementary to the substrate in the active site of the CA, while the sulfo groups induce the appearance of positively charged groups, which facilitate splitting of CO_2 . The authors' arguments in favour of this hapten are not completely clear; nevertheless, a highly effective CA able to accelerate the reaction 2×10^4 -fold in comparison with non-catalysed decarboxylation has been raised. It is of note that no active CA could be raised against the hapten **242**, which matches more closely the substrate but is devoid of polar sulfo groups.

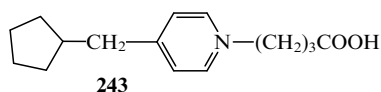


This reaction has been studied in detail using inhibitory analysis, fluorescence spectra and the kinetic isotope effect.¹⁰⁷ It was shown that the active site of the CA is very hydrophobic, and that the catalytic effect of the CA is achieved owing to the formation of a hydrophobic environment around the substrate. This conclusion was confirmed, in particular, by comparison of the rates of CA-catalysed reactions occurring in solvents of different polarity.¹⁰⁸

Preparation of a CA catalysing decarboxylation of 4-pyridylacetic acid has been reported.¹⁰⁹



Compound **243** with a cyclopentyl substituent, which was introduced to form a hydrophobic cavity in the active site of the CA, was used as a hapten.



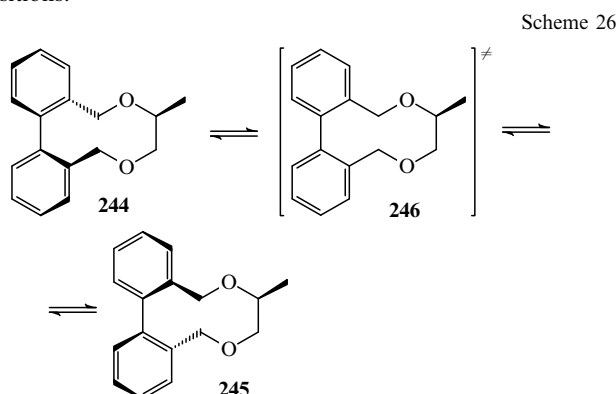
The CA obtained accelerated the decarboxylation of 4-pyridylacetic acid and some of its methyl-substituted analogues 10^4 – 10^5 -fold. It was shown that the catalytic effect of such CA was largely due to the formation of a hydrophobic environment around the substrate in the complementary region of the active site of the CA. The main role in the formation of such a hydrophobic environment is played by the cyclopentyl substituent in the hapten **243**. Preparation of this kind of CA is of fundamental importance, since it demonstrates the possibility to attain a catalytic effect by the formation of hydrophobic zones in CA. This allows one to gain more insight into the mechanisms of action of natural decarboxylases.

4. Isomerisation of cyclic biphenyl derivatives

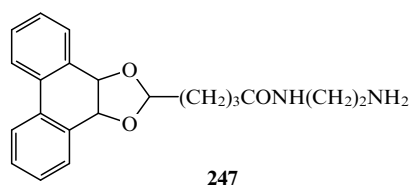
Isomerisation of the biphenyl derivative **244** incorporated in a cyclic system into its diastereomer **245** requires rather high (~ 20 – 26 kcal mol^{-1}) activation energy (Scheme 26).¹¹⁰

At room temperature, this reaction proceeds very slowly, because the rotation of phenyl nuclei around the common axis is

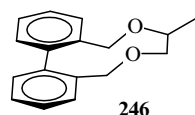
impeded due to the presence of methylene groups in *ortho*-positions.



Presumably, the effect of a CA is associated exclusively with the geometric factors favouring isomerisation rather than with stereoelectronic effects or acid–base catalysis. Assuming that this isomerisation occurs *via* the planar transition state **246**, a dihydrophenanthrene derivative **247** with fixed coplanar benzene rings was used in the preparation of CA as a hapten.

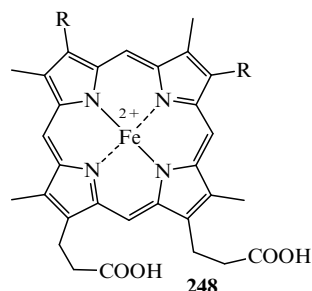


The most active CA obtained accelerated the isomerisation **244** → **245** approximately 3000-fold. This CA was subjected to a more detailed physicochemical analysis. It was demonstrated that the transition state **246** actually has a step-like conformation but its phenyl nuclei lie in the same plane.



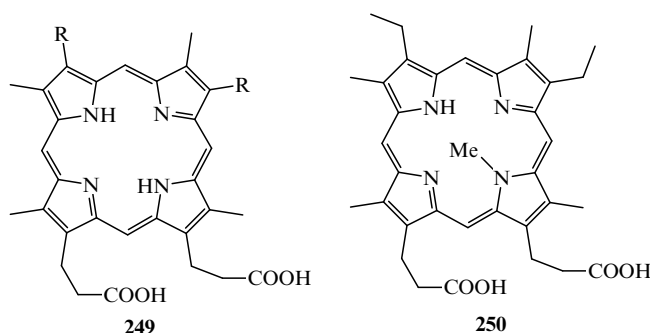
5. The formation of metal–porphyrin complexes

The formation of metal–porphyrin complexes is the key step in many vital processes. Thus, Fe^{2+} incorporates into protoporphyrin IX at the final step of heme (**248**, $\text{R} = \text{CH}=\text{CH}_2$) biosynthesis.



This reaction is catalysed by a natural enzyme, ferrochelatase, and inhibited by *N*-methylprotoporphyrin IX. It is assumed that the inhibiting effect of the latter is due to the non-planar structure, which resembles that of the transition state formed in the reaction **249** → **248**. Therefore, *N*-methylprotoporphyrin IX competes with the transition state for binding with the active site of the enzyme.

N-Methylmesoporphyrin **250** in which propionic acid residues served as a spacer for immobilisation was used to generate an active CA catalysing the formation of metal–porphyrin complexes.¹¹¹

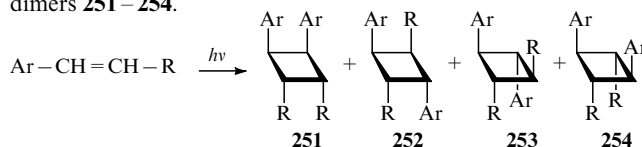


In this case, the choice of a hapten was based on the principle of mimicking the 'strained transition state'.

The most active CA obtained accelerated the formation of complexes of dihydroporphyrin **249** ($\text{R} = \text{C}_2\text{H}_5$) with Zn^{2+} and Cu^{2+} 2600- and 1700-fold, respectively. This reaction followed Michaelis–Menten kinetics and was inhibited by the hapten **250**. The catalytic effect of this CA varied for different metals and depended specifically on the porphyrin structure. Thus complex formation of protoporphyrin **249** ($\text{R} = \text{CH}=\text{CH}_2$) and its analogue ($\text{R} = \text{H}$) was not catalysed by this CA. This makes the effect of CA strongly different from that of ferrochelatase, which also catalyses the reactions of these analogues.

6. Photochemical reactions

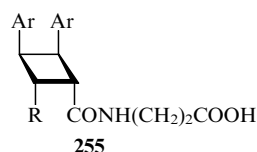
Several CA affecting UV-induced reactions (*e.g.*, dimerisation of methyl 4-nitrocinnamate in acetone) have been obtained.¹¹² Under ordinary conditions, this reaction gives a mixture of the dimers **251**–**254**.



$\text{Ar} = p\text{-O}_2\text{NC}_6\text{H}_4$, $\text{R} = \text{COOMe}$.

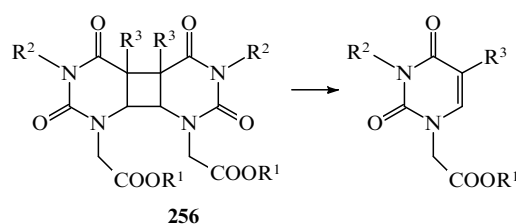
With the use of a CA it was possible to change the ratio of the two main isomers **251** and **253** (0.45 : 1).

In order to increase the yield of the isomer **251**, it is necessary that the cavity of the active site of the CA matched the spatial structure of the dimer **251**. Therefore, the hapten **255** was used to generate the CA.



Irradiation of methyl 4-nitrocinnamate in the presence of the CA raised against the hapten **255** gave the dimers **251** and **253** in a 1.13 : 1 ratio. The reaction was accelerated by the CA. Thus, the formation of the active site favouring the appropriate configuration of the transition state directs the reaction towards the formation of the corresponding isomer. The structure of the group catalysing the dimerisation itself is still unknown.

Preparation of a CA catalysing UV-induced dissociation of the thymine dimer **256** ($\text{R}^1 = \text{R}^2 = \text{H}$, $\text{R}^3 = \text{Me}$) presents certain interest.¹¹³



UV-Induced dimerisation of the thymine residue of DNA is a cause of structural disturbances in this biopolymer, which has profound biological consequences. This reaction is reversible and DNA can be 'repaired' by irradiation in the presence of natural enzymes (DNA-photolyases).

The dissociation of the dimer **256** seems to occur through electron transfer with subsequent dissociation by a radical mechanism. Indole, quinone and flavin derivatives are sensitisers of the electron transfer. It was speculated that catalytic antibodies that catalyse effectively the dissociation of the dimer **256** ought to contain a group that sensitises the electron transfer in the cavity of the active site matching the substrate. The hapten **256** ($R^1 = \text{NHCH}_2\text{COOH}$, $R^2 = \text{H}$, $R^3 = \text{Me}$), which is the substrate analogue, was used to raise such CA. The efficiency of a CA raised against this hapten was comparable with that of the natural enzyme (DNA-photolyase from *E. coli*). The effect of the CA was specific: dissociation of the dimer **256** ($R^1 = \text{H}$, $R^2 = R^3 = \text{Me}$) was not catalysed. The changes in the fluorescence spectra during this reaction provide evidence that a tryptophan residue is responsible for sensitisation of this reaction in the active site of the CA.

The dissociation of the N_1 -carboxymethyluracil dimer **256** ($R^1 = R^2 = R^3 = \text{H}$) was studied in order to elucidate the mechanism of photochemical dissociation of nucleic bases.¹¹⁴ The corresponding CA was raised against the hapten **256** ($R^1 = \text{NHCH}_2\text{COOH}$, $R^2 = R^3 = \text{H}$), which is a structural analogue of the hapten used to obtain the CA catalysing the dissociation of the thymine dimer. The resulting CA accelerated the photodissociation of the uracil dimer 380-fold. A study of the effect of the wavelength of UV irradiation revealed the crucial role of a tryptophan residue on the electron transfer. Analysis of the isotope effect in the irradiation of C(5)- and C(6)-deuteriated uracil dimers has made it possible to suggest a general scheme for the photodissociation of nucleic base dimers.

XI. Conclusion

The creation of artificial catalysts having a protein structure and endowed with a predetermined specificity is one of the most impressive accomplishments in chemistry and biology. Considerable progress has been achieved over the decade elapsed since the preparation of the first catalytic antibody. A great number of such biocatalysts of a new generation have already been obtained. But what is most important is that the main principles of the design of catalytic antibodies of targeted action have been elucidated and the strategy of their preparation has been elaborated.

The design of a hapten determining the specificity of the antibody and the structure of its active site is the crucial step in the generation of a CA.

At present, the choice of a hapten is governed by different principles which reflect the diversity of mechanisms of conversion of organic compounds.¹¹⁵ In the simplest case, a compound the structure of which is spatially and electronically similar to that of the transition state, is used as a hapten, which stabilises this transition state in the active site of the CA. Haptens generating active groups responsible for acid–base or nucleophilic catalysis in substrate conversions in the active site of CA are also used for this purpose. Catalytic antibodies that are effective in sigmatropic and pericyclic reactions are raised against haptens which form a cavity in the active site of a CA that enables optimum reciprocal arrangement of the reactants (in bimolecular reactions) or a required stereoelectronic state of the substrate. This lowers the entropy barrier to a chemical conversion (the 'entropic trap' principle). In some cases, the purpose of the hapten is to create local or more extended hydrophobic zones in the CA mimicking conversion of the substrate in a 'non-aqueous' medium. In practice, haptens meeting simultaneously two or several requirements have been employed, which made it possible to form an active site which acted on the substrate in several directions at once.

The most recent approaches make use of haptens which directly interact with the antibodies raised against them. In this way, CA acquire the ability not only to stabilise the transition state but also to mimic the very process of conversion of the substrate (the so-called 'reactive immunisation').¹¹ Yet another approach consists in catalysis in the presence of a cofactor which acts simultaneously with the antibody (and actually modifies it in the course of the reaction) and channels the catalytic reaction in the necessary direction.⁸²

Further progress in this area will depend first of all on new efficient approaches to the design of haptens. It is due, primarily, to the development of theoretical chemistry and the use of computation and computer modelling for gaining a deeper insight into molecular mechanisms of biocatalysis and elucidation of mechanisms of catalytic reactions.

Great diversity of reactions for which catalytic antibodies have been already obtained testify to the high potentialities of this novel field. At first glance, it may seem that a catalytic antibody can be generated for virtually any conversion of an organic compound. However, it is still too premature to prognosticate and outline the real scope of the method.

The 'exploration' period in this area seems to be over. In addition to purely academic research, studies devoted to the preparation of artificial enzymes for practical purposes are currently under way. Yet, many general problems still await their solution.¹¹⁶ Here it seems appropriate to mention two of such problems which present special importance from the point of view of a synthetic chemist.

In most cases, the activity of synthetic CA is inferior to that of natural enzymes. The inhibitory effect of reaction products on catalytic antibodies is one main reason for the low activity of CA which reduces their 'turnover' number and decreases their efficiency. The understanding of the mechanism of this phenomenon and the ability to overcome the problem through the correct choice of a hapten is the urgent task.

All in all, catalytic antibodies differ strongly from each other in their substrate specificity: some CA have narrow specificity and are effective with respect to only one substrate, while others are effective with respect to a vast variety of structurally close compounds. The former ensure high chemo-, regio-, and stereo-specificity of a specific reaction and exclude parallel and side processes. The latter are more suitable for wide application and elaboration of a versatile synthetic procedure. As a matter of fact, both types of CA may coexist, and it would be important to learn how to control the range of their substrate specificity in the targeted preparation. This requires knowledge of mechanisms of the catalytic effect and the role of the fine structure of the active site in manifestation of specificity, and hence the correct choice of a hapten determining these properties.

Further improvement of the primary monitoring of CA raised and the procedure for the choice of the most efficient catalysts (see Ref. 117) are problems of substantial importance facing specialists in biological sciences. One may also hope that the efficiency of antibody biosynthesis in the immune apparatus will also be enhanced as a result of fundamental or methodological modifications of the existing immunisation protocols and further utilisation of the hybridomas obtained.

However, CA have already proved to be a very helpful tool in organic synthesis not only in enhancement of well-known reactions but, which is even more important, in increasing the specificity and stereoselectivity. It is therefore very tempting to obtain CA catalysing the reactions for which natural enzymes have not yet been found. Apparently, CA acquired the greatest importance in conversions of organic compounds which cannot be performed by purely chemical methods because of energetic and/or steric hindrances. In some cases, CA facilitate the formation of a required transition state and channel the reaction through a 'forbidden' route by changing its chemo-, regio- or stereospecificity, *i.e.*, opening up a way for a new synthetic method.

For chemists, the use of CA opens up new opportunities in the studies of the 'intimate' aspects of mechanisms of many reactions, the role of thermodynamic and kinetic factors, acid–base catalysis, effects of the medium, *etc.*

Catalytic antibodies may hold a particular position in bioorganic chemistry, specifically, in the chemistry of biopolymers where enzymes find especially wide uses.

Studies of CA are of considerable importance for the understanding of basic principles of biocatalysis.¹¹⁵ The possibility to obtain CA with targeted action and their comparison with natural enzymes of analogous action patterns, studies of the molecular structure of the active site of CA by X-ray analysis and other physicochemical methods, the use of targeted chemical modification or selective mutagenesis and many other features make catalytic antibodies an indispensable tool in studies on the mechanisms of enzymic catalysis, the structure of enzyme–substrate complexes and their role in the catalytic process. The problem of specificity of natural enzymes can be followed by preparing a series of CA with analogous action, elucidating their molecular structures, structure–specificity relationships and so on. Studies in this area are currently under way and have been briefly mentioned in this review.

Investigations of CA will probably make a significant contribution to the elucidation of other problems related to immunochemistry, immunology, protein biosynthesis, *etc.* Thus it is known that CA have already been used to study such specific problems as the formation and alteration of the structures of natural enzymes in the course of chemical evolution.¹¹⁸

Attempts have been made to use CA in medicinal practice (see a review¹¹⁹), *e.g.*, as preparations neutralising the effects of certain toxins, narcotics, *etc.* Their application in the creation of 'prodrugs' is another perspective trend.^{120–122}

This creates a problem of a large-scale preparation of CA. The first steps in this direction aimed at obtaining large batches of CA and their utilisation in the synthesis of gram quantities of compounds as well as the design and construction of a laboratory unit operating in a semi-automatic regime have already been undertaken.^{53,54} In the state-of-the-art biotechnology and protein engineering, preparation of large amounts of highly purified catalytic antibodies does not face any serious problems. Of course, their practical application on a large laboratory or industrial scale will require the solution of many other problems including technological ones. One problem is related to the most rational form of their application, *viz.*, in solution, in biphasic systems,¹²³ immobilised on carriers¹²⁴ or under conditions of micellar catalysis.¹⁵ Many of these problems connected with the use of natural enzymes have been successfully solved, which facilitates their solution in the case of CA.

As far as the economical aspect is concerned, the benefits of CA applications (*e.g.*, in asymmetric synthesis) may have fully paid off despite the labouriousness and expensiveness of the technological procedures involved in the preparation of these biocatalysts. However, their application in large-tonnage processes is still premature.

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2,3,4,5-Tetrahydropyridine (Δ^1 -piperidine) and its derivatives. Synthesis and chemical properties

M-G A Shvekhgeimer

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Abstract. The data on the synthesis and transformations of 2,3,4,5-tetrahydropyridine and its derivatives published after 1970 are surveyed and described systematically. The bibliography includes 251 references.

I. Introduction

The enhanced interest in the pyridine derivatives is due to some specific chemical and physical properties peculiar to this class of compound. The fact that pyridine bases exhibit a broad spectrum of biological activities is equally important. 2,3,4,5-Tetrahydropyridine (Δ^1 -piperidine) and its derivatives also attract attention. Δ^1 -Piperidine itself is a key compound participating in the biosynthesis of some alkaloids (for example, alkaloids of the coniine and lobeline groups). Substituted 2,3,4,5-tetrahydropyridines are convenient starting compounds for the synthesis of other families of alkaloids, the structures of which are often fairly complex.

Published data on the chemistry of tetrahydropyridines were surveyed for the first time in a volume.¹ This volume contains only one mention of Δ^1 -piperideines, namely, it presents a scheme for the synthesis of 3,5-dimethyl-2-phenyl- Δ^1 -piperidine. More recent volumes^{2,3} contain data on the methods of synthesis and properties of 1,2,3,4-tetrahydropyridines, 2,3,4,5-tetrahydropyridines and 1,2,5,6-tetrahydropyridines, mostly published before 1971. The chemistry of 2-alkoxy-3,4,5,6-tetrahydropyridines has been discussed in a review⁴ devoted to the lactim ethers containing heterocyclic nuclei of various sizes.

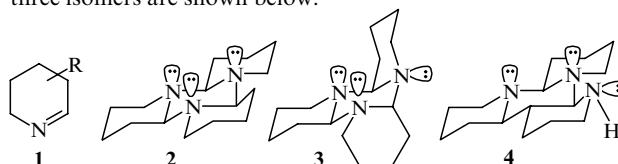
In the present review, we consider systematically the data on the chemistry of Δ^1 -piperideines published from 1970 to the present time. Among the compounds synthesised, the products belonging to one or another family of alkaloids are mentioned, and their biological activities are discussed.

II. Structure of Δ^1 -piperideines

The unsubstituted 2,3,4,5-tetrahydropyridine (**1**) stands out in the series of Δ^1 -piperideines. In fact, almost all 2,3,4,5-tetrahydropyr-

idine derivatives are monomers under ordinary conditions, whereas unsubstituted 2,3,4,5-tetrahydropyridine (**1a**) exists at pH ≥ 7 as three isomeric trimers, α -isomer **2**, β -isomer **3** and isotripiperidine **4**.⁵

The structures, configurations and conformations of these three trimers were determined by ^{13}C NMR spectroscopy.^{5,6} It was established that at low temperatures, the compound occurs as the trimer **3**, while at room temperature, it is converted into the trimer **2**. The trimer **4** can also exist at room temperature. The trimer **2** has C_3 symmetry and exists as a racemic mixture of the *RRR* and *SSS* configurations, while the trimer **3** is characterised by C_1 symmetry and is a racemic mixture of the *RRS* and *SSR* configurations. The most favourable conformations for all the three isomers are shown below.⁵



The monomer – trimer equilibrium has been studied by NMR, UV and IR spectroscopy.⁷ It was found that at pH 7, the compound **1a** occurs as a trimer, while in solutions in anhydrous acids, aqueous acids and aqueous alcohols, the equilibrium shifts towards the monomer. In strongly acidic solutions 2,3,4,5-tetrahydropyridine exists only as the monomer **1a**.

All the bond lengths and the internal angles in the six-membered ring of 2,3,4,5-tetrahydropyridine (**1a**) have been determined by *ab initio* quantum-chemical calculations.^{8,9}

Bond	Length / Å	Angle	Magnitude / deg.
a	1.5080	1	111.5
b	1.5242	2	108.6
c	1.5233	3	109.5
d	1.5241	4	115.5
e	1.4670	5	118.2
f	1.2830	6	128.0

The cyclic imine **1** exists in a half-chair conformation, having the lowest energy. Of the three piperideines, Δ^1 -piperidine **1a** is

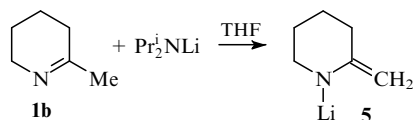
M-G A Shvekhgeimer A N Kosygin Moscow State Textile Academy,
ul. Malaya Kaluzhskaya 1, 117918 Moscow, Russian Federation.
Fax (7-095) 952 14 40. Tel. (7-095) 955 35 96

Received 24 February 1997

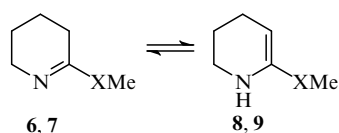
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characterised by the minimum energy; if the relative energy of the compound **1a** is taken to be zero, the energy of 1,2,3,4-tetrahydropyridines is 6.39 kcal mol⁻¹ and that of 1,2,5,6-tetrahydropyridine is 11.9 kcal mol⁻¹. The calculated bond lengths and internal angles are in good agreement with the corresponding values determined for substituted Δ^1 -piperideines by X-ray diffraction analysis.^{8,9}

Some derivatives of the imine **1a** containing substituents at the 2-position exist as two tautomers. Thus 2-methyl-3,4,5,6-tetrahydropyridine **1b** is readily converted into the lithium derivative of 2-methylenepiperidine (**5**) on treatment with lithium diisopropylamide (LDA).¹⁰ In the presence of perchloric acid, the compound **1b** also reacts as 2-methylenepiperidine.¹¹

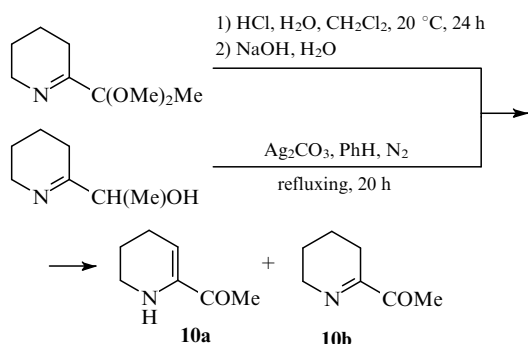


2-Methoxy-3,4,5,6-tetrahydropyridine **6**^{12–14} and 2-methylthio-3,4,5,6-tetrahydropyridine **7**¹⁴ can participate in reactions as the enamine forms **8** and **9**.



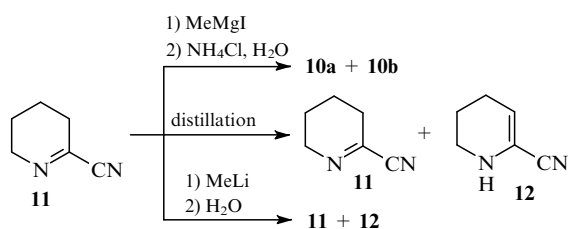
X = O (**6, 8**), S (**7, 9**).

In the case of 2-acetyl-3,4,5,6-tetrahydropyridine **10**, the equilibrium is shifted towards the enamine form **10a**. Having been formed, the compound **10** first exists as the less stable tautomer **10b**, which is then partially converted into the more stable tautomer **10a** (the **10a** : **10b** ratio is 2 : 1).^{15,16}



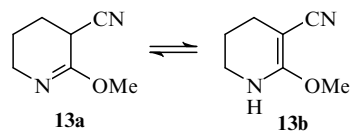
When 2-cyano-3,4,5,6-tetrahydropyridine **11** is made to react with MeMgI and then the reaction mixture is treated with an aqueous solution of ammonium chloride, a mixture of the tautomers **10a** and **10b** in 1 : 4 ratio is formed. During storage, the content of **10a** increases (**10a** : **10b** = 2 : 1).¹⁷

On distillation, the nitrile **11** is partially converted into 6-cyano-1,2,3,4-tetrahydropyridine **12** (ratio **11** : **12** = 1 : 1.3).¹⁷ The compound **11** isomerises to **12** upon the reaction with MeLi and subsequent treatment with water.

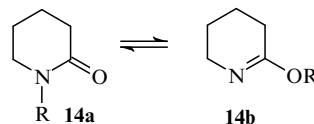


3-Cyano-2-methoxy-3,4,5,6-tetrahydropyridine **13** exists as two tautomers **13a** and **13b**, which is confirmed by the presence of two absorption bands in its IR spectrum, at 2180 cm⁻¹ (for the

conjugated CN group) and 2260 cm⁻¹ (for the non-conjugated CN group).¹³



It was found by ion cyclotron resonance that in the series of alkylated derivatives, tautomers **14b** are stronger bases than **14a**.¹⁸



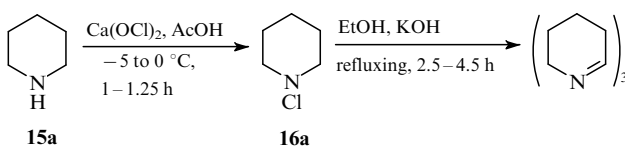
R = H, Me.

III. Methods of synthesis of Δ^1 -piperideines

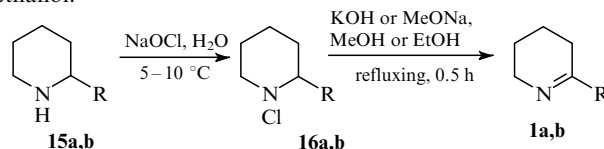
1. Synthesis from piperidine and its derivatives

The unsubstituted imine **1a** is commonly prepared by a two-stage procedure which includes treatment of piperidine with chlorinating agents and reaction of the resulting 1-chloropiperidine with nucleophilic reagents.

Treatment of amine **15a** with calcium hypochlorite in acetic acid gave the chloro-derivative **16a**, which was converted into the trimerised compound **1a** (yields 39% – 64%) by treatment with an ethanolic solution of KOH .^{19–21}

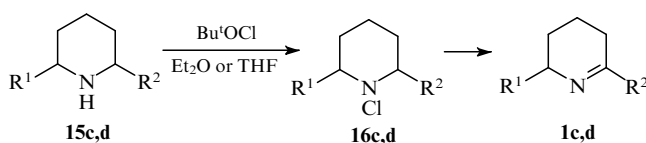


In other studies,^{22,23} piperidine and 2-methylpiperidine were converted into the cyclic imines **1a, b** on treatment with sodium hypochlorite in water followed by refluxing of the resulting *N*-chlorinated derivatives **16a, b** in a 10% ethanolic solution of potassium hydroxide²² or in a solution of sodium methoxide in methanol.²³



R = H (a), Me (b).

On treatment with Bu^tOCl in ether¹⁷ or THF,²⁴ the derivatives **15c, d** are transformed into the *N*-chlorinated compounds **16c, d**, which react with MeONa in MeOH , triethylamine in Et_2O ¹⁷ or KOH in EtOH and THF²⁴ to give the Δ^1 -piperideines **1c, d**.

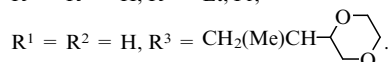
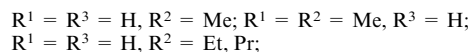
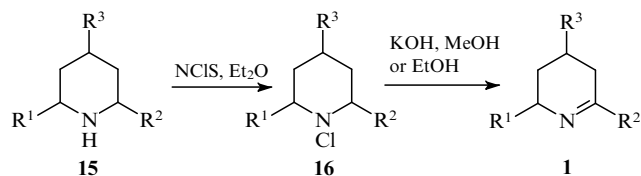


R¹ = H, R² = CN (c); R¹ = R² = Ph (d).

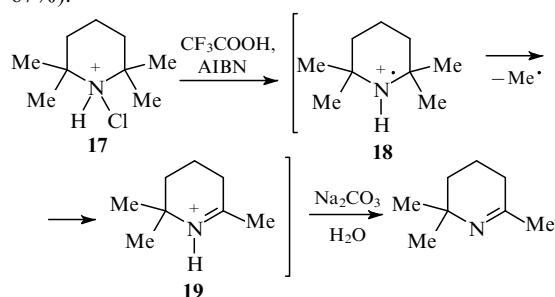
In several studies,^{25–27} *N*-chlorosuccinimide in Et_2O was used to convert the amine **15a** into 1-chloropiperidine **16a**, and dehydrochlorination of the chloro-derivative was carried out using potassium hydroxide.

Gas-phase chlorination of piperidine **15a** with *N*-chlorosuccinimide (47°C , 10^{-1} – 10^{-2} mm Hg) and gas-phase dehydrochlorination of the resulting *N*-chloropiperidine **16a** (which is formed in 90% yield) over AdOK (Ad is 1-adamantyl) at 2°C ²² or over Bu^tOK at -97 to -77°C ^{22,28} have been reported.

N-Chlorosuccinimide (NCIS) has been used to chlorinate the substituted piperidines **15**; the resulting chlorinated derivatives **16** were converted into the Δ^1 -piperideines **1** using KOH in an alcohol.^{29–32}

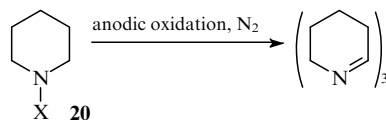


Heating of tetramethylpiperidinium chloride **17** in trifluoroacetic acid in the presence of azobisisobutyronitrile yields radical cation **18**, which is converted into cation **19** with elimination of Me[•]. Treatment of the reaction mixture with an aqueous solution of sodium carbonate affords 2,6,6-trimethyl- Δ^1 -piperidine (yield 67%).³³



AIBN is azoisobutyronitrile.

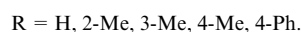
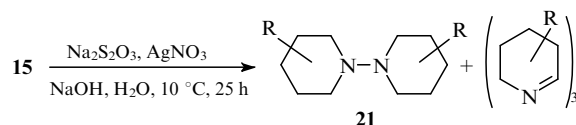
The piperidine trimer is formed in a relatively low yield upon anodic oxidation of piperidine derivatives **20** under an inert atmosphere.³⁴



X	Anolyte	Current density /A dm ⁻²	The charge passed /F mol ⁻¹	Yield (%)
Li	LiClO ₄	0.21	1	6
MgBr	—	0.84	1	15

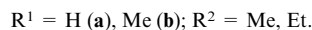
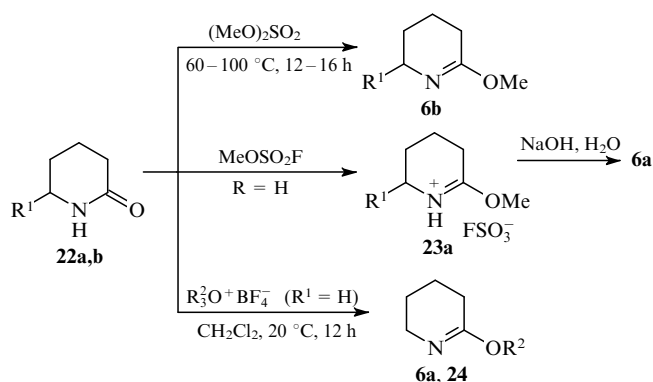
The transformation of piperidine **15a** into the piperidine trimer (yield 58%) upon oxidation with chloroiron(III) mesoporphyrin IX dimethyl ester has been reported.³⁵

The piperidines **15** react with sodium hyposulfite in the presence of catalytic amounts of silver nitrate giving a mixture of 1-(1-piperidyl)piperidines **21** and piperidine trimers.³⁶



A popular method for the synthesis of Δ^1 -piperideines is treatment of piperidin-2-one **22a** or piperidine-2-thione or their substituted derivatives with various reagents.

Thus heating of the lactam **22a** with dimethyl sulfate in benzene or toluene gives 2-methoxy-3,4,5,6-tetrahydropyridine **6a** in 70%–90% yield.^{37–42} 2-Methoxy-6-methyl-3,4,5,6-tetrahydropyridine **6b** was prepared by treatment of methylpiperidone **22b** with dimethyl sulfate.⁴⁰



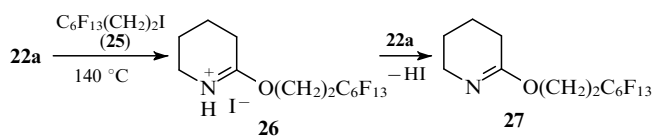
The imide **6a** is produced in 78% yield in the reaction of the lactam **22a** with methyl fluorosulfonate followed by treatment of the resulting salt **23a** with aqueous sodium hydroxide.⁴³

The imideate **6a** and 2-ethoxy-3,4,5,6-tetrahydropyridine **24** have been synthesised in 92% and 89% yields, respectively, by the reaction of lactam **22a** with trimethyloxonium or triethyloxonium tetrafluoroborate.⁴¹

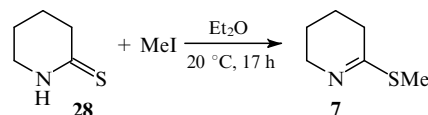
A method for the synthesis of the methoxy-derivative **6a** consisting in the reaction of the lactam **22a** with diazomethane in ether in the presence of silica gel and sodium bicarbonate has been patented⁴⁴

When piperidin-2-one **22a** reacts with POCl₃ at 20 °C, 2-chloro-3,4,5,6-tetrahydropyridine is formed.⁴⁵

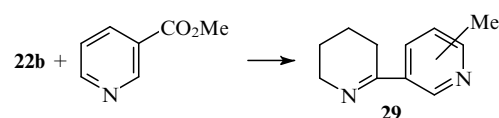
Heating of iodo-derivative **25** with the lactam **22a** in a sealed tube affords salt **26**, which reacts with a second molecule of the lactam **22a** yielding lactim ether **27** and the hydroiodide of the lactam **22a**.⁴⁶



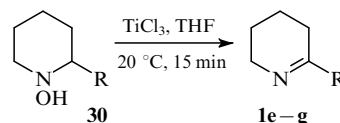
The reaction of piperidine-2-thione **28** with methyl iodide in anhydrous ether at 20 °C gives rise to 2-methylthio-3,4,5,6-tetrahydropyridine **7**.⁴⁷



The synthesis of piperidine **29** from the lactam **22b** and methyl nicotinate has been patented.⁴⁸

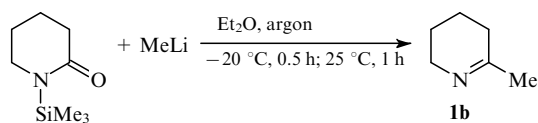


In the presence of TiCl_3 , 1-hydroxypiperidines **30**, substituted at the 2-position, are rapidly converted into the Δ^1 -piperidines **1e–g**, which are formed in high yields.^{49, 50}

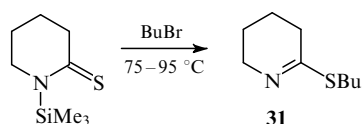


Compound	R	Yield (%)	Ref.
1e	Pr	83	49
1f	CH = CH ₂	73	49
1g	Ph	89	49
		70	50

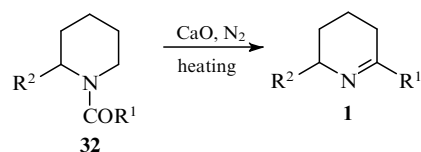
1-Trimethylsilylpiperidin-2-one is converted into 2-methyl-3,4,5,6-tetrahydropyridine **1b** on treatment with methyl lithium under an inert atmosphere.⁵¹



2-Butylthio-3,4,5,6-tetrahydropyridine **31** has been synthesised in 59% yield by heating 1-trimethylsilylpiperidine-2-thione with butyl bromide.⁵²

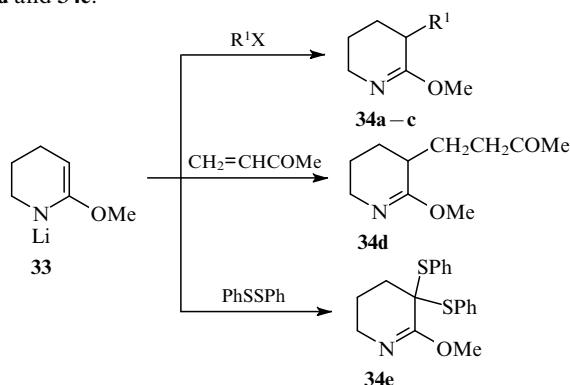


When piperidine derivatives **32**, containing an acyl group at the nitrogen atom, are heated with calcium oxide, carbon monoxide is removed and the R¹ radical migrates to the α-position of the heterocyclic ring to give the piperideines **1**.^{53–55}



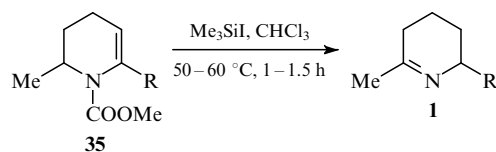
R ¹	R ²	Yield (%)	Ref.
Pr	H	69	53
	H	62	53
CH ₂ =CH(CH ₂) ₃	Me	39	54

Methods for the preparation of Δ¹-piperideines from N-substituted Δ²-piperideine derivatives have been reported. Thus the reaction of 1-lithio-2-methoxy-Δ²-piperideine **33** with alkyl halides resulted in the synthesis of imideate **34**, substituted at the 3-position of the heterocyclic centre; the reactions of **33** with methyl vinyl ketone and diphenyl sulfide yielded the corresponding ethers **34d** and **34e**.⁵⁶



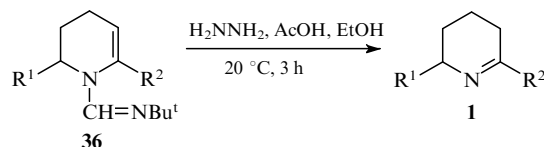
Compound	R ¹	X	Temperature / °C (time / h)	Yield (%)
34a		I	20(4)	56
34b	CH ₂ =C(Me)CH ₂ CH ₂	I	–78(3) to 22(0.3)	60
34c	Me(Cl)C=CHCH ₂	Cl	–78(2) to 20(12)	37
34d			–78(0.1) to 20(0.3)	31
34e			–78(0.05) to 20(0.3)	66

The Δ²-piperideine derivatives **35** lose the methoxycarbonyl group when heated with iodotrimethylsilane and are thus converted into Δ¹-piperideines **1** in almost quantitative yields.^{57, 58}



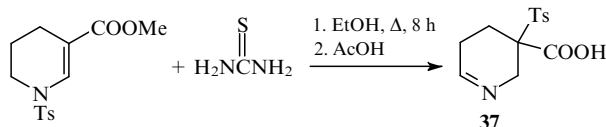
R = C₁₁H₂₃, C₈H₁₇.

Hydrazinolysis of the C–N bond in the Schiff's bases **36** affords the Δ¹-piperideines **1** in almost quantitative yields.⁵⁹



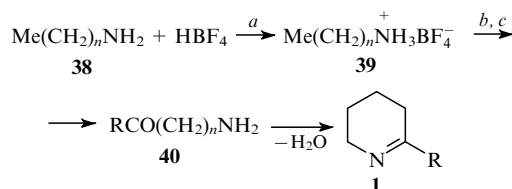
R¹, R² = H, C₁₁H₂₃; H, CH₂Ph; Me, C₁₁H₂₃.

Methyl 1-tosyl-1,4,5,6-tetrahydronicotinate has been found to undergo an unexpected transformation on heating with thiourea yielding acid **37**.⁶⁰



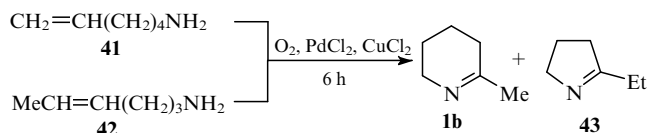
2. Synthesis from primary amines and their derivatives

Primary amines **38** react with HBF₄ to give the corresponding salts **39**, which are converted into the imines **1** upon reaction with methyl(trifluoromethyl)dioxirane at 0 °C followed by treatment with sodium carbonate. Presumably, this reaction yields initially amino ketones **40**.^{61, 62} The reaction can be carried out either with or without isolation of the intermediate salts **39**.

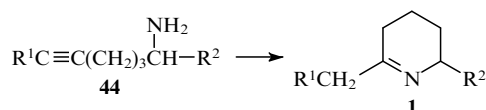


(a) H₂O, MeCN, pH 2–3; (b) methyl(trifluoromethyl)dioxirane, CH₂Cl₂; (c) Na₂CO₃; n = 5–7, R = Me (90%), Et (95%), Pr (92%).

Oxidative cyclisation of aminoalkenes **41** and **42** in the presence of palladium(II) chloride and copper(II) chloride gives rise to a mixture of the imine **1b** and 2-ethyl-Δ¹-pyrroline in 66 : 34 ratio and in a total yield of 75% and 71%, respectively.⁶³



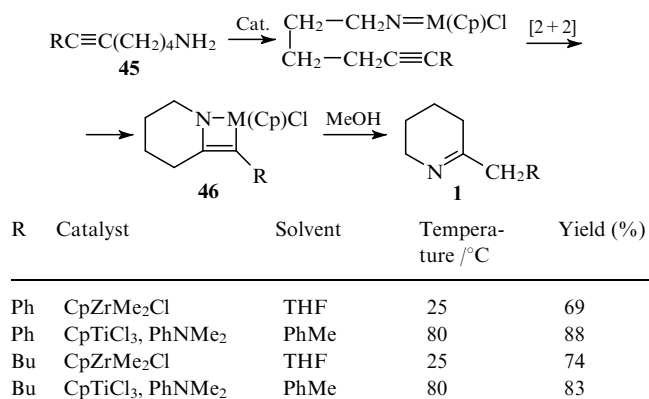
Alkynylamines **44** have been converted into the Δ¹-piperideines **1** by refluxing in acetonitrile or THF in the presence of NaAuCl₂·2 H₂O for 1–2 h (yield 64%–90%)⁶⁴ or by refluxing in propionitrile in the presence of PdCl₂·(MeCN)₂ for 10–20 h (yield 42%–92%).⁶⁵



R¹ = H, Et, C₅H₁₁, C₆H₁₃, C₇H₁₅, CH₂=CH(CH₂)₂, Ph;
R² = H, Me, C₁₁H₂₃.

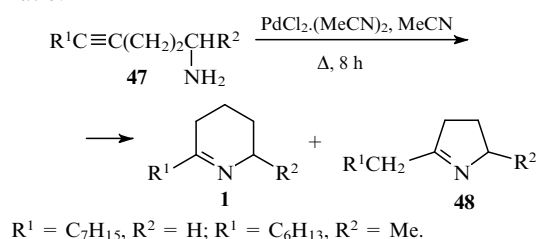
Cyclisation of the amines **44** ($R^1 = \text{Ph}, \text{Me}_3\text{Si}; R^2 = \text{H}$) in the presence of catalytic amounts of the samarium complex ($\eta^5\text{-Me}_5\text{C}_5\text{SmCH}(\text{SiMe}_3)_2$) also results in the formation of the Δ^1 -piperidines **1** ($R^1 = \text{Ph}, \text{Me}_3\text{Si}; R^2 = \text{H}$).⁶⁶

The synthesis of the Δ^1 -piperidines **1** from alkynylamines **45** in the presence of Group IV metal complexes occurs as intramolecular [2+2]-cycloaddition with the intermediate formation of metalocyclic compounds **46**.⁶⁷

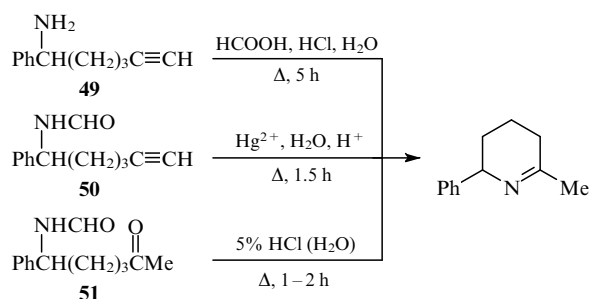


The transformation of the alkynylamine **45** ($R = \text{C}_7\text{H}_8$) into the corresponding Δ^1 -piperidine **1** ($R = \text{C}_7\text{H}_8$) was carried out in *N,N*-dimethylaniline in the presence of CpTiCl₃ at 80 °C.⁶⁷

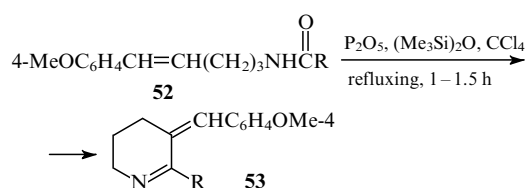
In the presence of PdCl₂·(MeCN)₂ as a catalyst, alkynylamines **47** are converted into mixtures of the Δ^1 -piperidines **1** and Δ^1 -pyrrolines **48**, which are formed in a quantitative yield in 4:1 ratio.⁶⁵



Three procedures have been proposed for the synthesis of 2-methyl-6-phenyl-3,4,5,6-tetrahydropyridine,⁶⁸ namely, heating of 6-amino-6-phenylhex-1-yne **49** with formic and hydrochloric acids, Kucherov hydration of its *N*-formyl derivative **50** and cyclisation of keto amide **51** in boiling hydrochloric acid.

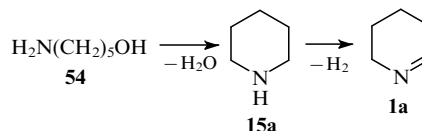


Heating of unsaturated amides **52** with P₂O₅ in CCl₄ in the presence of hexamethyldisiloxane is accompanied by their cyclisation to give Δ^1 -piperidines **53**.⁶⁹

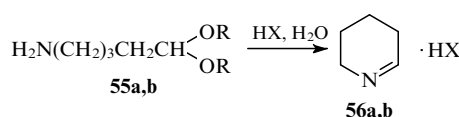


$R = \text{Me}, (\text{CH}_2)_2\text{CH}(\text{CH}_2\text{Ph})\text{COOEt}.$

The transformation of the amino alcohol **54** into Δ^1 -piperidine **1a** in the presence of various catalysts and at a temperature of 200, 225, 250 or 300 °C (in some cases, under a hydrogen atmosphere) has been studied. The process was shown⁷⁰ to occur in two stages comprising cyclodehydration of the amino alcohol **54** and dehydration of the piperidine **15a** thus formed. The highest yields of the piperidine **15a** were attained in the presence of Cu/Al₂O₃ at 200 °C or Cu/MgO at 225 °C (99% and 62%, respectively). The yield of piperidine **1a** at 250 °C was not greater than 20%–22%, while at 300 °C, it was only 5%.

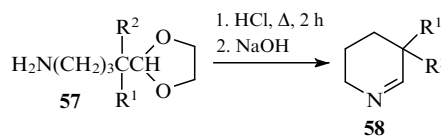


On treatment with 20% sulfuric acid, 5-aminopentanal acetal **55** is converted into sulfate **56a** in 92% yield.⁷¹ A similar cyclisation of the acetal **55b** induced by hydrochloric acid gives hydrochloride **56b**.⁷¹



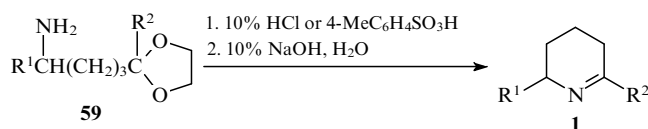
$R_2 = \text{Me}_2$ (**a**), CH_2CH_2 (**b**); $X = \text{HSO}_4$ (**a**), Cl (**b**).

3,3-Disubstituted Δ^1 -piperidines **58** have been synthesised by heating amino aldehyde acetals **57** with hydrochloric acid followed by treatment with NaOH.⁷²



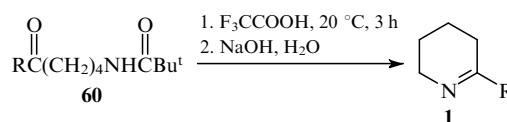
$R^1 = \text{H}; R^2 = \text{Me, Et}; R^1 = R^2 = \text{Me}.$

Treatment of amino ketone ketals **59** with dilute hydrochloric acid in ether⁷³ or THF⁷⁴ as well as treatment with toluene-*p*-sulfonic acid in acetone⁷⁵ gives the Δ^1 -piperidines **1** in 70%–90% yields.



$R^1, R^2 = \text{C}_5\text{H}_{11}, \text{Me, Br, C}_{11}\text{H}_{23}, (\text{MeO})_2\text{CH}(\text{CH}_2)_3.$

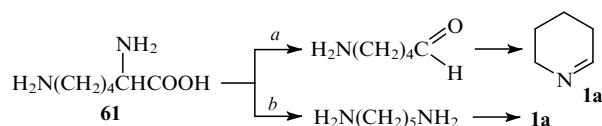
The 2-substituted 3,4,5,6-tetrahydropyridines **1** are formed upon cyclisation of oxo amides **60** in the presence of trifluoroacetic acid.⁷⁶



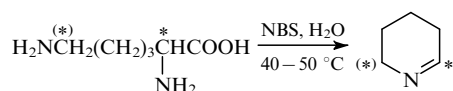
$R = \text{C}_6\text{H}_{13}$ (74%), Ph (71%), Pr (44%), $\text{C}_{11}\text{H}_{23}$ (48%), 3-pyridyl (56%).

2,6-Diaminocaproic acid (lysine **61**) serves as the starting compound in the biosynthesis of about 150 alkaloids, which are produced from this acid *via* oxidative rearrangements occurring in plants with the intermediate formation of the imine **1a**.

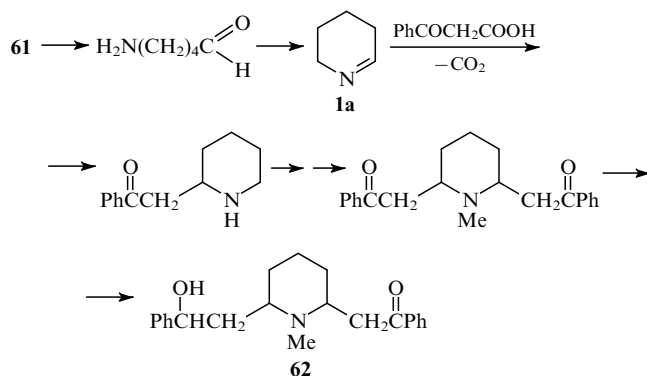
In nature, 2,3,4,5-tetrahydropyridine **1a** can arise from lysine **61** *via* two routes, namely, Strecker degradation to 5-aminopentanal followed by intramolecular dehydration (a) and decarboxylation of the acid **61** to give 1,5-diaminopentane (cadaverine) and its subsequent cyclisation (b).^{77, 78}



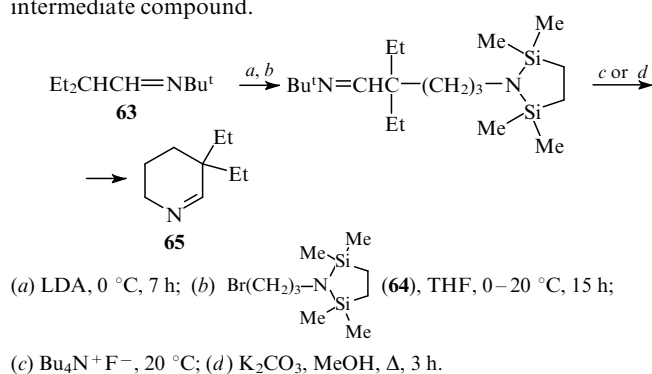
In order to identify the intermediate compounds which may form in these reactions, 2,3,4,5-tetrahydropyridines labeled by ^{14}C at the 2- or 6-position have been synthesised^{79,80} by the reaction of the corresponding labelled D,L-lysine hydrochlorides with *N*-bromosuccinimide.



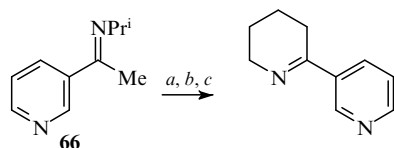
In another study,⁷⁷ ^{14}C -labelled ($\pm$)-[2- ^{14}C]-lysine, [1,5- ^{14}C]-cadaverine and [2- ^{14}C]- Δ^1 -piperidine were introduced into the *Lobelia inflata* plant, together with non-labelled lobeline **62**. After some time, ^{14}C -containing lobeline **62** was found in the plant. Based on the ratio of the introduced to recovered ^{14}C , it was concluded that biosynthesis of the alkaloid **62** involves the intermediate formation of 5-aminopentanal. A probable scheme for the formation of lobeline **62** was proposed.



3,3-Diethyl- Δ^1 -piperidine **65** was prepared in 53% yield by the reaction of amine **63** with bis-silylated aminobromopropane **64** in the presence of LDA followed by desilylation of the intermediate compound.

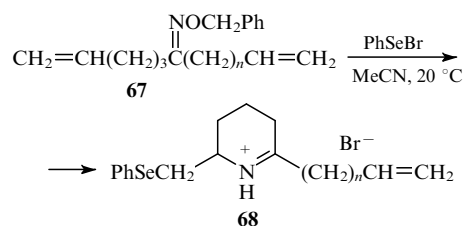


2-(3-Pyridyl)-3,4,5,6-tetrahydropyridine was synthesised from imine **66** and bromide **64** in 88% yield.⁸¹



(a) LDA, THF, 0 °C, 2 h; (b) **64**, THF, 0–20 °C, 15 h; (c) K_2CO_3 , MeOH, Δ , 3 h.

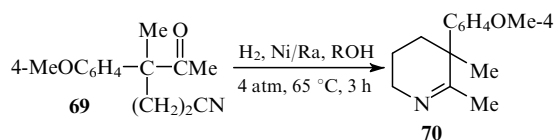
The hydrobromides of selenium-containing Δ^1 -piperideines **68** are formed in the reaction of *O*-benzoyloximes **67** with PhSeBr at room temperature.⁸²



$n = 3, 4$.

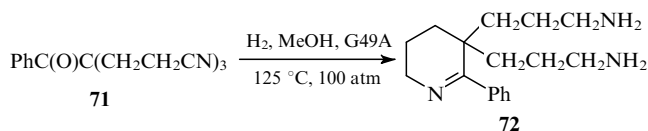
3. Synthesis from nitriles

Nitriles containing functional groups such as carbonyl or alkoxy-carbonyl groups, halogen atoms or a multiple bond in their molecules are convenient starting compounds for the synthesis of Δ^1 -piperideines. The reduction of oxo nitriles **69** over Raney nickel in ethanol or methanol results in the formation of compound **70** as a mixture of equal amounts of enantiomers in 65% and 83% total yield, respectively.

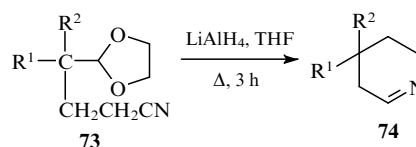


R = Me, Et.

During hydrogenation of trinitrile **71** in the presence of the G49A catalyst (manufactured by Gierdler company), all the three nitrile groups are reduced to CH_2NH_2 ; after that, cyclisation giving a tetrahydropyridine nucleus occurs. The reaction affords 3,3-bis(2-aminopropyl)-2-phenyl- Δ^1 -piperideine **72** (yield 22%).⁷²

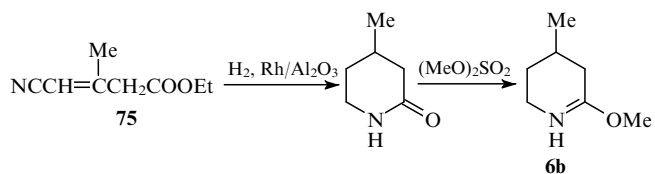


Compounds **74** have been synthesised by reductive cyclisation of acetals or ketals **73** on treatment with lithium aluminium hydride in boiling THF. The piperideine **74** [$\text{R}^1-\text{R}^2 = (\text{CH}_2)_5$] was patented as a repellent.^{85,86}



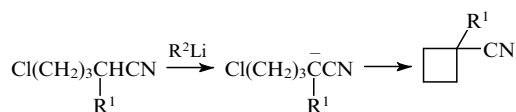
$\text{R}^1-\text{R}^2 = (\text{CH}_2)_2\text{CH}=\text{CHCH}_2$, $\text{CH}(\text{Me})\text{CH}_2\text{CH}=\text{CHCH}_2$, $(\text{CH}_2)_5$, $(\text{CH}_2)_6$, $(\text{CH}_2)_{10}$, $(\text{CH}_2)_3\text{CH}(\text{OH})\text{CH}_2$, $(\text{CH}_2)_2\text{C}(\text{Me})=\text{C}(\text{Me})\text{CH}_2$; $\text{R}^1, \text{R}^2 = \text{H, Me, Et, Pr, Ph, CH}(\text{Me})\text{Et, C}_9\text{H}_{19}, \text{cyclo-C}_5\text{H}_9$.

2-Methoxy-4-methyl-3,4,5,6-tetrahydropyridine **6b** has been prepared by reductive cyclisation of nitrile **75** on a rhodium catalyst followed by treatment of the resulting 4-methylpiperidin-2-one with dimethyl sulfate.⁸⁷

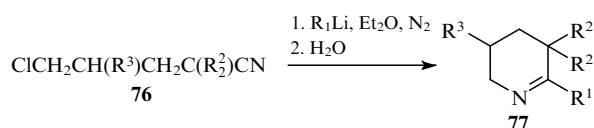


Cyclisation of 5-halo-substituted nitriles induced by organo-metallic compounds is used quite often to synthesise Δ^1 -piperideines.

French investigators⁸⁸ established that the transformation of 5-chloro-substituted nitriles into the corresponding Δ^1 -piperidines on treatment with lithium reagents occurs successfully only when no hydrogen atoms are present in the α -position relative to the nitrile group. Otherwise, the reaction results in the formation of cyclobutane derivatives.

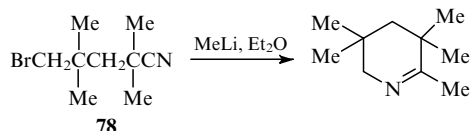


The reaction of nitriles **76** with organolithium compounds was carried out in ether under an inert atmosphere for 0.5 h at 0–5 °C and then for 4 h at 20 °C (in the case of phenyllithium, the reaction mixture should be refluxed for 4 h). After hydrolysis, compounds **77** were isolated in 48%–93% yields.⁸⁸

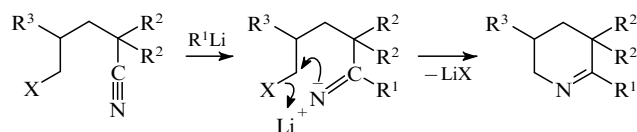


$\text{R}^1 = \text{Me, Bu, Ph}$; $\text{R}^2 = \text{Me}_2, (\text{CH}_2)_5$; $\text{R}^3 = \text{H, Me}$.

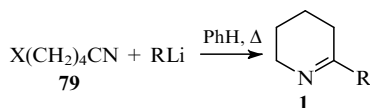
2,3,3,5,5-Pentamethyl- Δ^1 -piperidine was also synthesised from bromo-derivative **78** and methylolithium (yield 84%).⁸⁸



The following scheme was proposed⁸⁸ for the formation of Δ^1 -piperidines from 5-halo-substituted nitriles:

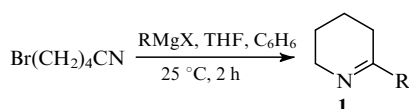


When studying cyclisation of 5-halo-substituted nitriles **79** induced by organolithium compounds on refluxing in benzene, Gallulo *et al.*⁸⁹ found that with bromo-substituted nitriles **79** the reaction time is shorter and the yields of the piperidines **1** are higher than those attained with chloro-derivatives. In another study,⁹⁰ the piperidine **1** ($\text{R} = \text{Ph}$) was prepared in 37% yield in a similar way by refluxing 5-chloropentanenitrile and PhLi in an Et_2O –cyclohexane mixture.



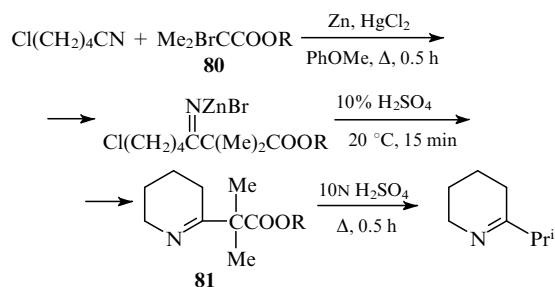
$\text{X} = \text{Cl, Br}$; $\text{R} = \text{Bu, Ph, Me}$.

The reaction of 5-bromopentanenitrile with Grignard reagents in a THF– C_6H_6 mixture affords the corresponding Δ^1 -piperidines **1** in good yields.⁹¹



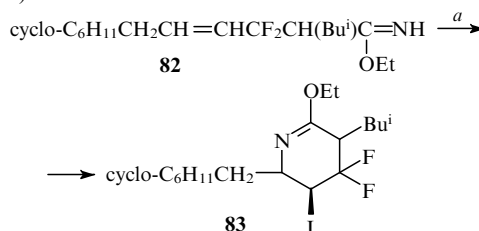
$\text{X} = \text{Cl, Br}$; $\text{R} = \text{Bu}$ (75%), Ph (85%), Bu^i (58%), PhCH_2 (64%), Me (34%), Pr^n (84%).

The modified Favorsky reaction between 5-chloropentanenitrile and brominated esters **80** was used to prepare alkyl 2-(3,4,5,6-tetrahydropyridin-2-yl)-2-methylpropanoates **81**. On boiling in sulfuric acid, these products are hydrolysed with decarboxylation to give 2-isopropyl-3,4,5,6-tetrahydropyridine.⁹²



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

Imide **82**, prepared from the corresponding nitrile, cyclises in the presence of iodine and 4,4'-thiobis(2-*tert*-butyl-6-methylphenol) (TBP) in the dark giving rise to Δ^1 -piperidine **83** (yield 83%).⁹³

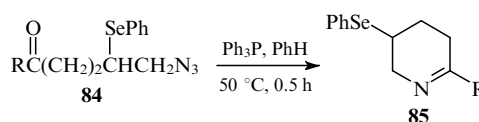


(a) I_2 , TBP, NaHCO_3 , CH_2Cl_2 , H_2O , 25 °C, 24 h.

The rates of cyclisation in the CH_2Cl_2 – H_2O and CHCl_3 – H_2O biphasic systems are higher than that in the CCl_4 – H_2O system; the lowest reaction rates were observed in THF and MeCN. The compound **83** is produced in 75%–80% yield upon ultrasonic treatment of the imide **82** in a nonaqueous medium (Bransonic 221 bath).⁹³

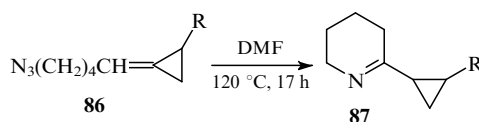
4. Synthesis from azides

When selenium-substituted azido ketones **84** are heated with triphenylphosphine in benzene, they cyclise to give the corresponding 2,5-disubstituted Δ^1 -piperidines **85**.⁹⁴



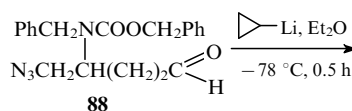
$\text{R} = \text{Me}$ (74%), Ph (83%), 2-thienyl (67%).

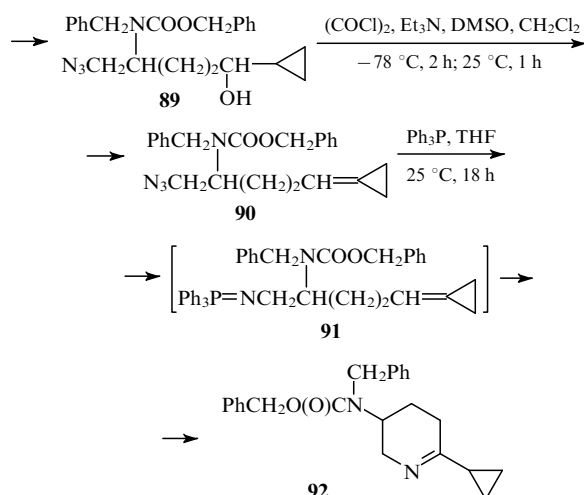
Δ^1 -Piperidines containing a cyclopropane ring at the 2-position are prepared by cyclisation of methylenecyclopropane azides. Heating of azides **86** in DMF affords cyclopropane-substituted piperidines **87** (yield ~60%).⁹⁵



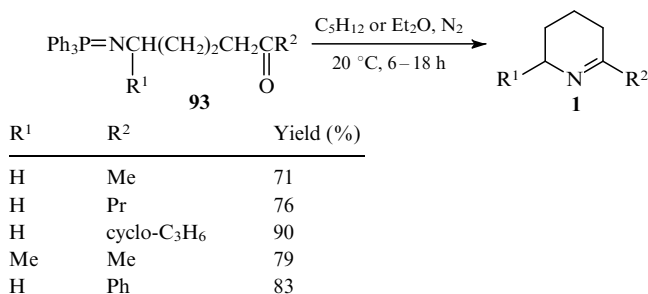
$\text{R} = \text{H, Me}$ (a 3 : 1 mixture of isomers).

To synthesise compound **92**, the starting compound in the synthesis of the alkaloid (–)-8*a*-*epi*-desacetoxyslaframine, azide **88** was made to react with cyclopropyllithium, and the resulting alcohol **89** (yield 89%) was converted into methylenecyclopropane azide **90** (yield 85%) by treatment with oxalyl chloride in the presence of triethylamine. Cyclisation of the azide was induced by triphenylphosphine. The reaction proceeds *via* unstable ylide **91**.⁹⁵

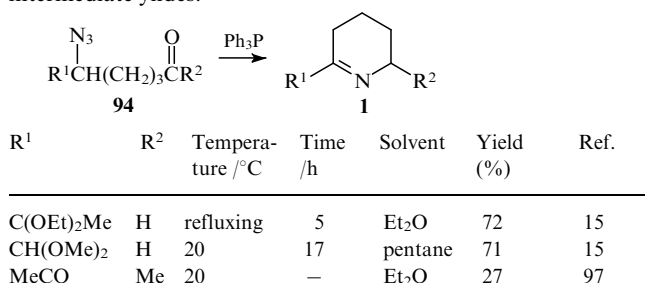




The intramolecular Wittig aza reaction has been used⁹⁶ in the synthesis of several Δ^1 -piperideines **1** from oxo ylides **93**.

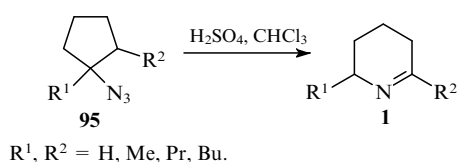


The Δ^1 -piperideines **1** were synthesised by the reaction of δ -azido ketones **94**, containing one more carbonyl group (either free or as acetal), with triphenylphosphine without isolation of the intermediate ylides.^{15, 97}

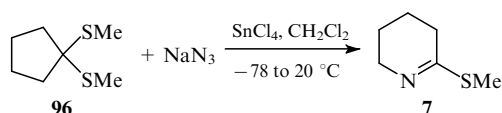


5. Synthesis by recyclisation reactions

1-Azido-1-alkylcyclopentanes **95** recyclise on treatment with sulfuric acid in chloroform to give the cyclic imines **1** in good yields.⁹⁸

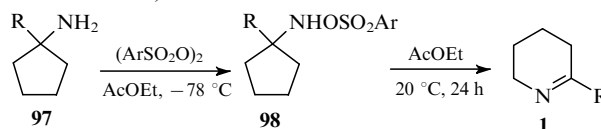


1,1-Bis(methylthio)cyclopentane **96** reacts with sodium azide in the presence of tin chloride giving 2-methylthio-3,4,5,6-tetrahydropyridine **7** in 95% yield.⁹⁰



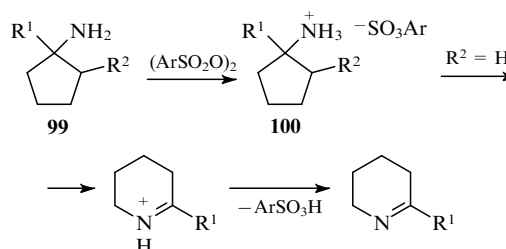
When L-proline is heated with monosaccharides or aldehydes of the furan series for 1.5 h at 150 °C, the corresponding Δ^1 -piperideines are produced.¹⁰⁰

Recyclisation of aminocyclopentane derivatives **98**, formed in the reaction of amines **97** with arylsulfonyl peroxides, occurs at room temperature to give 2,6-disubstituted- Δ^1 -piperideines **1** (yields 43%–79%).¹⁰¹

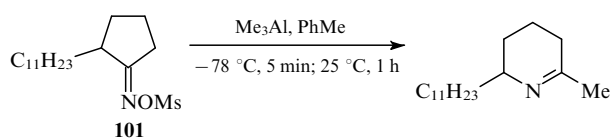


R = Me, Bu, PhCH₂; Ar = 3-F₃CC₆H₄, 4-O₂NC₆H₄.

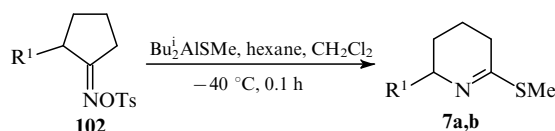
If the compound **97** contains a substituent at the 2-position, recyclisation does not occur. This fact was explained¹⁰¹ by assuming that salts **100**, formed from amines **99** in the first stage of the process, are unable to recyclise if R² ≠ H.



On treatment with trimethylaluminium, 2-undecylcyclopentanone oxime mesylate **101** is converted into 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine in 54%–57% yield.^{102, 103}

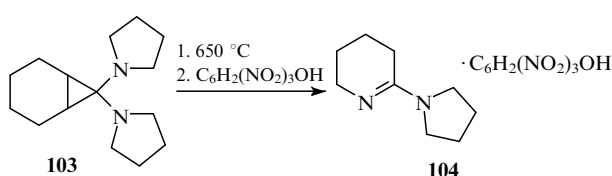


Transformation of oxime tosylates **102** into Δ^1 -piperideines **7a,b** was attained by heating these substrates in the presence of diisobutyl(methylthio)aluminium.¹⁰³

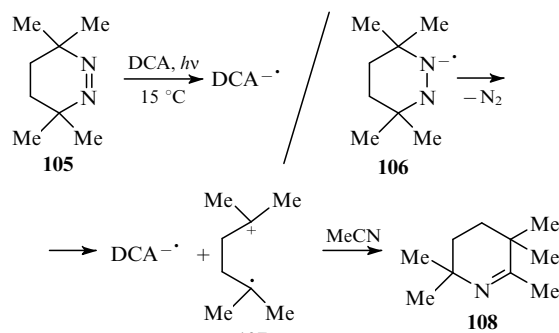


R = H (**a**, 5%), Me (**b**, 46%).

2-(Pyrrolidin-1-yl)-3,3,5,6-tetrahydropyridine picrate **104** was obtained in 88% yield by the pyrolysis of 7,7-bis(pyrrolidin-1-yl)bicyclo[4.1.0]heptane **103** followed by treatment of the reaction product with picric acid.¹⁰⁴



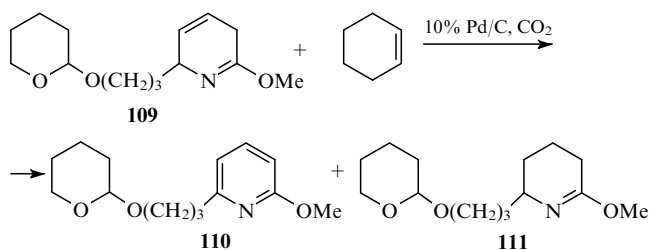
Exposure of 3,3,3,6-tetramethyl-1,2-diazacyclohex-1-ene **105** to radiation ($\lambda = 420$ nm) in the presence of 9,10-dicyanoanthracene in acetonitrile gives 2,3,3,6,6-pentamethyl- Δ^1 -piperideine **108** in 75% yield. Evidently, this reaction occurs *via* the successive formation of radical anion **106** and radical cation **107**.¹⁰⁵



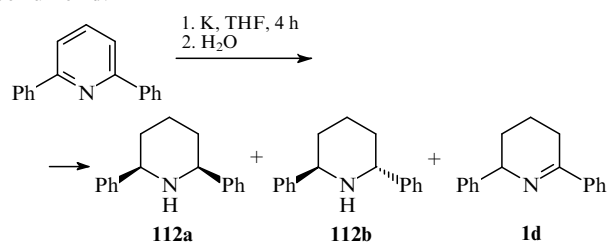
DCA is 9,10-dicyanoanthracene.

6. Other methods

To synthesise the substituted piperidine **111** from the 2,5-dihydropyridine derivative **109**, the modified Zelinsky method of irreversible catalysis has been used.¹⁰⁶ In the presence of Pd/C under an inert atmosphere, the compound **109** undergoes an exothermic reaction with cyclohexene giving a mixture of the pyridine derivative **110** (yield 68.4%) and the piperidine derivative **111** (yield 10.6%).

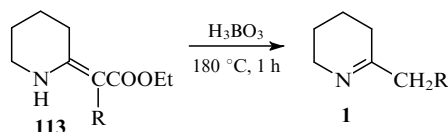


The reaction of 2,6-diphenylpyridine with metallic potassium gives rise to a mixture of *cis*-2,6-diphenylpiperidine **112a**, *trans*-2,6-diphenylpiperidine **112b** and 2,6-diphenyl-3,4,5,6-tetrahydropyridine **1d**.¹⁰⁷



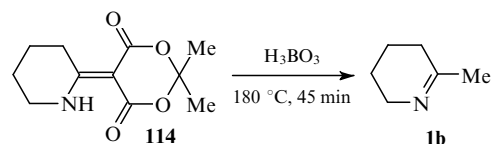
At 25 °C, the compounds **112** are the main reaction products (total yield 34%, **112a**:**112b** ratio ~1:2), while the imine **1d** is formed in 11% yield. At -75 °C, the yield of **1d** increases to 31%, while the compounds **112** are formed in 21% yield (the **112a**:**112b** ratio is ~1.5:1).¹⁰⁷

When substituted piperideines **113** are heated with boric acid, hydrolysis of the ester group, decarboxylation and subsequent isomerisation with double bond migration occur to give the Δ^1 -piperideines **1** in good yields.^{10, 108}

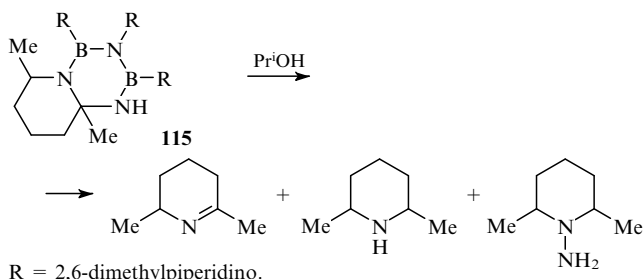


R = H (70%), Me (65%), PhCH₂ (70%), CH₂=CH(CH₂)₈ (70%), Me(CH₂)₉ (80%).

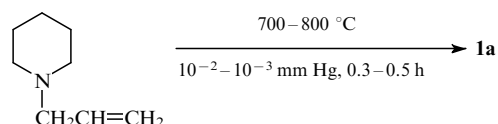
Under the same conditions, compound **114** is converted into 2-methyl-3,4,5,6-tetrahydropyridine **1b** in a yield of only 47%.¹⁰⁹



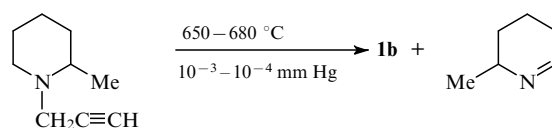
The reaction of compound **115** with isopropyl alcohol gives 2,6-dimethyl-3,4,5,6-tetrahydropyridine, in addition to the piperidine derivatives.¹¹⁰



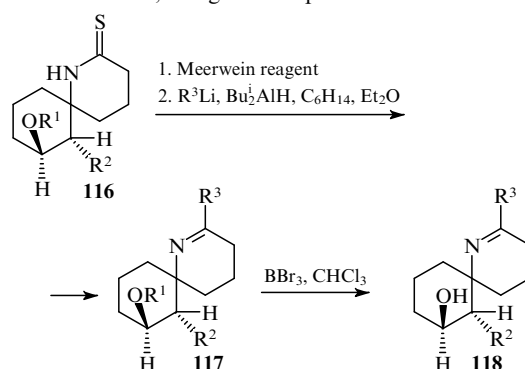
Under conditions of vacuum flash pyrolysis, *N*-allylpiperidine is converted into 2,3,4,5-tetrahydropyridine **1a**.¹¹¹



Under similar conditions, 2-methyl-1-(propyn-3-yl)piperidine is converted into a mixture of the imine **1b** and 2-methyl-2,3,4,5-tetrahydropyridine (quantitative yield; ratio 5:1). The imine **1b** was isolated in a pure state in 54% yield using preparative TLC.¹¹²

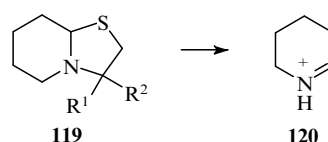


On treatment with the Meerwein reagent, spiro compounds **116** (R' = tetrahydropyran-2-yl) are converted into thioimides, which react with organolithium compounds in the presence of diisobutylaluminium hydride giving 1-azaspiro[5.5]undec-1-ene derivatives **117**. The protection of the hydroxyl group is removed by boron bromide; this gives compounds **118**.^{113, 114}



R¹, R², R³ = C₅H₁₁, Prⁱ, Buⁿ; CH₂=CH(CH₂)₃, tetrahydropyran-2-yl, CH₂=CH(CH₂)₂.

It was found that fragmentation of bicyclic compounds **119** under the action of the electron impact yields cation **120**.¹¹⁵

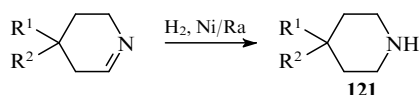


IV. Reactions of Δ^1 -piperideines

1. Reduction

Addition of hydrogen to the double bonds of Δ^1 -piperideine can be attained by catalytic hydrogenation and also by other reduction techniques.

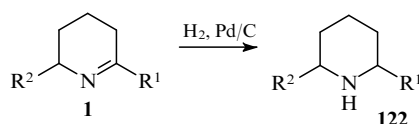
The addition of hydrogen to the C=N bond in 4,4-disubstituted Δ^1 -piperideines in the presence of the Raney nickel (2–8 atm; 2 h) gives piperidine derivatives **121**.⁸⁵



$R^1-R^2 = (CH_2)_5$ (90%), $CH_2CH=CH(CH_2)_2$, $CH(Me)CH_2CH=CHCH_2$, $(CH_2)_6$, $(CH_2)_{10}$, $CH_2O(CH_2)_3$, $CH_2C(Me)C=C(Me)(CH_2)_2$, $CH_2CH(OH)(CH_2)_3$;
 $R^1, R^2 = H, Me, Et, Pr, Ph, Bu, C_9H_{19}, cyclo-C_5H_9$.

2,6,6-Trimethyl-3,4,5,6-tetrahydropyridine was converted into 2,6,6-trimethylpiperidine (yield 87%) by hydrogenation over the Raney nickel at 80 °C and 100 atm.³³

2,6-Disubstituted Δ^1 -piperideines **1** are hydrogenated to the corresponding piperidine derivatives **122** in the presence of palladium supported on carbon.⁹⁸

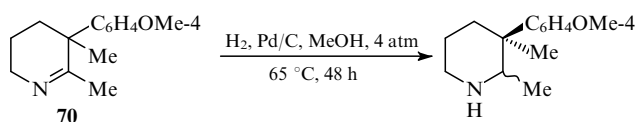


$R^1, R^2 = H, Me, Pr, Bu, Ph$.

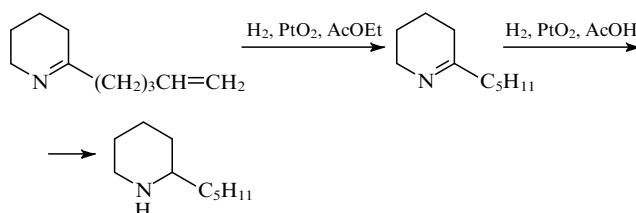
2,6-Dimethyl-3,4,5,6-tetrahydropyridine is hydrogenated over Pd/C in the presence of 10% hydrochloric acid over a period of 35 h to give 2,6-dimethylpiperidine in 74.5% yield.⁵⁵

The heat of hydrogenation of the piperideine trimer to piperidine over Pd/C was found to be $-30.2 \pm 0.5 \text{ kcal mol}^{-1}$; this value was used to estimate the enthalpy of hydrogenation of monomeric piperideine **1a**, $\Delta H^0 = -20.8 \text{ kcal mol}^{-1}$.¹¹⁶

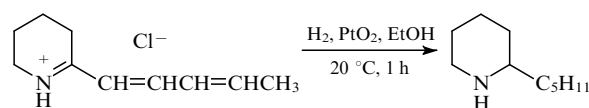
Hydrogenation of 2,3-dimethyl-3-(4-methoxyphenyl)- Δ^1 -piperideine **70** over Pd/C in methanol affords equal amounts of diastereoisomeric 2,3-dimethyl-3-(4-methoxyphenyl)piperidines.⁸⁴



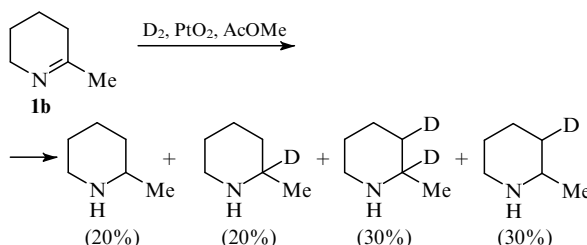
Stepwise hydrogenation of 2-(pent-4-en-1-yl)-3,4,5,6-tetrahydropyridine to 2-pentylpiperidine has been reported.⁵⁴ Hydrogenation was carried out in the presence of PtO_2 . In the first stage, a hydrogen molecule adds to the double bond of the substituent to give 2-pentyl-3,4,5,6-tetrahydropyridine, which is subsequently converted into 2-pentylpiperidine by hydrogenation over PtO_2 in acetic acid.



During hydrogenation of 2-(penta-1,3-dien-1-yl)-3,4,5,6-tetrahydropyridine over PtO_2 in ethanol at room temperature and atmospheric pressure, hydrogen adds to the three double bonds, and 2-pentylpiperidine is formed.¹¹⁷



Catalytic deuteration of 2-methyl-3,4,5,6-tetrahydropyridine **1b** was carried out over PtO_2 in methyl acetate. This yielded a complex mixture of products with different deuterium contents.¹¹⁷

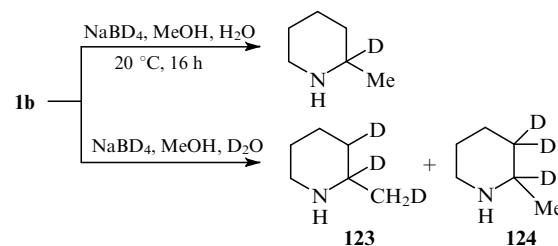


The last two compounds result presumably from deuteration of 6-methyl-3,4,5,6-tetrahydropyridine, a tautomer of the imine **1b**.¹¹⁸

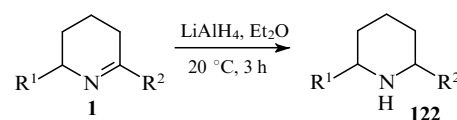
Most often, Δ^1 -piperideines are reduced by complex metal hydrides, lithium aluminium hydride or sodium borohydride.

Treatment of the imine **1b** with $NaBD_4$ in aqueous methanol gives 2-deuterio-2-methylpiperidine in 80% yield.¹¹⁸

If the reaction of the imine **1b** with $NaBD_4$ is carried out in the presence of D_2O , a mixture of deuterated compounds, **123** and **124**, is produced.¹¹⁷

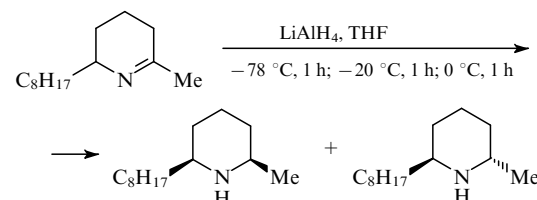


Reduction of the Δ^1 -piperideines **1** to the corresponding piperidine derivatives **122** has been attained by treatment with lithium aluminium hydride in ether at room temperature.⁵⁹

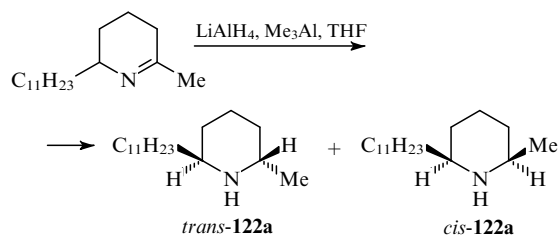


$R^1, R^2 = H, Me, C_{11}H_{23}, PhCH_2$.

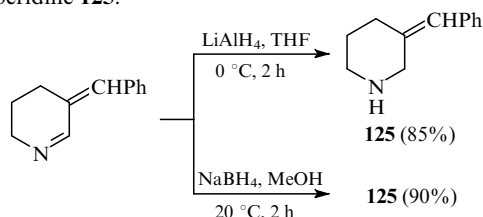
2-Methyl-6-octyl-3,4,5,6-tetrahydropyridine is reduced by lithium aluminium hydride in THF at -78 to 0 °C giving rise to a mixture of *cis*- and *trans*-isomers of the corresponding piperidine in 5 : 7 ratio; their overall yield is 70%.^{57, 58}



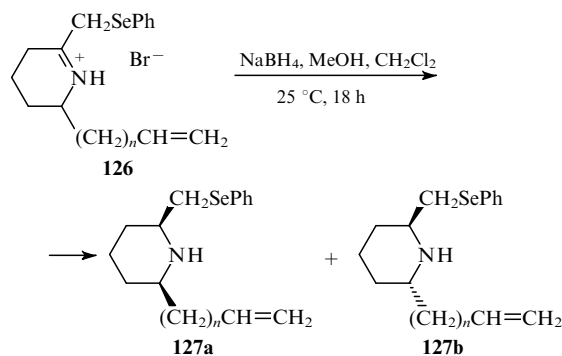
On treatment with lithium aluminium hydride and trimethylaluminium in hexane, 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine is reduced to give 2-methyl-6-undecylpiperidine [alkaloid ($\pm$)-solenopsine] as a mixture of diastereoisomers *trans*-**122a** and *cis*-**122a** in 95 : 5 ratio.^{57, 58, 119}



When the benzylidene derivative of piperidine is treated with lithium aluminium hydride in ether or with sodium borohydride in methanol, only the C=N bond is reduced to give 3-benzylidene-piperidine **125**.¹²⁰



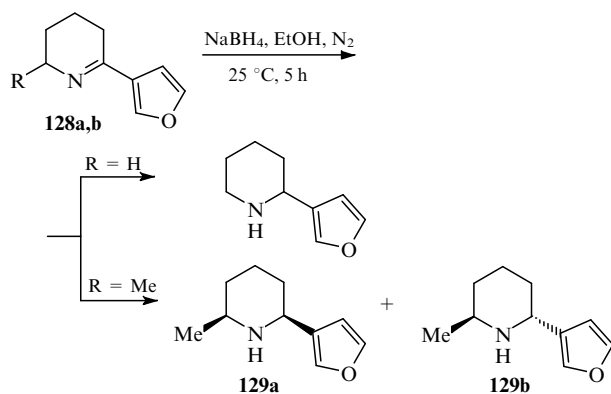
The reduction of compounds **126** by sodium borohydride occurs regioselectively, only the intracyclic bond being involved in the reaction. This affords a mixture of diastereoisomeric piperidines in which the *cis*-isomers **127a** predominates.⁸²



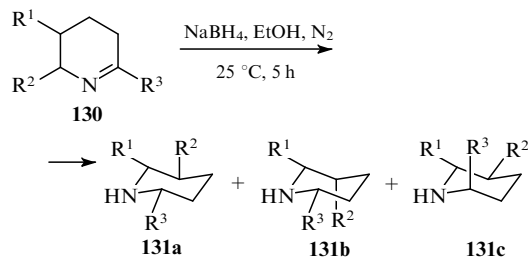
$n = 3, 4$.

The reduction of Δ^1 -piperidine **70** with sodium borohydride in methanol gives rise to a mixture of diastereoisomers of 2,3-dimethyl-3-(4-methoxyphenyl)piperidine (yield 70%).⁸³

The reduction of Δ^1 -piperidines **128a,b**, containing a furyl substituent at the 2-position, has been studied.¹²¹ The compound **128a** is converted into one reaction product, while the imine **128b** gives two isomeric products, **129a** and **129b**, in 91:9 ratio. Piperidine **130** is reduced by sodium borohydride yielding three isomeric piperidines [ratio **131a** : (**131b** + **131c**) = 85:15].

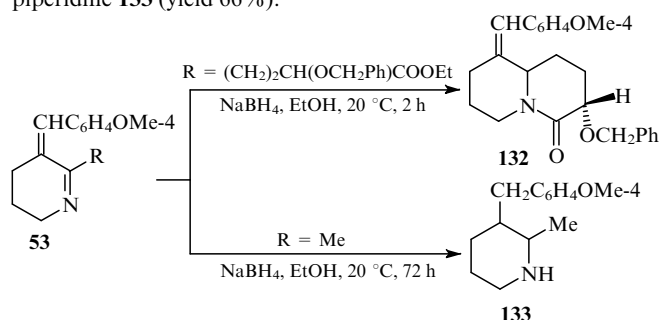


R = H (**128a**), Me (**128b**).

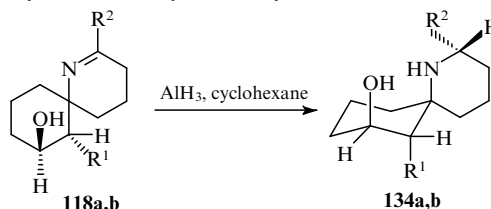


$R^1 = Me_2C=CHCH_2$, $R^2 = Me$, $R^3 = 3\text{-furyl}$.

The structure of the products of reduction of the compounds **53**, containing an intracyclic C=N bond and an exocyclic C=C bond at the 3-position, depends on the nature of the substituent. When $R = (CH_2)_2CH(OCH_2Ph)COOEt$, reduction of the C=N bond and subsequent cyclisation occur over a period of 2 h to give bicyclic derivative **132** (yield 70%). When $R = Me$, both double bonds are reduced over a period of 72 h affording substituted piperidine **133** (yield 66%).⁶⁹

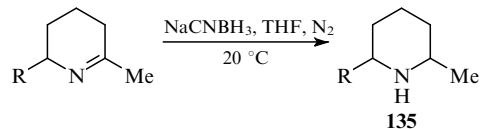


Alkaloids of the nicotoin group have been prepared by selective hydrogenation of the C=N bond in the Δ^1 -piperidines **118** by aluminium hydride in cyclohexane.^{113, 114}



$R^1 = Bu$, $R^2 = C_5H_{11}$ (**a**);
 $R^1 = (CH_2)_2CH=CH_2$, $R^2 = (CH_2)_3CH=CH_2$ (**b**).

6-Alkyl-2-methyl-3,4,5,6-tetrahydropyridines are reduced on treatment with sodium cyanoborohydride in THF in a citrate-phosphate buffer solution to give piperidines **135** in high yields.⁷⁴



R = Pr (81%), $C_{11}H_{23}$ (95%), $(MeO)_2CH(CH_2)_3$ (82%).

Study of the reduction of 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine by various reducing reagents and solvents has demonstrated that, depending on the reaction conditions, the ratio of the resulting *cis*- and *trans*-2-methyl-6-undecylpiperidines varies from 99:1 to 5:95. The results are summarised in Table 1.¹⁰²

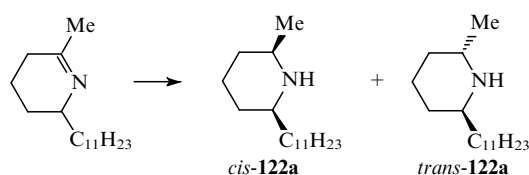
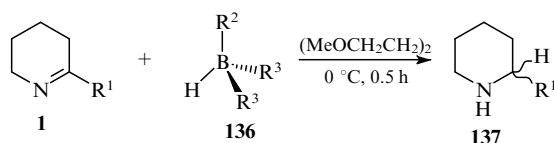


Table 1. Reduction of 2-methyl-6-undecyl-3,4,5,6-tetrahydropyridine.¹⁰²

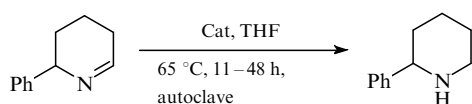
Reducing agent	Solvent	Ratio <i>cis</i> - 122a : <i>trans</i> - 122a
Bu ₂ AlH	CH ₂ Cl ₂	99 : 1
LiAlH ₄ –NaOMe	THF	99 : 1
NaCNBH ₃ –HCl	MeOH	98 : 2
LiAlH ₄ –Ti(OPr ⁱ) ₄	THF	90 : 10
BuLi–Bu ₂ AlH	Et ₂ O	83 : 17
LiAlH ₄ –LiCl	THF	80 : 20
LiAlH ₄ –NiCl ₂	THF	75 : 25
LiAlH ₄ –TiCl ₃	THF	67 : 33
LiAlH ₄	CH ₂ Cl ₂ (THF)	67 : 33
LiAlH ₄	Et ₂ O	20 : 80
Mg(AlH ₄) ₂	Et ₂ O	33 : 67
LiAlH ₄ –BF ₃ ·Et ₂ O	Et ₂ O	33 : 67
LiAlH ₄ –Bu ₃ Al	THF	6 : 94
LiAlH ₄ –Me ₃ Al	MeO(CH ₂) ₂ OMe	6 : 94
LiAlH ₄ –Me ₃ Al	THF	5 : 95
LiAlH ₄ –TiCl ₄	THF	25 : 75
LiAlH ₄ –Me ₃ Al	Et ₂ O	13 : 87

When 2-alkyl-Δ¹-piperideines react with lithium alkyl(or phenyl)bis(isopinocampyl)borates **136**, compounds **137** of the (+)-(*S*)- or (–)-(*R*)-series are formed, depending on the stereochemistry of the substituent R³ in the borate.³⁰ The results obtained are listed in Table 2.

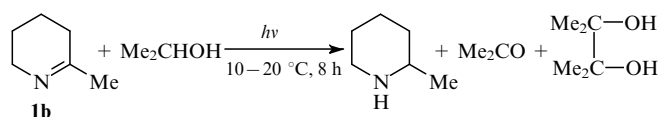
**Table 2.** Hydroboration of Δ¹-piperideines.

R ¹	R ²	R ³	Isomer [<i>ee</i> (%)]	Yield (%)
Me	Bu		<i>R</i> (25)	37
Me	Ph		<i>R</i> (10)	32
Et	Bu		<i>R</i> (5)	48
Pr	Bu		<i>R</i> (4)	75
Pr	Me		<i>R</i> (11)	82
Me	Bu		<i>S</i> (22)	32
Me	Ph		<i>S</i> (10)	30

Catalytic hydrogenation of 2-phenyl-3,4,5,6-tetrahydropyridine is highly enantioselective. The catalyst was prepared by treating (*R,R*)-ethylene-1,2-bis(η⁵-4,5,6,7-tetrahydroinden-1-yl)-titanium-(*R*)-1,1'-bisnaphthalene-2,2'-diolate with butyllithium and phenylsilane. The *R*-isomer of 2-phenylpiperidine was obtained in 70%–81% yield with *ee* 95%–98%.^{90, 122, 123}



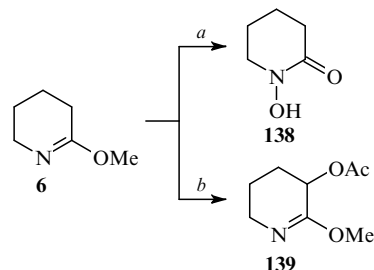
The irradiation of a mixture of 2-methyl-3,4,5,6-tetrahydropyridine **1b** and propan-2-ol with the light of a Hanovia-450W high-pressure mercury lamp through a quartz filter results in a redox process giving 2-methylpiperidine (yield 72%), acetone and the product of reductive dimerisation of acetone, 2,3-dimethylbutane-2,3-diol.¹²⁴



2. Oxidation

On treatment with 3-chloroperbenzoic acid at –60 °C, 2-methoxypiperidine **6** is oxidised to 1-hydroxypiperid-2-one **138** (yield 87%).¹²⁵

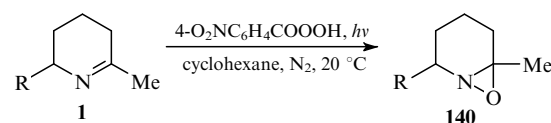
3-Acetoxy-2-methoxy-3,4,5,6-tetrahydropyridine **139** was obtained (yield 79%) upon oxidation of the imine **6** with lead tetraacetate in the presence of the polymer of 4-vinylpyridine.¹²⁶



(a) 3-ClC₆H₄COOH, CH₂Cl₂, –60 °C;

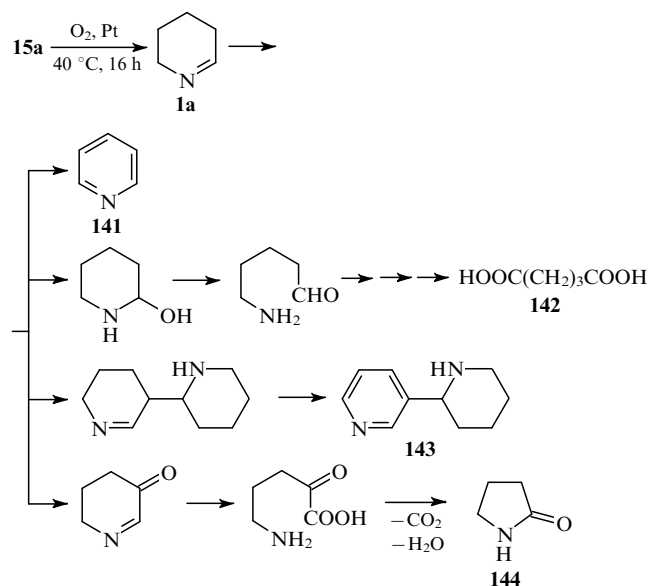
(b) Pb(OAc)₄, (N₂CH=CH₂)_n, THF, 20 °C, 2 h; 50 °C, 1 h.

1-Aza-7-oxabicyclo[4.1.0]heptanes **140** are formed in almost quantitative yields when the Δ¹-piperideines **1** are treated with 4-nitroperbenzoic acid on exposure to the light of a low-pressure mercury lamp (λ = 2537 Å) under an inert atmosphere.²⁹



R = H, Me.

Passing oxygen through the piperidine **15a** for 16 h at 40 °C in the presence of a platinum catalyst (according to Adams) affords 2,3,4,5-tetrahydropyridine **1a**, which is further oxidised to give a broad range of products, as shown in the scheme

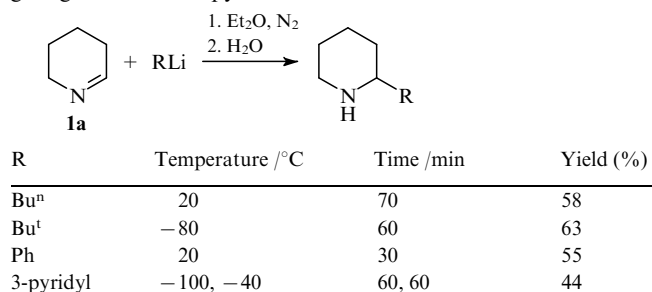


The following compounds were isolated from the oxidation products: piperidine (**1a**, 6%), pyridine (**141**, 8%), pentane-1,5-dioic acid (**142**, 10%), 3-(2-piperidyl)pyridine (**143**, 3%), pyrroli-

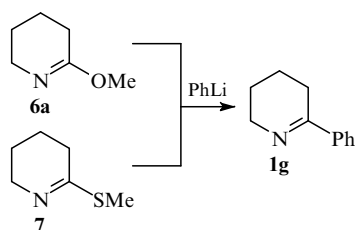
din-2-one (**144**, 7%), *N*-acetylpiperidine (8%) and *N*-formylpiperidine, resulting from acylation of piperidine with formic acid.¹²⁷

3. Reactions with organometallic compounds

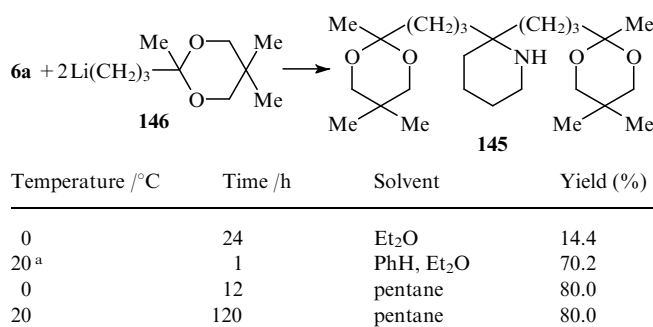
When unsubstituted piperidine **1a** is made to react with organolithium compounds, these reagents add to the C=N double bonds giving 2-substituted pyridine derivatives.³¹



The Δ^1 -piperidine **1g** is formed in 50% yield in the reaction of the imidate **6a** with phenyllithium or thioimide **7** with phenyllithium in the presence of diisobutylaluminium hydride.¹²¹

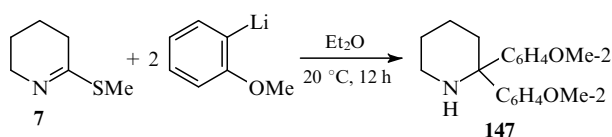


Piperidine derivative **145**, used as the initial compound in a total synthesis of the alkaloid ($\pm$)-porantherine, was prepared by the reaction of the imidate **6a** with two moles of organolithium derivative **146**; the yield of **145** varied over a wide range depending on the reaction conditions.¹²⁸

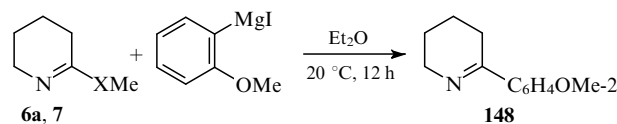


^a The reaction was carried out under argon.

2-Methylthio-3,4,5,6-tetrahydropyridine **7** reacts with 2-methoxyphenyllithium at room temperature to give the bisarylation product, 2,2-bis(2-methoxyphenyl)piperidine **147**, its yield being only 2%.¹²⁹

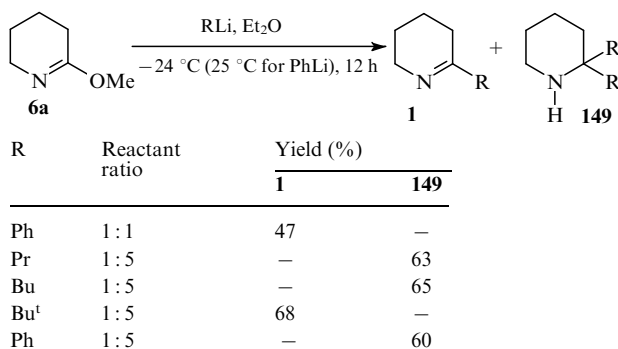


When the imidate **6a** and thioimide **7** react with one equivalent of 2-methoxyphenylmagnesium iodide under the same conditions, the monoarylation product, 2-(2-methoxyphenyl)-3,4,5,6-tetrahydropyridine **148**, is formed.¹²⁹

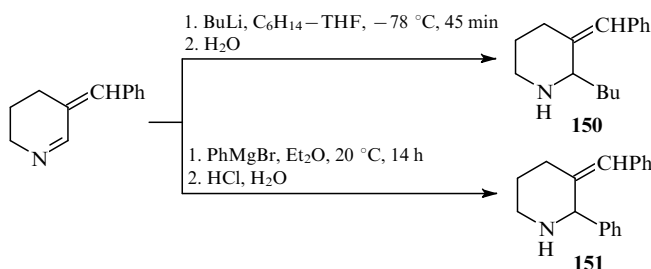


X = O (**6a**), S (**7**).

By varying the ratios of the reactants in the reaction of the imidate **6a** with organolithium compounds, one can synthesise selectively either only monosubstituted piperidines **1** or disubstituted piperidines **149**.¹³⁰

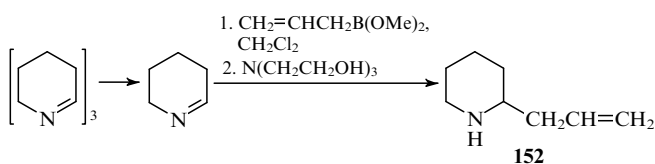


3-Benzylidene- Δ^1 -piperidine **124** was made to react with butyllithium or with phenylmagnesium bromide; after quenching of the reaction mixtures, the corresponding 2-substituted compounds **150** (yield 95%) or **151** (yield 56%) were isolated.¹²⁰



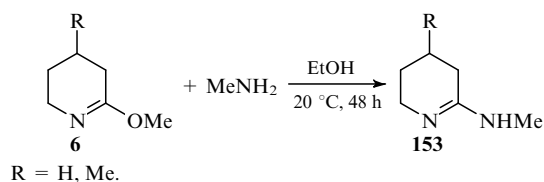
The reaction of 2-cyano-3,4,5,6-tetrahydropyridine with methylmagnesium iodide involves the C≡N bond and gives a mixture of 2-acetyl-3,4,5,6-tetrahydropyridine **10b** and 2-acetyl-1,2,3,4-tetrahydropyridine **10a** (ratio 4 : 1, total yield 44%).¹⁷

2-Allylpiperidine **152** has been prepared in 90% yield from the piperidine trimer and allyldimethoxyborane in the presence of triethanolamine.¹³¹



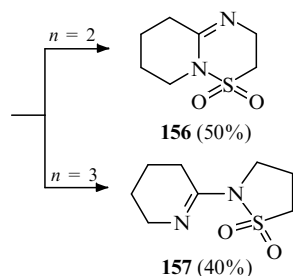
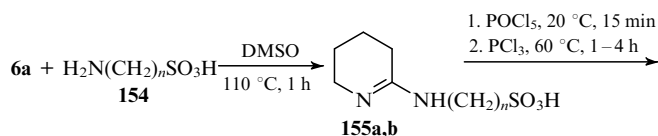
4. Reactions with amines and their derivatives

When the imidates **6** react with excess methylamine at room temperature, the methoxy group is substituted yielding amino-derivatives **153**.⁸⁷

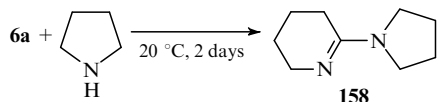


Treatment of 2-methoxy-3,4,5,6-tetrahydropyridine **6a** with diethylamine hydrochloride in methanol results in the formation of 2-dimethylamino-3,4,5,6-tetrahydropyridine.¹³²

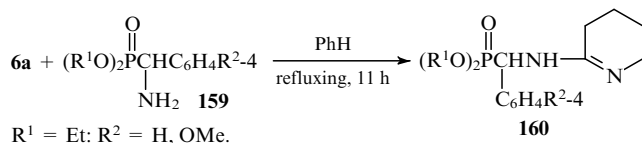
When the imide **6a** is heated with aminoalkanesulfonic acids **154** in DMSO, compounds **155a,b**, resulting from substitution of the methoxy group, are formed (yields 79% and 90%, respectively). On treatment with POCl_3 and PCl_5 , these products are converted into either bicyclic compound **156** or Δ^1 -piperidine **157**, depending on the number of methylene units in the initial amine.¹³³



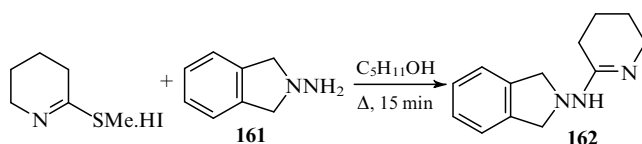
The imide **6a** reacts with pyrrolidine for 2 days at $20 ^\circ\text{C}$ to give 2-(pyrrolidin-1-yl)-3,4,5,6-tetrahydropyridine **158** in 94% yield.¹²⁰



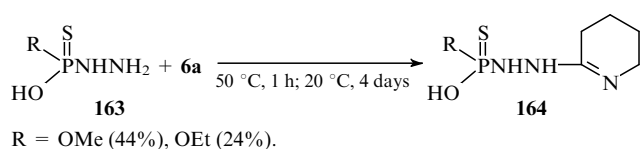
Refluxing of phosphorus-containing primary amines **159** with the imide **6a** in benzene gives rise to Δ^1 -piperidine **160**.¹³⁴



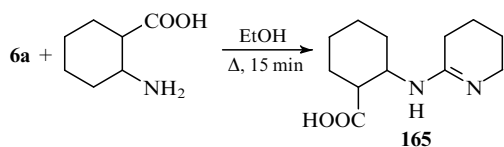
The reaction of 2-methylthiopiperidine hydroiodide with cyclic hydrazine derivative **161** in boiling pentyl alcohol yields compound **162**, which has been patented as a hypotensor.¹³⁵



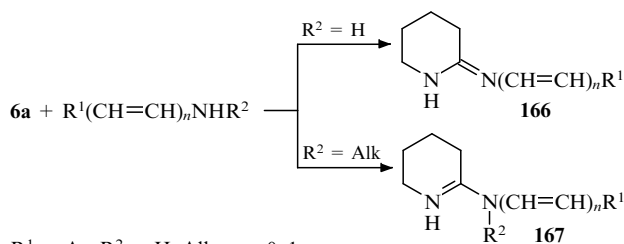
The reactions of the imide **6a** with *O*-alkyl phosphorothioic acid hydrazides **163** occur as substitution of the methoxy group by the hydrazide residue and give *N,N'*-disubstituted hydrazine derivatives **164**.¹³⁶



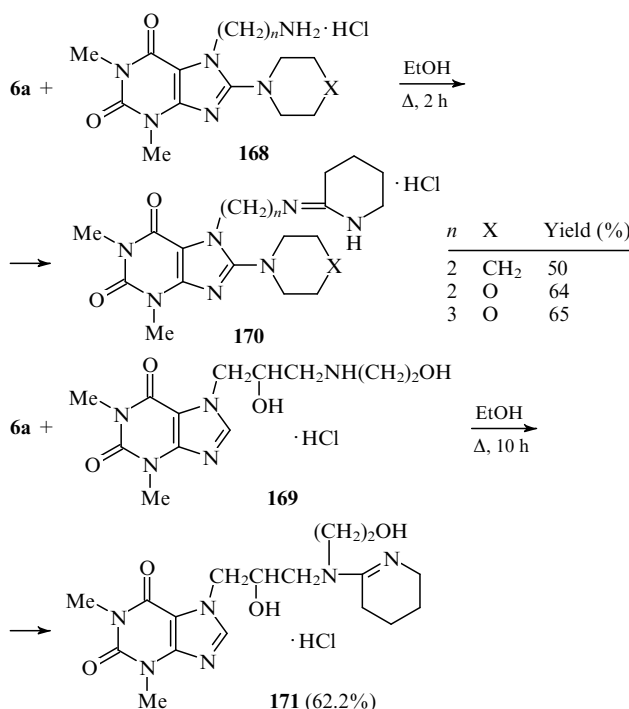
The reaction of the imide **6a** with *cis*-2-aminocyclohexane-carboxylic acid in boiling ethanol affords the product of substitution of the methoxy group **165** in 84% yield.¹³⁷



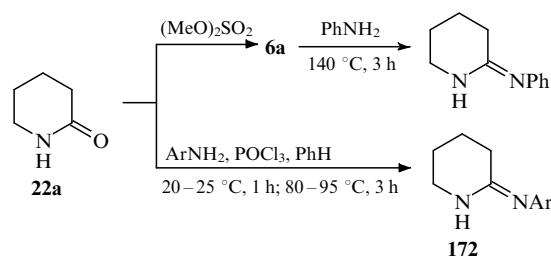
Compounds **166** and **167**, patented as animal growth stimulators, have been prepared by the reaction of the imide **6a** with primary or secondary amines.¹³⁸



On refluxing in ethanol, the imide **6a** reacts with hydrochlorides of primary (**168**) or secondary (**169**) amines being thus converted into compounds **170** or **171**.^{139, 140}

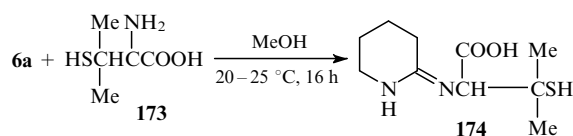


2-Phenyliminopiperidine has been synthesised from the lactone **22a**; first, the lactone was converted into the imide **6a** by treatment with dimethyl sulfoxide, and then the latter was made to condense with aniline. A large number of analogous aryliminopiperidines **172** were prepared directly from the lactone **22a** by its condensation with arylamines in the presence of POCl_3 .¹⁴¹

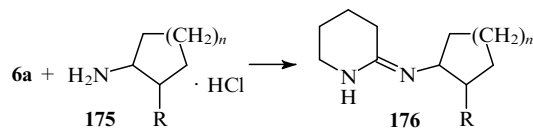


$\text{Ar} = 2\text{-ClC}_6\text{H}_4 \text{ (44.7\%)}, 4\text{-ClC}_6\text{H}_4 \text{ (50.9\%)}, 4\text{-BrC}_6\text{H}_4 \text{ (75.9\%)}, 4\text{-MeOC}_6\text{H}_4 \text{ (39.2\%)}, 2,4\text{-Cl}_2\text{C}_6\text{H}_3 \text{ (62.6\%)}, 3,4\text{-Cl}_2\text{C}_6\text{H}_3 \text{ (78.9\%)}, 3\text{-Cl-4-Me-C}_6\text{H}_3 \text{ (28.8\%)}, 3\text{-F}_3\text{CC}_6\text{H}_4 \text{ (63.2\%).}$

Penicillamine **173** reacts with the imide **6a** at room temperature to give Schiff's base **174** in 48% yield.¹⁴²

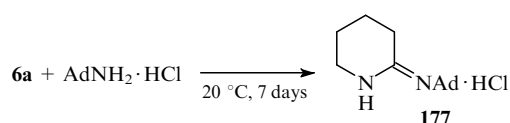


Piperidine derivatives **176** have been synthesised by the reaction of the imide **6a** with hydrochlorides of alicyclic amines **175**.¹⁴³



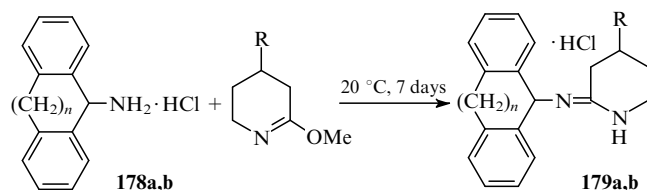
$n = 1-3$; $R = \text{Ph, 4-ClC}_6\text{H}_4, \text{cyclohexyl, 2-thienyl}$.

Adamantyliminopiperidine hydrochlorides **177**, which exhibit antiviral and antidiabetic activities, are produced by the reaction of the imide **6a** with adamantylamine hydrochlorides.^{144, 145}



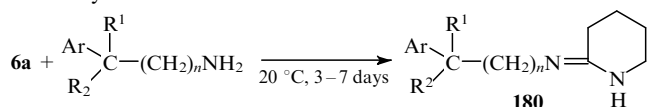
Ad is 1-adamantyl or 2-adamantyl.

The condensation of 9-aminofluorene (**178a**)^{146, 147} or 5-aminoindibenzocycloheptane (**178b**)^{147, 148} hydrochlorides with the Δ^1 -piperidines **6** gives compounds **179a,b**, possessing hypoglycemic,^{146, 147} antiphlogistic,^{147, 148} anticoagulant and diuretic¹⁴⁶⁻¹⁴⁸ properties.



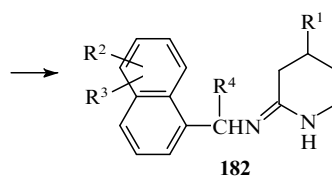
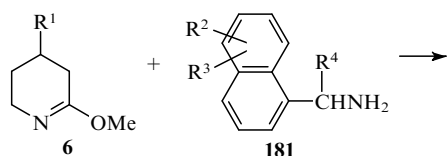
$n = 0$ (**a**), 2 (**b**); $R = \text{H, Bu}$.

Amidines **180**, which have been recommended as anticoagulants and diuretics^{147, 149-151} and also possess hypoglycemic activity^{152, 153} or are used in the synthesis of hypoglycemic preparations,¹⁴⁷ are obtained by the reaction of the imide **6a** with alkylaromatic amines.



$R^1 = \text{H, Pr}$; $R^2 = \text{Ph, 4-ClC}_6\text{H}_4, 3-\text{F}_3\text{CC}_6\text{H}_4, \text{cyclo-C}_3\text{H}_5$;
 $\text{Ar} = \text{Ph, 4-FC}_6\text{H}_4, 2-\text{ClC}_6\text{H}_4, 3-\text{ClC}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{Pr}^i\text{C}_6\text{H}_4,$
 $3-\text{F}_3\text{CC}_6\text{H}_4, 4-\text{F}_3\text{CC}_6\text{H}_4, 2-\text{MeOC}_6\text{H}_4, 3-\text{MeOC}_6\text{H}_4, 4-\text{MeOC}_6\text{H}_4,$
 $4-\text{BuOC}_6\text{H}_4, 4-\text{PhOC}_6\text{H}_4, 3,4-(\text{MeO})_2\text{C}_6\text{H}_3, 3,4,5-(\text{MeO})_3\text{C}_6\text{H}_2$;
 $n = 0, 1, 2$.

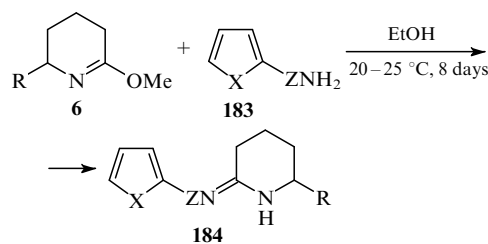
A series of piperidine derivatives **182** have been synthesised from the piperidines **6** and primary (1-naphthyl)alkylamines **181** or their hydrochlorides.¹⁵⁴



$R^1 = \text{H, Bu}^i$; $R^2 = \text{H}$; $R^3 = \text{H, 2-Me, 4-Cl, 4-F}$; $R^4 = 5-\text{Me, 8-Me}$; $R^4 = \text{H, Me, Pr}^i, \text{Bu}^n, \text{Ph, 2-MeC}_6\text{H}_4$.

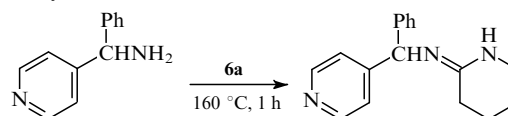
The compounds **182** exhibit hypoglycemic, diuretic and anti-coagulant activities.¹⁵⁴

Condensation of substituted imides with hydrochlorides of primary amines **183**, containing a furyl or a thienyl substituent, results in the synthesis of amidine hydrochlorides **184**, which possess hypoglycemic activity.^{38, 155}

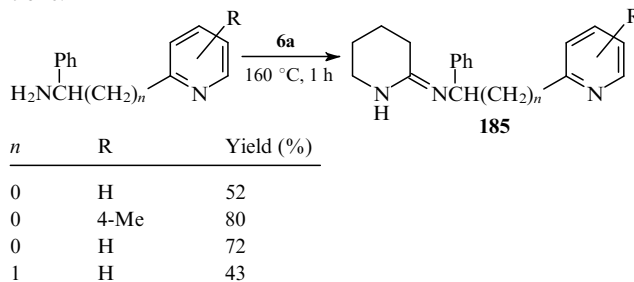


$X = \text{O, R} = \text{H, Z} = \text{CHCH}_2\text{Ph}$;
 $X = \text{S, R} = \text{H, Z} = \text{cyclo-C}_3\text{H}_5, \text{C(Me)Et}$;
 $X = \text{O, S, R} = \text{H, Me, Z} = \text{CH}_2, \text{CHPh, (CH}_2\text{)}_3, \text{CH}_2\text{CH(Et), cyclo-C}_3\text{H}_5, \text{CH}_2\text{CH(Me), CH(Me)CH}_2\text{CH}_2$.

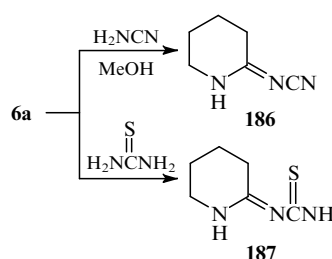
On heating without a solvent, α -(4-pyridyl)benzylamine reacts with the imide **6a** to give 2-[α -(4-pyridyl)benzylimino]piperidine in 48% yield.¹⁵⁶



Compounds **185** have been synthesised by the condensation of **6a** with the corresponding primary amines under similar conditions.¹⁵⁶



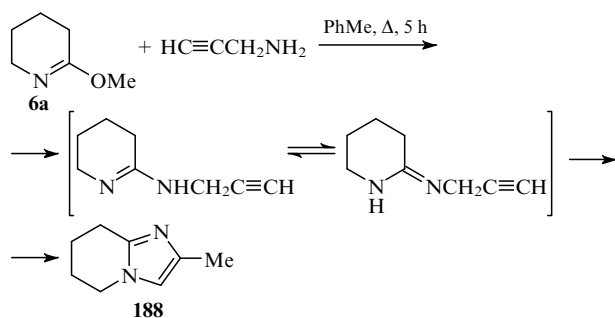
2-Cyanoiminopiperidine **186** has been prepared in 91% yield by the reaction of the imide **6a** with cyanamide at room temperature.¹⁵⁷ Piperidine derivative **187** is formed in 72% yield upon condensation of **6a** with thiourea.¹⁵⁸



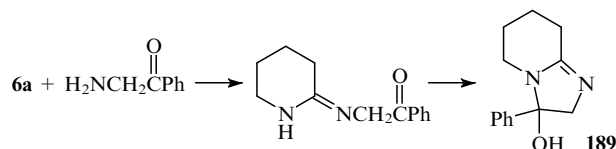
Compounds containing a primary amino group and a triple carbon-carbon bond or a carbonyl group at the 1- and 3-posi-

tions react with the imide **6a** with cyclisation giving five-membered heterocycles.

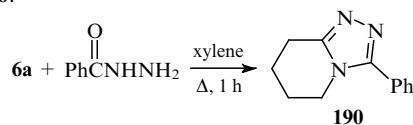
The product of condensation of the imide **6a** with prop-2-ynylamine, which exists as two tautomers, cyclises *in situ* to give 8-methyl-1,7-diazabicyclo[4.3.0]nona-6,8-diene **188** (yield 52%).¹⁵⁹



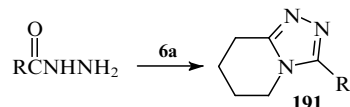
The product of condensation of **6a** and aminoacetophenone undergoes spontaneous cyclodehydration yielding bicyclic derivative of 2-imidazoline **189**.¹⁶⁰



Refluxing of benzoic acid hydrazide with the imide **6a** in xylene affords 9-phenyl-1,7,8-triazabicyclo[4.3.0]nona-6,8-diene **190**.¹⁶¹



Synthesis of 1,7,8-triazabicyclo[4.3.0]nona-6,8-diene derivatives **191** from acylhydrazides and the imide **6a** has been patented.^{162, 163}

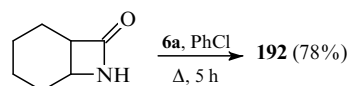
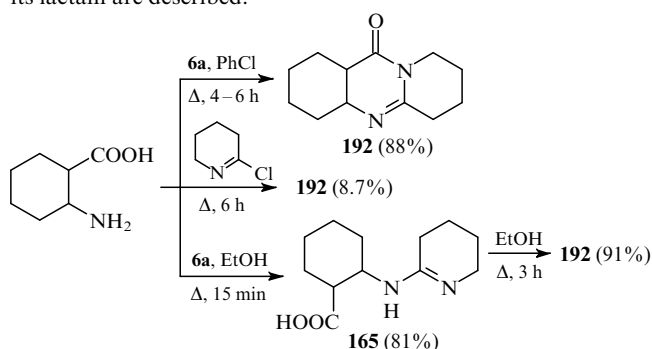


R = ArN(CH₂)_nN(X)_m; X = alkylene; n = 1–5.

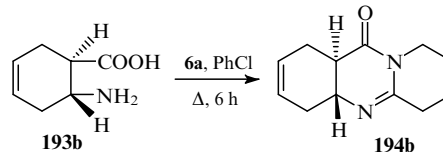
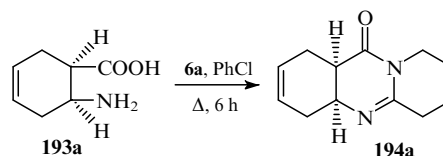
The compounds **191** are recommended as tranquilizers,¹⁶³ remedies against glaucoma^{162, 163} and schizophrenia.¹⁶²

Cyclocondensation of Δ¹-piperidine with compounds containing NH₂ (or NH) and carboxy (or alkoxy carbonyl, or nitrile) groups at neighbouring positions has been studied in detail. Polycyclic pyrimidine derivatives were synthesised in this way.

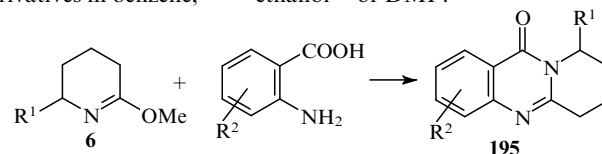
Thus heating of 2-aminocyclohexanecarboxylic acid with the imide **6a** in chlorobenzene gives 1,2,3,4,4a,6,7,8,9,11a-decahydropyrido[2,1-b]quinazolin-11-one **192** in 88% yield.¹³⁷ A similar reaction with 2-chloropiperidine affords the compound **192** in a yield of only 8.7%.¹⁶⁴ Several more methods for the synthesis of the compound **192** from 2-aminocyclohexanecarboxylic acid or its lactam are described.¹⁶⁴



The cyclocondensation of the imide **6a** with *cis*- and *trans*-2-aminocyclohex-4-enecarboxylic acids **193** occurs enantioselectively to give *cis*- and *trans*-1,4,4a,6,7,8,9,11a-octahydroquinazolin-11-ones **194a** and **194b**, respectively.¹⁶⁵

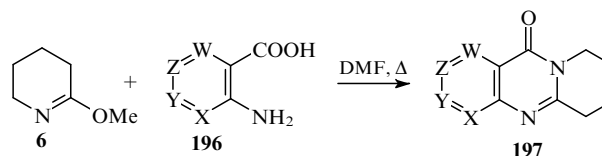


Tricyclic compounds **195** have been prepared in 64%–82% yields by heating the imides **6** with anthranilic acid or its derivatives in benzene,^{45, 166} ethanol⁴⁵ or DMF.⁴⁵



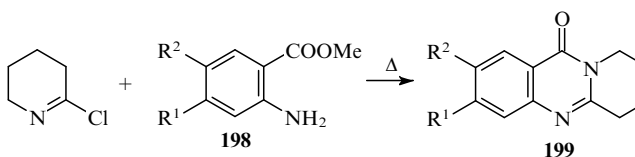
R¹ = H, Me; R² = H, 2-COOH, 2-COOEt.

Deoxyvasicinone analogues **197** have been prepared in relatively low yields by condensation of heterocyclic amino acids **196** with the imide **6a** in boiling DMF.¹⁶⁷



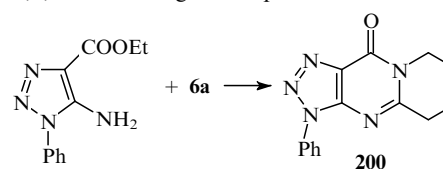
X	Y	Z	W	Time /min	Yield (%)
N	CH	CH	CH	10	12
CH	N	CH	CH	210	38
CH	CH	CH	N	150	20
N	CH	CH	N	120	12

The reaction of 2-chloro-3,4,5,6-tetrahydropyridine with methyl anthranilate derivatives **198** gives compounds **199**.^{45, 168}

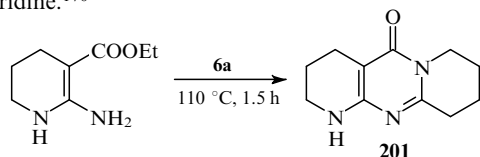


R ¹	R ²	Solvent	Time /h	Yield (%)	Ref.
H	COOMe	PhH	5	53	45
NO ₂	H	dioxane	1	94	168

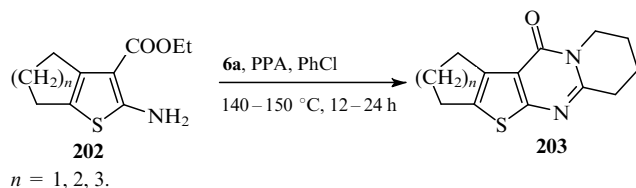
The imide **6a** reacts with 5-amino-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole to give compound **200** in 25% yield.¹⁶⁹



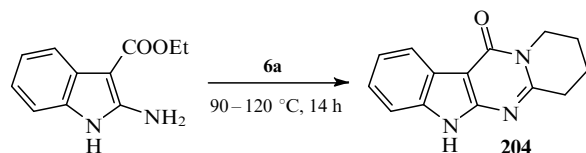
1,2,3,4,7,8,9,10-Octahydro-5*H*-dipyrido[1,2-*a*:2',3'-*d'*]pyrimidin-5-one **201** has been synthesised in 66% yield by heating the imide **6a** with 6-amino-5-ethoxycarbonyl-1,2,3,4-tetrahydropyridine.¹⁷⁰



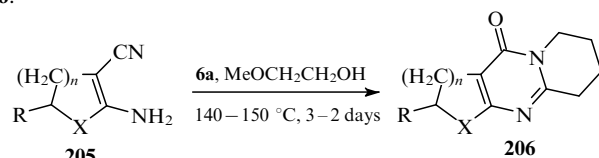
Tetracyclic compounds **203** are formed in 75%–85% yield as a result of cyclocondensation of 2-methoxy-3,4,5,6-tetrahydropyridine **6a** with 2-amino-3-ethoxycarbonyl-4,5-polymethylene-thiophenes **202** in the presence of polyphosphoric acid (PPA).¹⁷¹



Cyclocondensation of the imide **6a** with 2-amino-3-ethoxycarbonylindole gives rise to 5,7,8,9,10,12-hexahydropyrido[1',2':1,2]pyrimido[4,5-*b*]indol-12-one **204** in 39% yield.¹⁷²



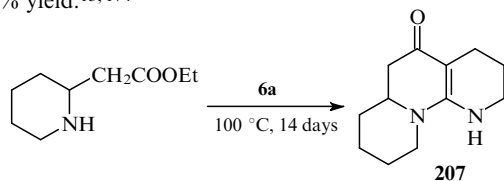
On heating in 2-methoxyethanol, compounds **205**, containing amino and nitrile groups in vicinal positions, enter into condensation with the imide **6a** to give pyrimidin-4-one derivatives **206**.¹⁷³



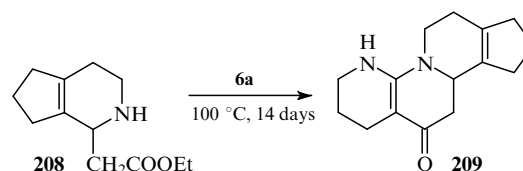
R	n	X	Yield (%)
Me	1	O	25
H	1	S	71
H	2	O	39

A well-studied synthesis of angular polynuclear heterocyclic compounds is cyclocondensation of Δ^1 -piperideines with cyclic compounds containing NH and CH_2COOEt groups in vicinal positions.

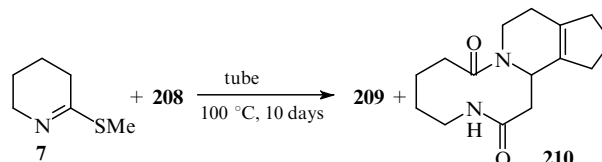
Thus prolonged heating of the imide **6a** with 2-ethoxycarbonylpiperidine in a sealed tube affords 1,2,3,4,6,7,8,9,9*a*,10-decahydro-13*H*-isoquino[2,1-*a*]-[1,8]naphthiridin-13-one **207** in 54% yield.^{13, 174}



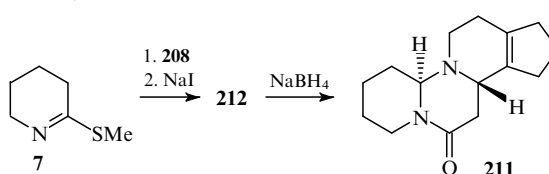
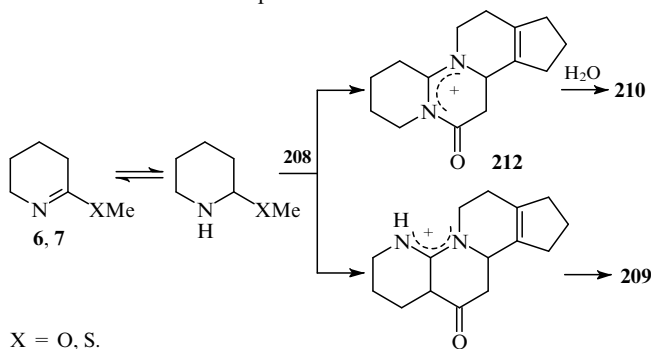
The yield of compound **209** formed in the condensation of the imide **6a** with compound **208** under similar conditions is only 20%.^{14, 174}



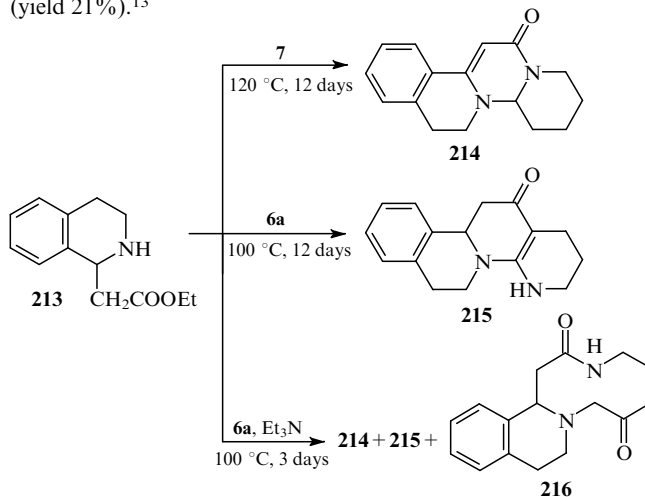
When the compound **208** is heated with methylthiopiperidine **7** in a tube at 100 °C, cyclic diamide **210** (yield 20.5%) is formed in addition to the condensation product **209** (yield 9%).¹⁴



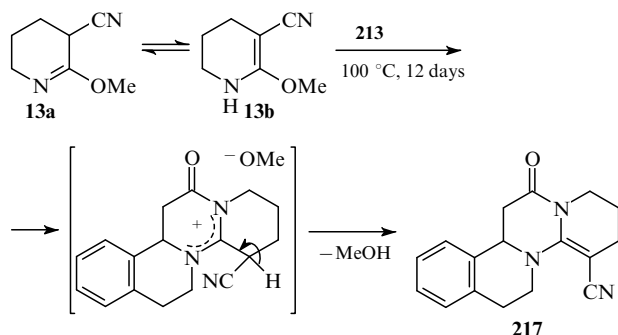
If the mixture formed upon the reaction of the compounds **7** and **208** is treated with 5% hydrochloric acid and then with sodium iodide and the reaction product is reduced with sodium borohydride in methanol (20 °C, 12 h), tetracyclic compound **211** is formed (yield 14%).¹⁴ The following scheme was proposed for the formation of the compounds **209**–**211**:



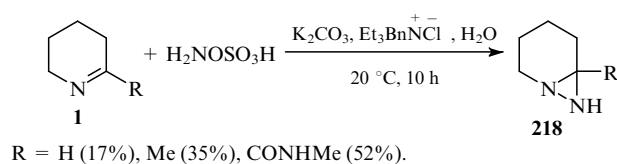
The reaction of 1-(ethoxycarbonylmethyl)-1,2,3,4-tetrahydroisoquinoline **213** with 2-methylthiopiperidine **7** on heating in a sealed tube affords compound **214** (yield 81.1%).⁴⁷ When the isoquinoline derivative **213** reacts with 2-methoxypiperidine **6a** under similar conditions, isomeric tetracyclic product **215** is produced.^{13, 174} The reaction between **6a** and **213** carried out in the presence of triethylamine affords tricyclic product **216** (yield 19%), together with the compounds **214** (yield 14%) and **215** (yield 21%).¹³



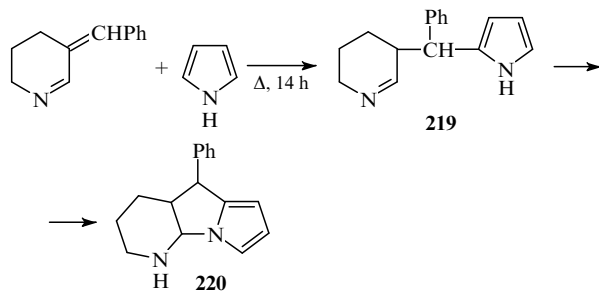
2-Methoxy-3-cyano-3,4,5,6-tetrahydropyridine **13** exists as a mixture of two tautomers, **13a** and **13b**, and can be converted into different products depending on which tautomer is involved in the reaction. Since only compound **217** was isolated (yield 36%) upon the reaction of the Δ^1 -piperidine **13** with the isoquinoline derivative **213**, it is clear that in this case the imide **13** reacts as the tautomer **13a**.



Treatment of the Δ^1 -piperidines **1** with *O*-hydroxylaminosulfonic acid in the presence of potassium carbonate and benzyltriethylammonium chloride results in the formation of 1,7-diazabicyclo[4.1.0]heptanes **218**.^{23, 175}

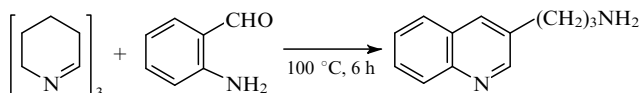


The formation of tricyclic compound **220** (yield 32%) from 3-benzylidene-3,4,5,6-tetrahydropyridine and pyrrole can be represented as two consecutive reactions — addition to the C=C bond in the benzylidene derivative owing to the C—H group at the 2-position of pyrrole and cycloaddition, involving pyrrole nitrogen, to the C=N bond in the intermediate compound **219**.¹²⁰

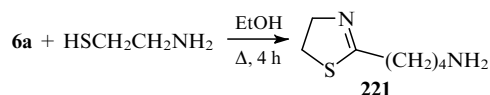


Some reactions of Δ^1 -piperidines with primary amines occur with opening of the heterocyclic ring.

Thus heating of the piperidine trimer with 2-aminobenzaldehyde in a citrate buffer solution gives 3-(3-aminopropyl)quinoline in 70% yield.⁸⁰

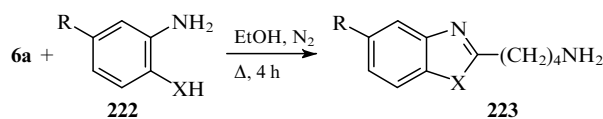


When the imide **6a** is refluxed with thioethanolamine in ethanol, the heterocyclic ring is cleaved and 1,3-thiazoline derivative **221** is formed as the reaction product (yield 69%).¹⁷⁶



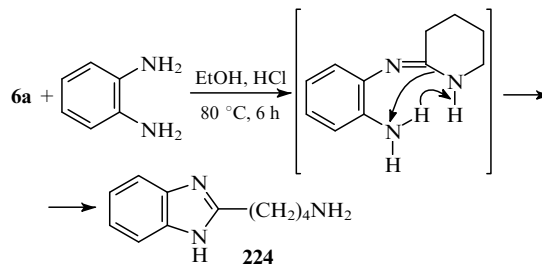
Compounds **223**, serving as the starting compounds in syntheses of medicines and pesticides, were prepared by condensation

of the imide **6a** with aniline derivatives **222** under an inert atmosphere. This reaction also proceeds with opening of the Δ^1 -piperidine ring.¹⁷⁶

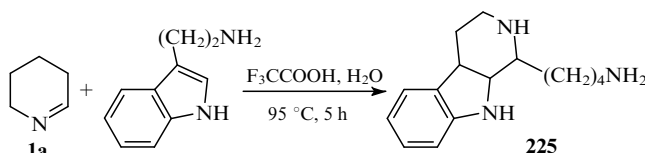


R = H, Me; X = O, S.

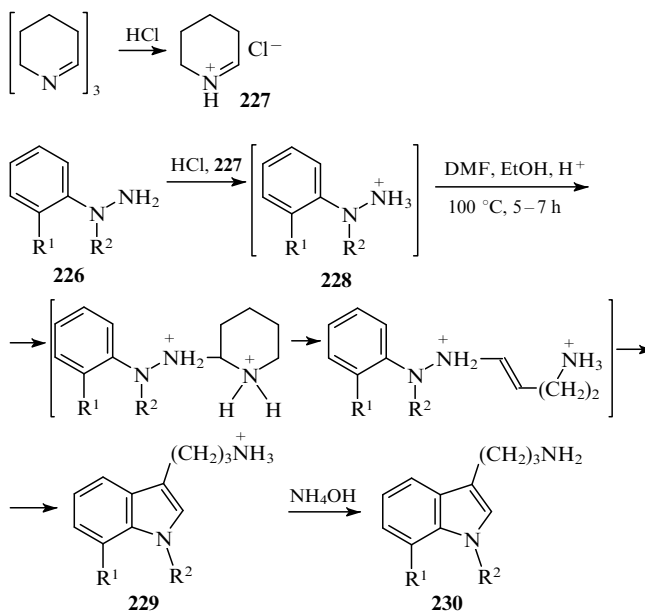
The reaction of the imide **6a** with *o*-phenylenediamine in boiling ethanol in the presence of hydrogen chloride gives rise to compound **224** in 74% yield.¹⁷⁷



The piperidine **1a** reacts with 3-(2-aminoethyl)indole in the presence of trifluoroacetic acid with opening of the imine heterocycle to give the alkaloid nazlinin **225** in 72% yield.¹⁷⁸

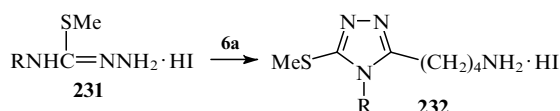


Arylhydrazines **226** and the piperidine trimer react in the presence of hydrogen chloride as salts **227** and **228** to give aminoalkylindole salts **229**. On treatment with aqueous ammonia, these products are converted into amines **230**.¹⁷⁹



R¹ = H: R² = H (18%), Me (33%), Ph (23%), CH₂Ph (52%);
R¹–R² = CH(Me)CH₂CH₂ (26%).

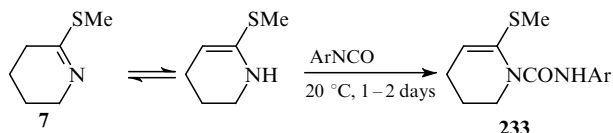
The reaction of 2-methoxypiperidine **6a** with *S*-methylisothiosemicarbazide hydroiodides **231** yields 1,3,5-triazole derivatives **232**.¹⁸⁰



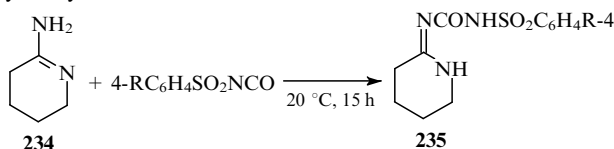
R = H, Ph.

5. Reactions with isocyanates

2-Methylthio-3,4,5,6-tetrahydropyridine **7** reacts with aryl isocyanates ArNCO giving rise to compounds **233**.¹⁸¹

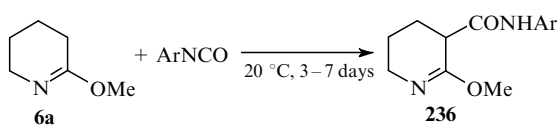
Ar = Ph (77%), 4-ClC₆H₄ (73%), 4-EtOC₆H₄ (82%).

Urea derivatives **235**, which exhibit high antiglycemic activity and decrease the level of glucose in blood, have been synthesised by the reaction of 2-amino-3,4,5,6-tetrahydropyridine with sulfonyl isocyanates **234**.¹⁸²



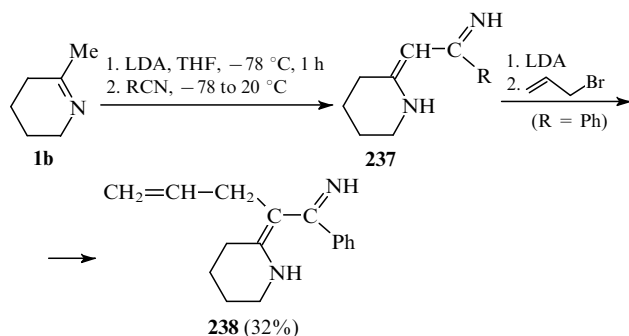
R = H (42%), Me (49%), Cl (44%).

2-Methoxy-3,4,5,6-tetrahydropyridine **6a** reacts with aryl isocyanates to give piperideines **236**, containing an arylamide group.¹²

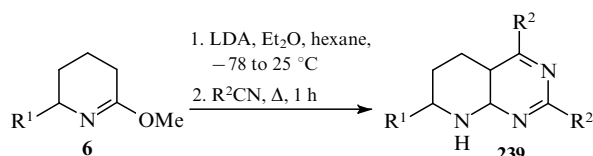
Ar = Ph (68%), 4-ClC₆H₄ (65%), 4-EtOC₆H₄ (70%).

6. Reactions with nitriles

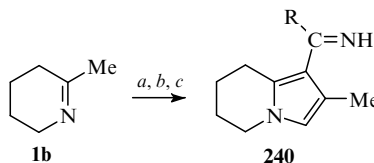
Treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA^{183, 184} and subsequent reaction of the lithiated product with nitriles RCN results in the formation of heterodienes **237**. If allyl bromide is added to the reaction mixture together with benzonitrile, compound **238** is formed in 32% yield.

R = C₅H₁₁ (94%), Ph (66%), cyclo-C₆H₁₁ (56%).

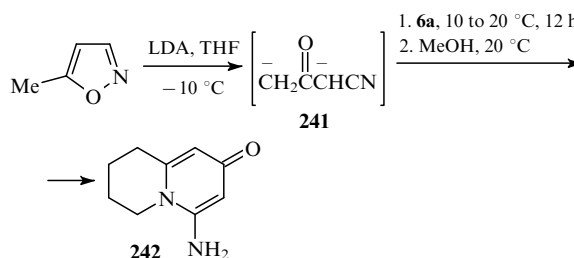
By heating lithium derivatives of the imidates **6** with nitriles, bicyclic pyrimidine derivatives **239** have been synthesised in 17%–26% yield.¹⁸⁵

R¹ = H, Me; R² = Ph, 2-furyl, 2-thienyl, 2-pyridyl, 4-pyridyl.

Indolizine derivatives **240** have been obtained by the reaction of lithium derivatives of the imine **1b** with nitriles followed by treatment of the product with propargyl bromide.¹⁸⁶

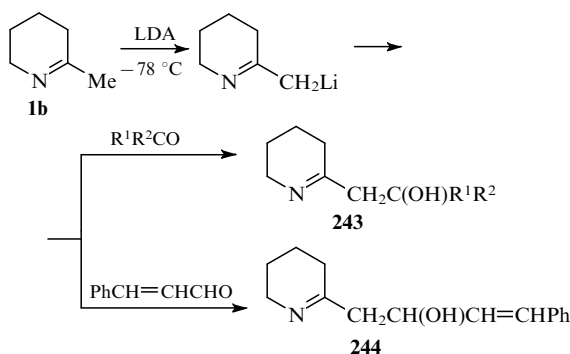
R = Ph (70%), cyclo-C₃H₅ (75%), 2-thienyl (71%);(a) LDA, THF, -78°C ; (b) RCN, 3.5 h;(c) HC $\equiv$ CCH₂Br, -78°C to -20°C , 14 h.

The dianion **241**, generated on treatment of 5-methylisoxazole with LDA in THF, reacts with the imide **6a** giving rise to 2-amino-1-azabicyclo[4.4.0]deca-2,5-dien-4-one **242** (yield 40%).¹⁸⁷

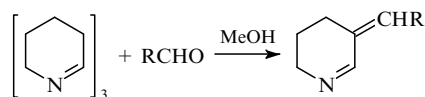


7. Reactions with aldehydes and ketones

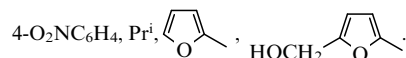
Alcohols **243** have been synthesised (yields 56%–88%) by treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA and subsequent condensation of the resulting lithium derivative with carbonyl compounds.^{188, 189} Treatment of the imine **1b** with LDA followed by the reaction with cinnamaldehyde gave secondary unsaturated alcohol **244**.¹⁹⁰

R¹ = H; R² = Me, Et, Prⁱ, Bu^t, Ph; R¹ = R² = Me

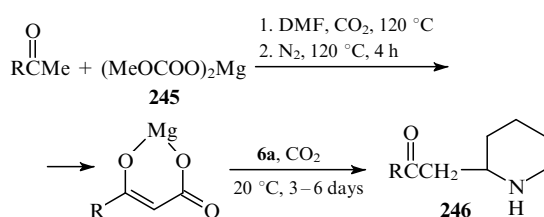
The piperidine trimer readily reacts with aromatic aldehydes according to the crotonic condensation route to give arylmethylenes derivatives.^{120, 191, 192}



R = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 4-NCC₆H₄,



An interesting method for the synthesis of ketones **246**, containing a 2-piperidyl fragment, has been developed. The method consists in the reaction of methyl ketones RCOMe with magnesium methyl carbonate **245** and the imide **6a**.^{19,20,193} Methyl ketones and the salt **245** were kept in DMF in a flow of CO₂ at 120 °C, then CO₂ was displaced by nitrogen and the reaction mixture was held at 120 °C under nitrogen, the MeOH evolved being evaporated. After cooling the reaction mixture, the imine **6a**¹⁹³ or its α-trimer^{19,20} was added, and the mixture was kept at 20 °C in an atmosphere of CO₂ for several days.

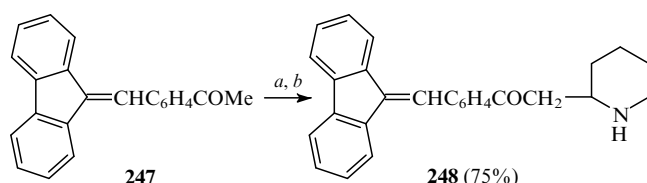


R = 2,5-(MeO)₂C₆H₃ (75%), 4-PhSC₆H₄ (50%), dibenzofuran-2-yl (32%), Ph₂CH (37%), 4-MeOC₆H₄CH=CH (43%), PhCH=C(Me)CH=CH (48%), PhCH=CHC₆H₄ (57%), 4-pyridyl, (8%) 1-adamantyl (6%), Ph, 4-MeOC₆H₄, 4-BuⁿC₆H₄, 4-BuⁿOC₆H₄, 3,4,5-(MeO)₃C₆H₂, 4-PhC₆H₄, 3,4-(MeO)₂C₆H₃CH=CH, PhCH=CMe, PhCH=CH, 4-MeSC₆H₄, 4-(fluoren-9-ylidenemethyl)-phenylene (73%).

When the reaction between the imide **6a** and 1-acetyladamantane is conducted for 28 h at 120 °C and then for 120 h at 20 °C, the yield of the ketone **246** (R = 1-adamantyl) increases to 37%.¹⁹ The compounds **246** were obtained in low yields from ketones RCOMe with R = 4-NCC₆H₄ or 4-Me₂NSO₂C₆H₄. In the case of R = 4-HOC₆H₄, 4-H₂NCC₆H₄, 4-O₂NC₆H₄, 4-HOOC₆H₄ or 4-HO₃SC₆H₄, these products did not form at all.¹⁹

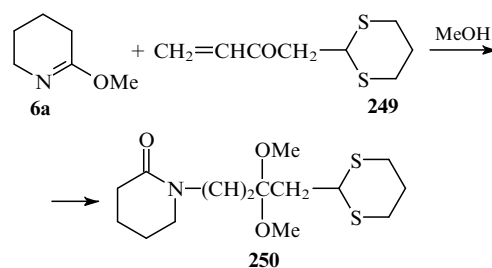
A similar procedure for the preparation of the ketones **246** at 20 °C over a period of 70 h has been described in a patent.²⁰ The synthesised compounds [R = 4-MeOC₆H₄CH=CH, PhCH=CH, 4-BuⁿC₆H₄CH=CH, 4-BuⁿOC₆H₄CH=CH, 3,4-(MeO)₂C₆H₃CH=CHCH=CH, 3,4,5-(MeO)₃C₆H₂CH=CH, 4-PhC₆H₄CH=CH, PhCH=CHCH=CH, 4-MeSC₆H₄CH=CH, PhCH=C(Me)CH=CH] were claimed to be anticoagulants.

Ketone **247** was introduced into the reaction with the salt **245** in an atmosphere of CO₂; then the piperidine trimer was added and condensation product **248** was obtained in 73% yield.¹⁹

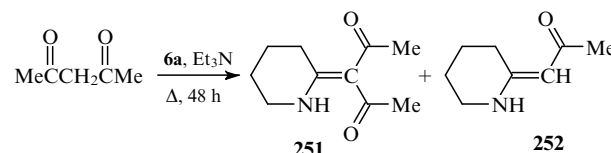


(a) **245**, CO₂, DMF, 120 °C, 4 h; (b) [piperidine]₃, CO₂, 24 h.

The reaction of the imide **6a** with unsaturated ketone **249** at 20 °C for 24 h affords piperidin-2-one derivative **250** in 46% yield. At a low temperature (−15 °C for 62 h), the yield increases to 65%.¹⁹⁴



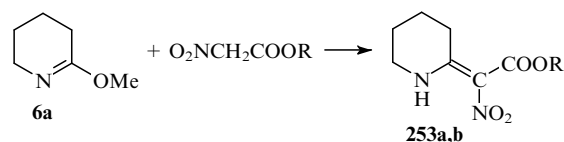
Condensation of acetylacetone with the imide **6a** results in the formation of a mixture of compounds **251** and **252** (yields 26% and 25%, respectively).¹⁹⁵



8. Reactions with acids and their derivatives

Carboxylic acids and their derivatives can be used as the methylene components in the condensation of Δ¹-piperidine.

Thus the imide **6a** condenses with methyl¹⁹⁶ or ethyl¹⁹⁷ nitroacetate giving rise to piperidine derivatives **253a,b**, which are used to synthesise insecticides.¹⁹⁶

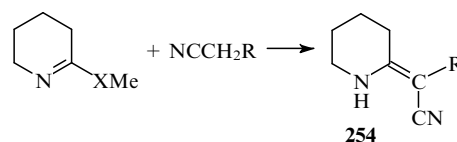


R = Me (**a**), Et (**b**).

The compound **253b** can also be synthesised by heating 2-methylthio-3,4,5,6-tetrahydropyridine **7** and ethyl nitroacetate in the presence of zinc chloride.¹⁹⁸

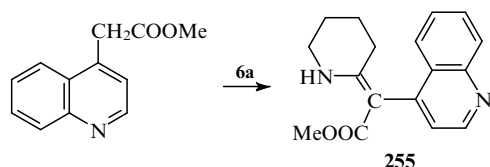


Condensation products **254** have been prepared in good yields from cyanoacetic acid derivatives and the imide **6a** or the thioimide **7**.^{199–202}

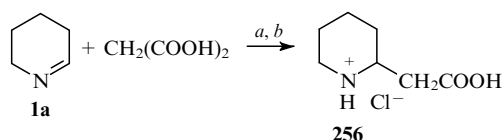


X	R	Reaction conditions	Yield (%)	Ref.
O	CONH ₂	DMF, refluxing for 3 h	77	199
O	CONHPh	the same	66	200
O	CONHCH ₂ Ph	"	75	200
O	CN	EtOH, 20 °C, 1 h	79	201
S	COOEt	diazabicyclononene, N ₂ , 120 °C, 12 h	60	202

The reaction of the imide **6a** with 4-methoxycarbonylmethylquinoline gives piperidine derivative **255**.²⁰³

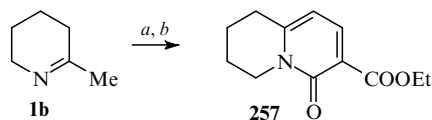


The hydrochloride of (2-piperidyl)acetic acid has been obtained in 69% yield by the reaction of 2,3,4,5-tetrahydropyridine **1a** with malonic acid in the presence of triethylamine at 50–60 °C.²⁰⁴



(a) Et₃N, Me₂CO, 50–60 °C, 2.5 h; (b) 20% HCl, H₂O.

Treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA and then with ethyl ethoxymethylenemalonate affords 9-ethoxycarbonyl-1-azabicyclo[4.4.0]deca-6,8-dien-10-one **257** in 90% yield.²⁰⁵



(a) LDA, hexane, THF, N₂, –30 °C, 15 min; (b) EtOCH=C(COOEt)₂, –78 °C, 12 h.

The condensation of the imidates **6** with cyclic malonates **258** giving compounds **259** has been reported.^{40, 195, 206, 207} The products **259** are recommended as pre- and post-emergent herbicides.²⁰⁷ The reaction conditions and product yields are listed in Table 3.

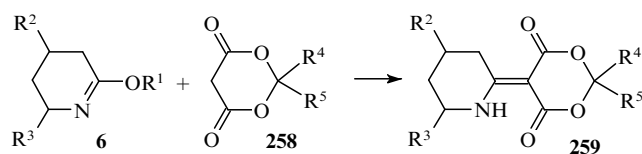


Table 3. Conditions of synthesis and yields of the compounds **259**.

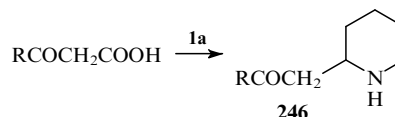
R ¹	R ²	R ³	R ⁴	R ⁵	T, °C	Time/h	Yield (%)	Ref.
Me	H	H	Me	Me	see ^a	12	—	40
Me	H	Me	Me	Me	see ^a	12	84	40
Me	H	H	Me	Me	see ^b	24	90	195
Me	H	H	Me	Me	see ^c	12	76	206
Et	Me	H	Me	Me	112–113	2	16	207
Et	H	H	Bu ⁱ	H	112–113	2	—	207
Et	H	H	Et ₂ CH	H	112–113	2	—	207
Et	H	H	(CH ₂) ₅	H	112–113	2	—	207
Et	H	Me	Me	Me	112–113	2	—	207
Et	H	H	Pr ⁱ	H	112–113	2	—	207
Et	H	H	Me	Me	112–113	2	—	207

^a Refluxing in CHCl₃ in the presence of Ni(OAc)₂; ^b refluxing in PhH in the presence of triethylamine and piperidine; ^c refluxing in the presence of triethylamine.

In the previous Section, we considered the reactions of the imine **1a** with ketones in the presence of magnesium methyl carbonate **245** to give the compounds **246**. These reactions involve the intermediate formation of magnesium enolates of β -oxo acids, which react with Δ^1 -piperidine **1a** to give, after decarboxylation,

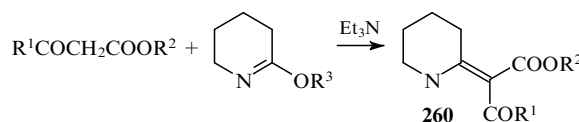
the compounds **246**. It is quite natural that in several other studies, it has been proposed to prepare the piperidine derivatives **246** by the condensation of the imine **1a** with β -oxo acids^{77, 79, 208–210} or their sodium salts.^{26, 27}

($\pm$)-Isopelletierine (**246**, R = Me) was synthesised in a higher yield (42%–51%) by condensation of the imide **1a** with sodium acetoacetate on refluxing in water for 4 h.^{26, 27}



R	Reaction conditions	Yield (%)	Ref.
Pr	20 °C, 24 h, H ₂ O, pH 7	—	77
Ph	the same	—	77
Me	"	7	79
3,4-(MeO) ₂ C ₆ H ₃	27 °C, 24 h, H ₂ O, pH 7	79	208, 209
3,4-(MeO) ₂ C ₆ H ₃	the same	55	210
4-MeOC ₆ H ₄	"	60	210

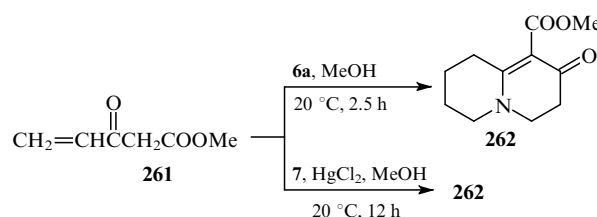
In the presence of Et₃N, esters of β -oxo acids condense with 2-methoxy-3,4,5,6-tetrahydropyridine, being thus converted into compounds **260**.^{211, 212}



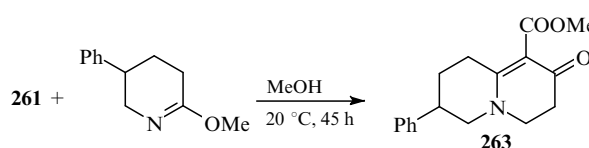
R ¹	R ²	R ³	Temperature / °C	Time / h	Yield (%)	Ref.
Me	Me	Me	100 ^a	50	47	211
Me	Et	Et	100 ^a	50	—	211
2,4-Cl ₂ -5-FC ₆ H ₂	Et	Me	80	48	63 ^b	212

^a The reaction was carried out in a tube; ^b a mixture of the methyl and ethyl ester **260** in 1 : 2 ratio was obtained.

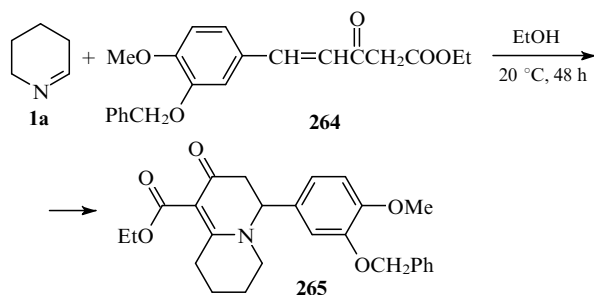
5-Methoxycarbonyl-1-azabicyclo[4.4.0]dec-5-en-4-one **262**, the initial compound in the synthesis of ($\pm$)-epilupinine, has been prepared from 3-oxopent-4-enoic acid **261** and the imide **6a** (yield 54%)¹⁹⁴ or the thioimide **7** (yield 62%).²¹³



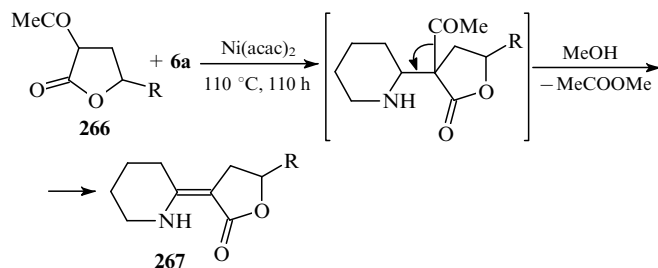
At room temperature, the dicarbonyl compound **261** reacts with 2-methoxy-5-phenyl-3,4,5,6-tetrahydropyridine to give 5-methoxycarbonyl-9-phenyl-1-azabicyclo[4.4.0]dec-5-en-4-one **263** (yield 65%).²¹⁴



When developing approaches to the synthesis of alkaloids of the *Lythraceae* family, Rosazza *et al.*²¹⁵ synthesised compound **265** (yield 84%) by cyclocondensation of the imine **1a** with unsaturated oxo ester **264**.

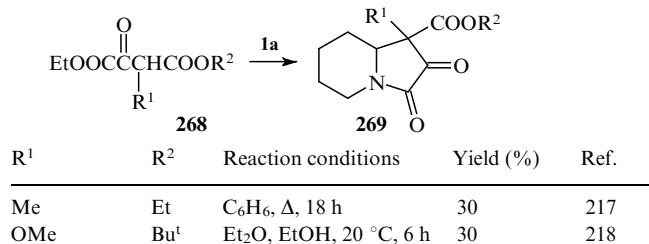


In the presence of nickel acetylacetonate, the imide **6a** enters into the reaction with oxo lactones **266** to give compounds **267**.²¹⁶

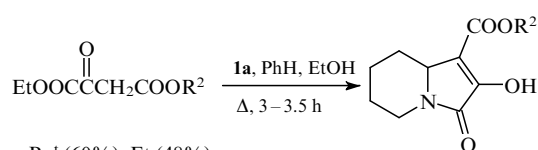


R = H (56%), Et (33%).

1-Azabicyclo[4.3.0]nonane-8,9-dione derivatives **269** have been synthesised from 2,3,4,5-tetrahydropyridine **1a** and esters of oxo dicarboxylic acids **268**.^{217, 218}

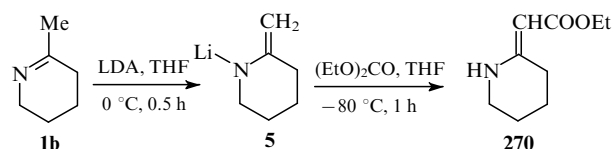


The reaction of the imine **1a** with alkyl oxalylacetates (**268**, R¹ = H) affords tautomers of the compounds **269**, 7-alkoxycarbonyl-8-hydroxy-1-azabicyclo[4.3.0]non-7-en-9-ones.²⁵

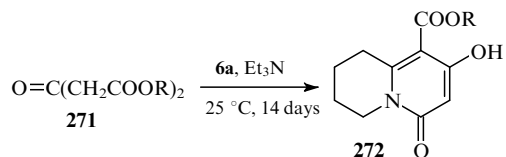


R² = Bu^t (60%), Et (48%).

N-Lithio-2-methylenepiperidine **5**, formed on treatment of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with LDA, reacts *in situ* with diethyl carbonate to give 2-ethoxycarbonylmethylenepiperidine **270** in 59% yield.¹⁰



Cyclocondensation of the imide **6a** with esters of oxo dicarboxylic acid **271** in the presence of Et₃N affords quinolizine derivatives **272**.²¹⁹

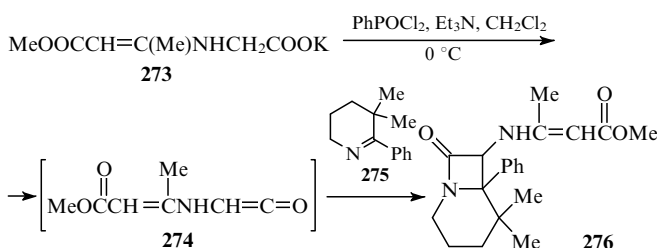


R = Me (57%), Et (92%).

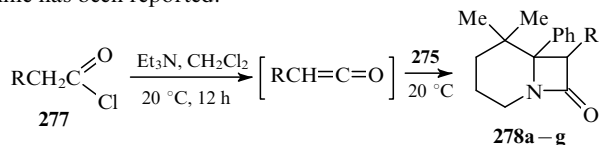
9. Reactions with ketenes

Δ¹-Piperideines and ketenes react according to the [2 + 2] cycloaddition pattern yielding bicyclic compounds — 1-azabicyclo[4.2.0]octane derivatives.

Thus treatment of potassium *N*-(2-methoxycarbonylpropen-2-yl)glycinate **273** with PhPOCl₂ and Et₃N gives ketene **274**, which enters *in situ* into the cycloaddition reaction with 3,3-dimethyl-2-phenyl-3,4,5,6-tetrahydropyridine giving rise to 7-(2-methoxycarbonylpropen-2-yl)amino-5,5-dimethyl-6-phenyl-1-azabicyclo[4.2.0]octan-8-one **276** in 74% yield.²²⁰



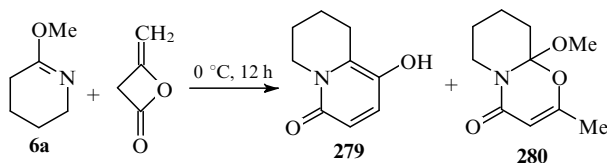
Synthesis of 1-azabicyclo[4.2.0]octane derivatives **278a–g** (yields 42%–87%) by the reaction of the imine **275** with the ketenes formed on treatment of acyl chlorides **277** with triethylamine has been reported.²²¹



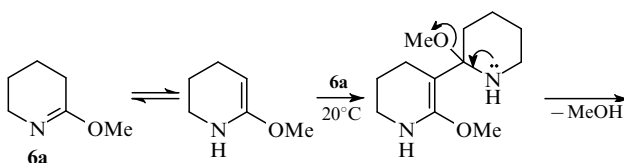
R = N₃ (a), MeO (b), PhO (c), PhCH₂O (d), 4-ClC₆H₄SO₃ (e), phthalimid-1-yl (f), Cl (g).

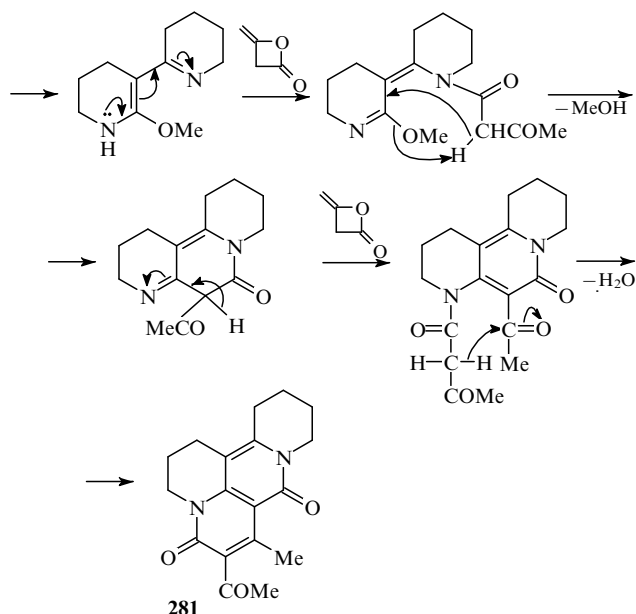
The azido-derivative **278a** is formed over a period of 2 h, while in the majority of cases, completion of the reaction requires 12 h. In the case of the synthesis of **278g** (yield 61%), more drastic conditions were used: the reaction mixture was refluxed for 1.5 h and then kept at room temperature for 16 h.²²¹

The imide **6a** reacts with diketene even at 0 °C according to two pathways — giving quinolizine derivative **279** (yield 10%) and pyrido[2.1-*b*]oxazine **280** (yield 43%).²²²

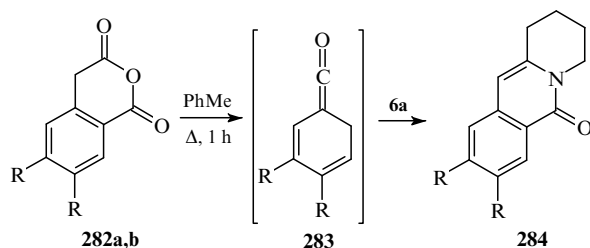


When the reaction is carried out in acetic acid at 20 °C, only the tetracyclic compound **281** is formed; this product results from condensation of two molecules of **6a** with two diketene molecules. The following scheme has been proposed for this reaction:²²³



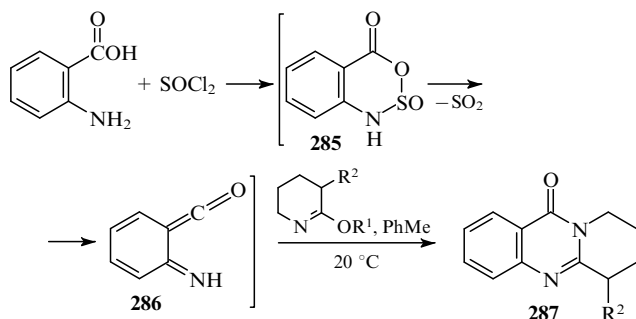


In some cases, ketenes synthesised by other methods have also been introduced in reactions with Δ^1 -piperideines. Thus on refluxing in toluene, homophthalic anhydride **282a** and 4,5-dimethoxyhomophthalic anhydride **282b** eliminate a CO_2 molecule being thus converted into the corresponding ketenes **283**, which react with 2-methoxy-3,4,5,6-tetrahydropyridine **6a** to give tricyclic compounds **284**.²²⁴



R = H (52%), OMe (55%).

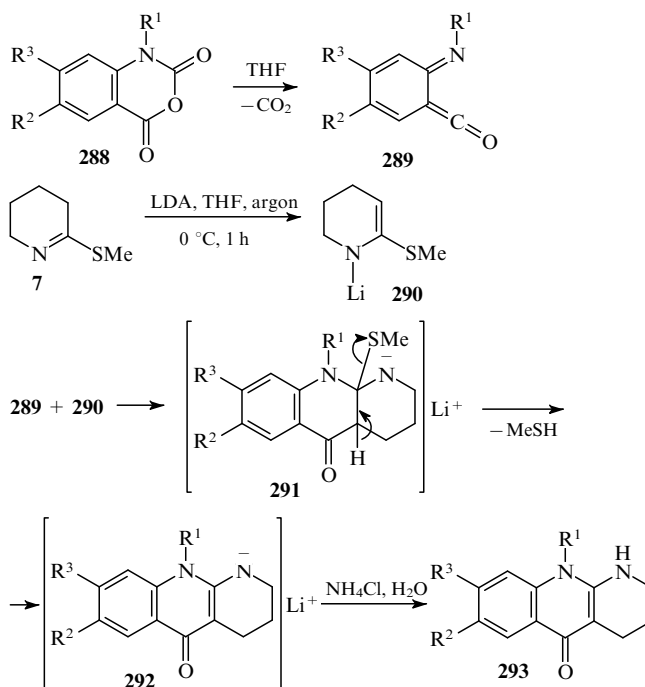
Compound **285**, formed from anthranilic acid under the action of thionyl chloride, eliminates an SO_2 molecule even at room temperature and is thus converted into ketene **286**, which enters into cyclocondensation with imidates to give quinazoline derivatives **287** (yields 71%–82%).^{225, 226}



R¹ = Me, Et; R² = H, OMe.

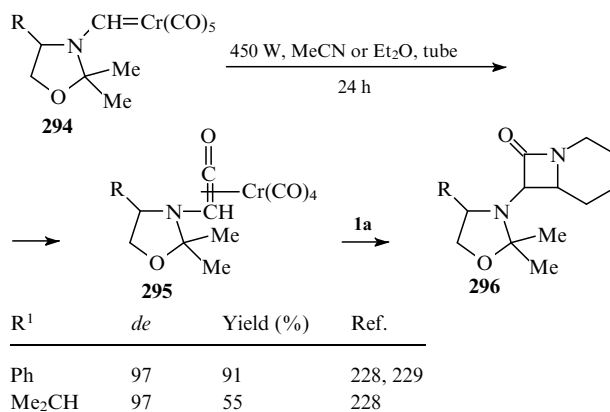
Benzo[*b*]-1,8-naphthiridine derivatives **293** have been prepared by the reaction of 2-methylthio-3,4,5,6-tetrahydropyridines **7** with N-substituted isatic anhydrides **288** in the presence of LDA. Evidently, the anhydrides **288** lose a CO_2 molecule under the reaction conditions giving rise to ketenes **289**, which react according to the [4 + 2] cycloaddition pattern with the lithium derivative **290**, resulting from the reaction of the thioimide **7** with LDA. The salts **291** thus formed are converted into salts **292** upon

elimination of an MeSH molecule. The latter give the final products **293** upon treatment with an aqueous solution of ammonium chloride.²²⁷



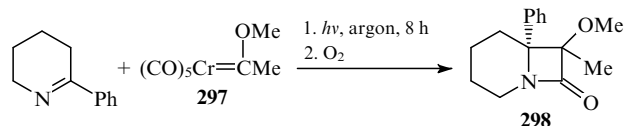
R ¹	R ²	R ³	Yield (%)
Me	H	H	64
PhCH ₂	H	H	53
Me	Me	H	42
Me	H	Cl	62
Ph	H	Cl	14

Ketene chromium tricarbonyl complexes **295**, which are produced upon photolysis of the carbene complexes **294**, react *in situ* with 2,3,4,5-tetrahydropyridine **1a** yielding 1-azabicyclo[4.2.0]octan-8-one **296**.^{228, 229}



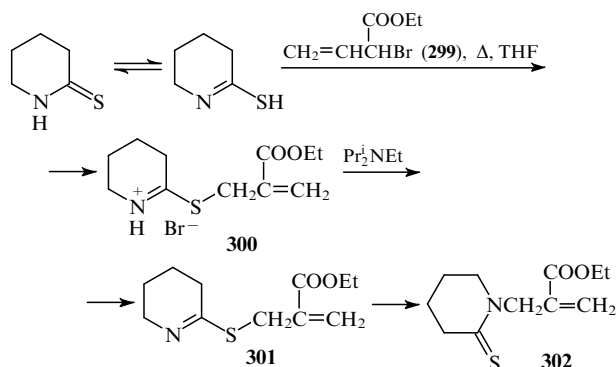
R ¹	de	Yield (%)	Ref.
Ph	97	91	228, 229
Me ₂ CH	97	55	228

When a mixture of 2-phenyl-3,4,5,6-tetrahydropyridine and carbene complex **297** is exposed to sunlight under an argon atmosphere and then oxidised by atmospheric oxygen, 7-methoxy-7-methyl-6-phenyl-1-azabicyclo[4.2.0]octan-8-one **298** is formed in 63% yield.²³⁰

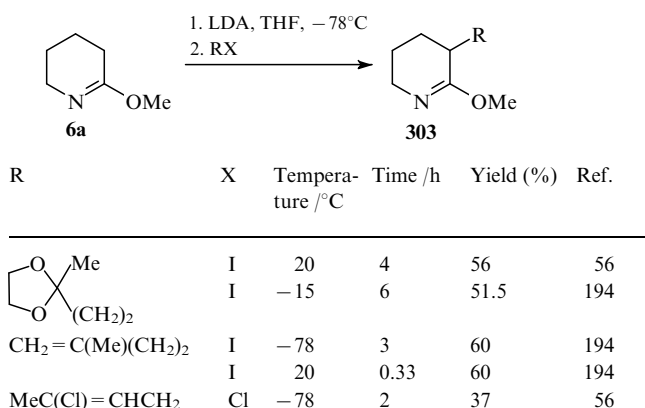


10. Reactions with alkyl halides

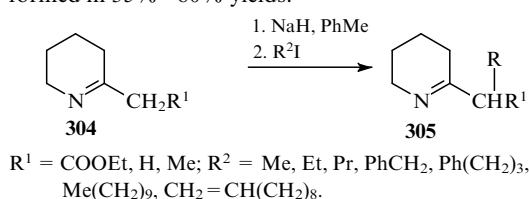
Piperidine-2-thione in the thiol tautomeric form reacts with ethyl 2-bromobut-3-enoate **299** to give salt **300**. Subsequent treatment of the compound **300** with ethyldiisopropylamine affords N-substituted piperidine-2-thione **302** (yield 70%); the formation of this product was explained by the S,N-allyl rearrangement of intermediate **301** under the reaction conditions.²³¹



Treatment of the imide **6a** with LDA and then with halogenated compounds results in the formation of product **303**, alkylated at the 3-position.^{56, 194}



When Δ^1 -piperideines **304** ($R^1 = \text{COOEt}$) are treated successively with sodium hydride and halo-derivatives R^2X , alkylation of the side-chain methylene group occurs and compounds **305** are formed in 35%–80% yields.¹⁰⁹



The compounds **305** ($R^1 = \text{H, Me; } R^2 = \text{Me}$) have been synthesised in >95% yields by the reaction of the Δ^1 -piperideines **304** ($R^1 = \text{H, Me}$) with methyl iodide in the presence of LDA in THF at -78 to 20 °C for 1 h.²³²

When imidates **306** are heated with halo-containing compounds, the nitrogen atom in the heterocyclic nucleus is alkylated giving substituted piperidones **307**.^{39, 233} The reaction conditions and the product yields are listed in Table 4.

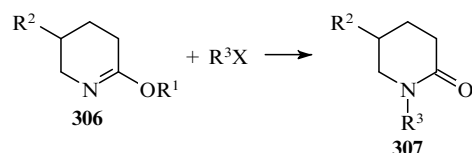


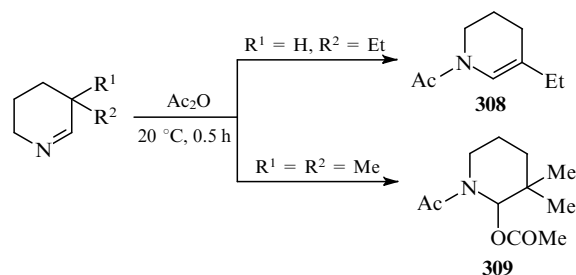
Table 4. Alkylation of the imidates **306**.

R ¹	R ²	R ³	X	Temperature / °C	Time / h	Yield (%)	Ref.
Me	H	Me	I	60	6	93	39
Me	H	Et	I	60	48	52	39
Me	H	PhCH ₂	Br	60	10	80	39
Me	H	Ph(CH ₂) ₂	Br	100	28	7	39
Me	H	3,4-(MeO) ₂ C ₆ H ₃ (CH ₂) ₂	Br	90	24	8	39
Et	H	Ph(CH ₂) ₂	Br	100	48	27	39
Me	H	PhCOCH ₂	Br	60	3	91	39, 233
Et	H	PhCOCH ₂	Br	60	4	94	39
Me	H	3,4-(MeO) ₂ C ₆ H ₃ COCH ₂	Br	60	5	88	39, 233
Et	H	3,4-(MeO) ₂ C ₆ H ₃ COCH ₂	Br	60	5	92	39
Me	Et	PhCOCH ₂	Br	60	3	—	233
Me	Et	3,4-(MeO) ₂ C ₆ H ₃ COCH ₂	Br	60	5	—	233

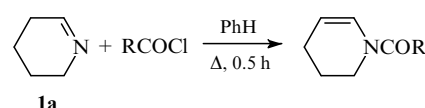
11. N-Acylation reactions

N-Acylation of 3-substituted Δ^1 -piperideines with acylating agents is accompanied by isomerisation of the double bond.

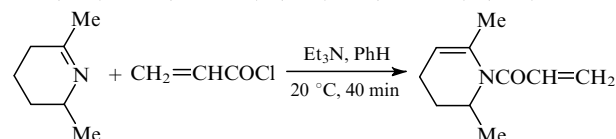
Thus treatment of 3-ethyl- Δ^1 -piperideine with acetic anhydride affords compound **308** (yield 57%). Under the same conditions, 3,3-dimethyl- Δ^1 -piperideine is converted into diacetyl derivative **309** in 78% yield.⁷²



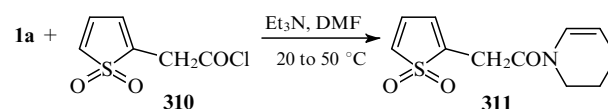
N-Acylation of the imine **1a** with polyunsaturated acid chlorides was carried out by refluxing in benzene.^{234, 235} 2,6-Dimethyl-3,4,5,6-tetrahydropyridine was N-acylated with acryloyl chloride in the presence of triethylamine at room temperature.²³⁶



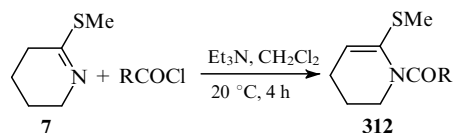
$R = \text{Me(CH}_2)_2\text{C}\equiv\text{C(CH=CH)}_2$ (60%), Me(CH=CH)_4 (35%).



Compound **311** was synthesised in 76% yield by the reaction of the imine **1a** with chloride **310** in the presence of Et₃N in DMF.²³⁷

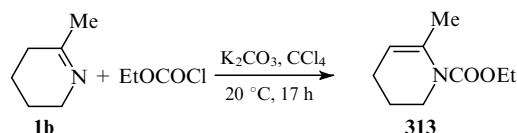


The thioimide **7** reacts with acetyl or benzoyl chloride at room temperature to give N-acylated derivatives **312**.²³⁸



R = Me (73%), Ph (83%).

Ethyl chlorocarbonate reacts with the imine **1b** in the presence of potassium carbonate to give N-acylated product **313** (yield 79%).²³⁹



When the Δ^1 -piperideines **6** are heated with lithium hydride in THF and the resulting organolithium compounds are treated with acyl chlorides, N-acylation products **314** are formed in low yields, acyclic compounds **315** being the main products (yields 72%–77%). Treatment of the Δ^1 -piperideines **6** with lithium or sodium hydride or lithium hydroxide in benzene and subsequent reaction with acid chlorides give the N-acylated derivatives **314** as the main reaction products (see Table 5).¹⁸⁵

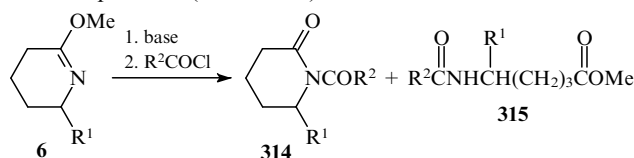
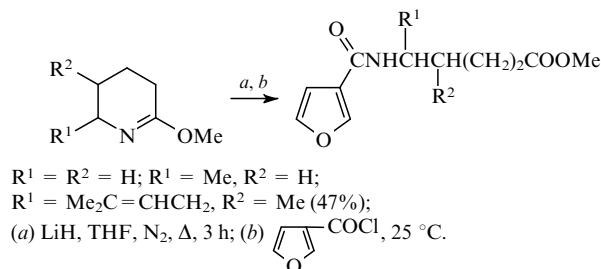


Table 5. N-Acylation of the piperideines **6**.

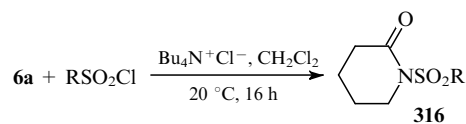
R ¹	R ²	Base	Solvent	Reaction conditions		Yield of 314 (%)
				1st stage	2nd stage	
Me	3-furyl	LiH	THF	Δ , 3 h	25 °C, 88 h	4
H		LiH	THF	Δ , 3 h	25 °C, 88 h	6
Me		LiOH	C ₆ H ₆	Δ , 3 h	25 °C, 19 h	75
H		NaH	C ₆ H ₆	Δ , 3 h	25 °C, 19 h	70
H	Ph	LiH	C ₆ H ₆	Δ , 3 h	25 °C, 19 h	67

Heating of the imide **6a** with lithium hydride in benzene for 3 h followed by treatment of the reaction product with benzoyl chloride also gives compound of the type **315** (R¹ = H, R² = Ph) in 32% yield.¹⁸⁵

Later the investigation of the reaction of Δ^1 -piperideines with lithium hydride and the chloride of furan-3-carboxylic acid has been continued. The formation of only the product of piperidine ring opening in this reaction has been reported.¹²¹



The reaction of the imide **6a** with sulfonyl chlorides in the presence of Bu₄N⁺Cl[−] in CH₂Cl₂ at room temperature results in the formation of N-sulfonyl-substituted derivatives **316**.⁴¹

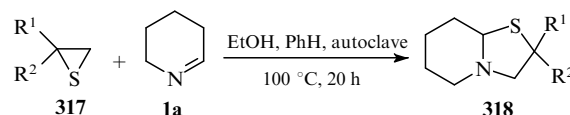


R = Me (73%), Ph (66%), 4-C₆H₄ (66%).

12. Reactions with labile cyclic systems

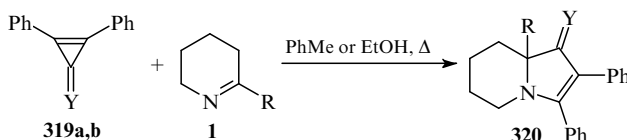
In this Section, we discuss the reactions of Δ^1 -piperideines with labile cyclic systems accompanied by ring opening or recyclisation.

Thus 2,3,4,5-tetrahydropyridine **1a** enters into the reaction with thiiranes **317** on heating to 100 °C; these reactions yield 1-aza-7-thiabicyclo[4.3.0]nonane **318**.²⁴⁰



R¹ = R² = H (63%); R¹ = H, R² = Me (67%); R¹ = R² = Me (32%).

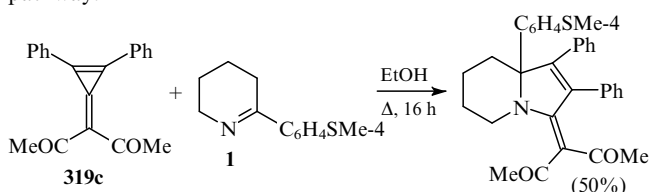
Bicyclic compounds **320** have been synthesised by heating the Δ^1 -piperideines **1** with diphenylcyclopropenone **319a**²⁴¹ or methylenecyclopropene derivative **319b**.²⁴²



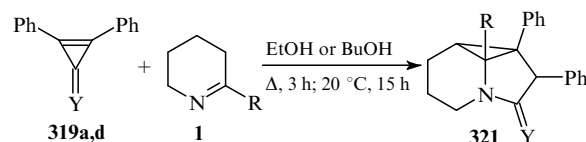
Y = O: R = Me (79%), Et (76%), 2,5-(MeO)₂C₆H₃ (80%).

Y = : R = MeSC₆H₄ (60%), 2,5-(MeO)₂C₆H₃ (77%).

The reaction of 2-(4-methylthio)phenyl-3,4,5,6-tetrahydropyridine with the methylenecyclopropene **319c** follows a different pathway.²⁴²

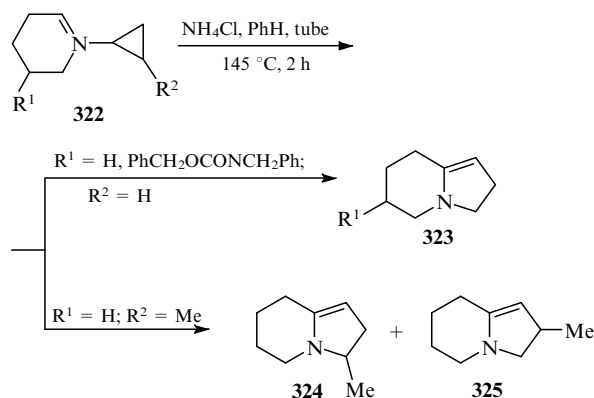


The reaction of the Δ^1 -piperideines **1** with diphenylcyclopropenone **319a** or with the cyclopropenethione **319d** giving tricyclic compounds **321** (yields 46%–82%) is evidently a two-stage process. The first stage gives bicyclic compounds of the type **320**; under the reaction conditions, these products undergo intramolecular cyclisation involving the CH₂ group at the 5-position of the piperidine ring and the C=C bond of the five-membered ring.²⁴¹

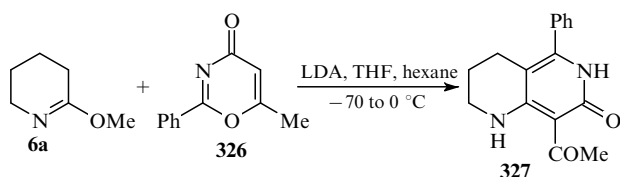


Y = O: R = Ph, 4-MeSC₆H₄; Y = S: R = Me, Et, Ph, 4-MeSC₆H₄, 2,5-(MeO)₂C₆H₃.

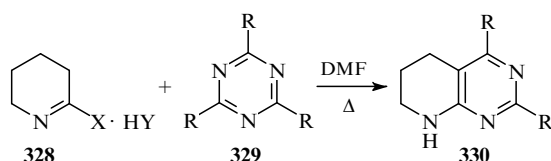
Δ^1 -Piperideines **322**, containing a cyclopropyl substituent at the 2-position, isomerise on heating in the presence of ammonium chloride to give 1-azabicyclo[4.3.0]non-6-ene derivatives; the imines **322** (R² = H) are converted into individual compounds **323**, whereas the imine **322** (R¹ = H, R² = Me) gives two isomeric reaction products **324** and **325**.⁹⁵



10-Acetyl-7-phenyl-2,8-diazabicyclo[4.4.0]deca-6,10-dien-9-one **327** is formed in 56% yield in the reaction of the imide **6a** with 6-methyl-2-phenyl-1,3-oxazin-4-one **326**.²⁴³

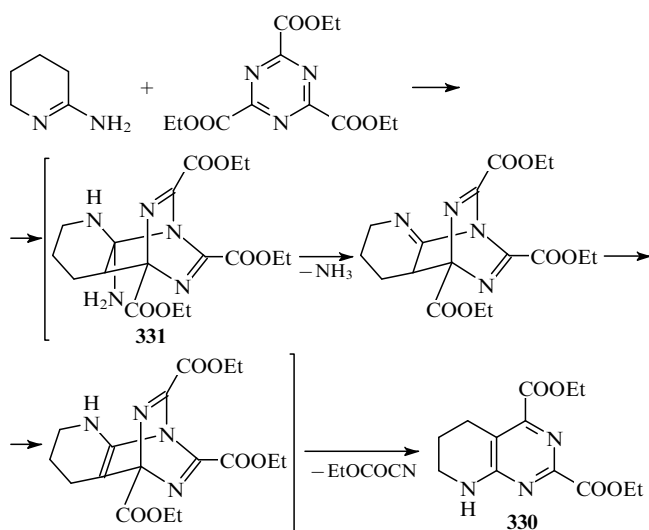


Heating of 2-amino-3,4,5,6-tetrahydropyridine hydrochloride **328** with 1,3,5-triazine or its 2,4,6-tris(triethoxycarbonyl) derivative **329** in DMF gives rise to bicyclic compounds **330** in 63%–75% yields. The reaction of 2-methylthio-3,4,5,6-tetrahydropyridine hydroiodide **328** ($X = \text{SMe}$, $Y = \text{I}$) with triazines follows a similar pathway; however, the corresponding derivatives **330** are formed in low yields.²⁴⁴



$X = \text{NH}_2$, $Y = \text{Cl}$; $X = \text{SMe}$, $Y = \text{I}$; $R = \text{H}$, COOEt .

It was shown that the first stage in the reaction of 2-amino-3,4,5,6-tetrahydropyridine with 1,3,5-triazine is [2 + 4] cycloaddition giving tricyclic compound **331**; this product loses an NH_3 molecule and undergoes the retro Diels–Alder reaction to give the final product **330**.²⁴⁴

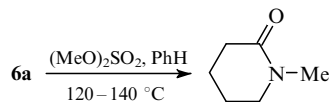


Neither interaction of the imide **6a** with the triazines **329** ($R = \text{H}$, COOEt) nor the reaction of the hydrochloride **328**

($X = \text{NH}_2$, $Y = \text{Cl}$) with 2,4,6-tris(methylthio)triazine gives products of the type **330**.²⁴⁴

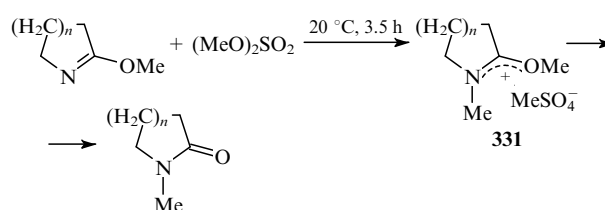
13. Isomerisation

When the imide **6a** is heated with a catalytic amount of dimethyl sulfate, it is converted into *N*-methylpiperidin-2-one in a yield of $>90\%$.³⁷



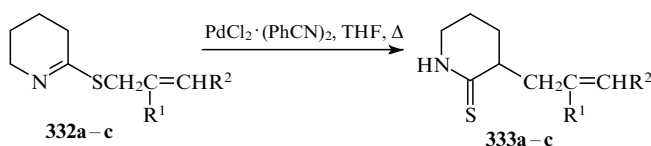
N-Methylpiperidone is also formed (yield 76%) in the absence of dimethyl sulfate when the imide **6a** is heated in boiling benzene for 6 h.²⁴⁵

In a study of the isomerisation of imides into *N*-methylated lactams, it has been found that the rate of formation of the intermediate adducts **331** decreases as the size of the ring increases.²⁴⁶



$n = 1$ – 3 .

On heating in THF in the presence of $\text{PdCl}_2 \cdot (\text{PhCN})_2$, allyl thioimides **332** isomerise to allyl-substituted piperidinethiones **333**.²³¹

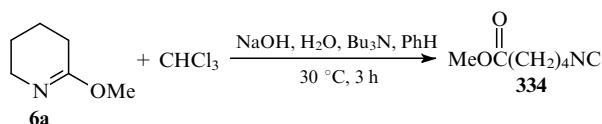


$R^1 = R^2 = \text{H}$ (**a**, 74%), $R^1 = \text{H}$, $R^2 = \text{Ph}$ (**b**, 58%), $R^1 = \text{Me}$, $R^2 = \text{H}$ (**c**, 25%).

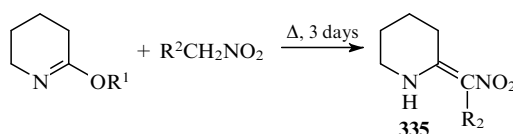
When the rearrangement of the compound **332a** is carried out without a catalyst for 40 h, the yield of the product **333a** is 60%.²³¹

14. Other reactions

The reaction of the imide **6a** with chloroform in the presence of 50% aqueous sodium hydroxide and tributylamine at 30°C is accompanied by opening of the tetrahydropyridine ring and gives isonitrile **334** in 41% yield.²⁴⁷

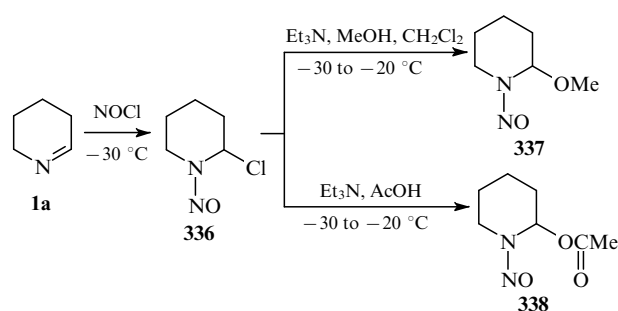


Compounds **335**, serving as the initial compounds in the synthesis of insecticides, have been prepared by condensation of 2-methoxy-3,4,5,6-tetrahydropyridine or 2-ethoxy-3,4,5,6-tetrahydropyridine with nitromethane or nitroethane.^{42, 248}

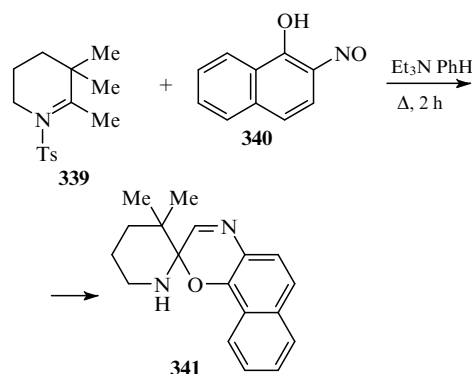


$R^1 = \text{Me}$, Et ; $R^2 = \text{H}$, Me .

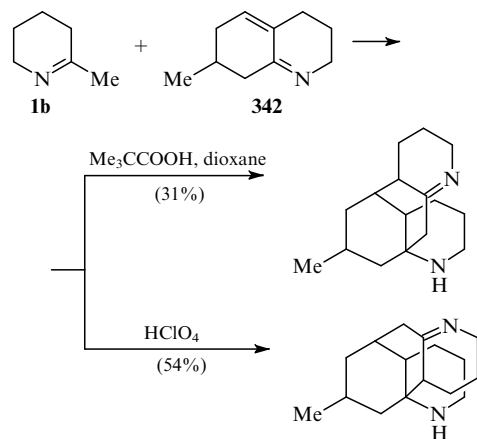
Nitrosyl chloride adds to the $\text{C}=\text{N}$ bond of 2,3,4,5-tetrahydropyridine **1a** at -30°C yielding unstable product **336**. Subsequent treatment of this product with methanol or acetic acid in the presence of triethylamine affords relatively stable methoxy-derivative **337** (yield 30%) or acetoxy-derivative **338** (yield 20%).²⁴⁹



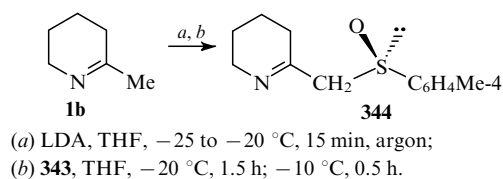
Spiro compound **341** has been synthesised by condensation of 2,3,3-trimethyl-3,4,5,6-tetrahydropyridine tosylate **339** with 1-hydroxy-2-nitronaphthalene **340** in the presence of Et_3N .²⁵⁰



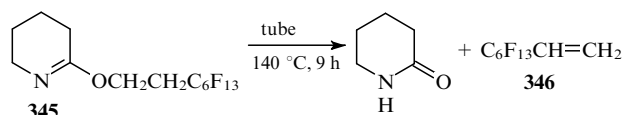
The cyclocondensations of 2-methyl-3,4,5,6-tetrahydropyridine **1b** with 9-methyl-2-azabicyclo[4.4.0]deca-1,7-diene **342** in the presence of trimethylacetic and perchloric acid give different products.¹¹



The reaction of the imine **1b** with (–)-(1*R*,2*S*,5*R*)-menthyl-(*S*)-*p*-tolylsulfate **343** in THF in the presence of LDA gives (+)-2,3,4,5-tetrahydro-6-(*R*)-(–)-*p*-tolylsulfonylethylmethylpyridine **344**.²⁵¹



On heating, imide **345** is cleaved to give piperidin-2-one and the corresponding alkene **346**.⁴⁶



V. Conclusion

The data considered above demonstrate that piperidine and its derivatives arouse obvious and continuing interest. At the same time, some aspects of the chemistry of these highly reactive compounds receive undeservedly little attention. For example, addition to the endocyclic $\text{C}=\text{N}$ bond has not been adequately studied. Virtually no data on the cycloaddition involving the piperidine $\text{C}=\text{N}$ bond, except for the reactions with ketenes, have been reported, although these reactions would provide the possibility of preparing starting compounds for the synthesis of other interesting heterocyclic systems.

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Methods for the immobilisation of hydroxyl-containing stationary liquid phases in capillary gas chromatography

V P Mukhina, V G Berezkin, Ya A Levin

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Abstract. The main results concerning the immobilisation of hydroxyl-containing stationary phases in capillary gas chromatography are surveyed and treated systematically. Attention is concentrated on the influence of the chemical reactions occurring during immobilisation and on the characteristics of the capillary column. It is noted that, together with the improvement of the methods for the immobilisation of known phases, the syntheses of new stationary liquid phases, the properties and the immobilisation conditions of which have been optimised taking into account the characteristics of the objects analysed, are promising. The bibliography includes 176 references.

I. Introduction

Capillary chromatographic methods are mainly employed in modern gas chromatography. This situation became possible as a consequence of the development of a fundamentally new technology for the preparation of open capillary columns with a stationary liquid phase immobilised within the capillary.

The idea of immobilising the stationary liquid phase on the inner surface of a capillary column appeared at the junction of the 1960s–1970s^{1,2} and acquired its present form a decade later as a consequence of the studies by K Grob and G Grob,^{3–7} Blomberg *et al.*,⁸ and Sandra *et al.*⁹

Immobilisation constitutes a method for the stabilisation of a film of a polymeric stationary phase as a result of its structuring (cross-linking) and (in certain cases) grafting to the walls of the capillary column. Immobilisation differs from the traditional methods for the stabilisation of a stationary phase employing different versions of the geometrical and/or chemical modification of the surface of the capillary column^{10–17} by the fact that not only the walls of the column but also the stationary phase film are acted upon directly.

As a result of the immobilisation, the macromolecules of the stationary phase lose their ability to migrate along the inner surface of the column and to form significant local thickened regions. At the same time, the stationary phase acquires a new important property — nonextractibility, which appreciably simplifies the use and regeneration of capillary columns. On comparing the properties of the phase before and after immobilisation, an increase in the reproducibility and stability of the chromatographic characteristics of the column and the expansion of the range of working temperatures were noted and the possibility of obtaining thick (up to 100 μm)^{18,19} and multilayer films of the stationary phase was discovered.^{20,21}

The evident practical advantages of capillary columns with immobilised stationary phases promoted very vigorous research in this field in recent years and led to the rapid practical application of the advances made. Effective methods have been developed to date for the immobilisation of nonpolar and moderately polar polysiloxanes (PS).^{16,22–33} As a rule, the immobilisation of stationary phases of this class is accompanied by minimal changes in their chemical nature and chromatographic characteristics. The methods for the immobilisation of polar stationary phases are associated with considerable difficulties and are being improved.

The review gives a systematic account of experimental data on the immobilisation of hydroxyl-containing stationary phases. Compounds such as di- and poly-ols are of special interest in connection with their unique selectivity in the separation of polar and polarisable sorbates.^{34–40} Poly(ethylene glycols) (PEG) with a high molecular mass (not less than 2×10^4) comprising the commercial brands Carbowax, Superox, CP-WAX, DB-WAX, *etc.* are most often employed as hydroxyl-containing stationary phases in capillary gas chromatographic practice.^{41–44} The chemical structure of the polymer macromolecules corresponds to the general formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_m\text{H}$.⁴⁵

Together with organic hydroxyl-containing stationary phases, α,ω -dihydroxypolysiloxanes are considered in the review.

It is noteworthy that the studies on the method of preparation of capillary columns are within the sphere of commercial interests of the firms manufacturing chromatographic equipment. For this reason, many publications are concerned with advertising, which hinders the interpretation of the results. Although the questions which we have considered have been described to some extent in a series of reviews (see, for example, Refs 12, 28, 46, and 47), new experimental data, which need to be surveyed, have accumulated in recent years.

V P Mukhina, Ya A Levin A E Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre, Russian Academy of Sciences, ul Arbuzova 8, 420088 Kazan, Russian Federation. Fax (7-843) 275 22 53. E-mail: vp@iopc.kcn.ru (V P Mukhina)

V G Berezkin A V Topchiev Institute of Petrochemical Synthesis, Russian Academy of Sciences, Leninskii prosp. 29, 117912 Moscow, Russian Federation. Fax (7-095) 230 22 24. E-mail: berezkin@ips.ac.ru

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II. Radiation-induced initiation

The essential feature of the radiation-induced initiation of the immobilisation of stationary phases is that high-energy radiation is employed for the formation of the initial active centres.

The possibility of the immobilisation of a series of hydroxyl-containing stationary phases, such as Carbowax 20M, CP-WAX 51 ($M = 2 \times 10^4$), Superox 0.1 ($M = 1 \times 10^5$), and Superox 6 ($M = 6 \times 10^6$), under the influence of ^{60}Co γ -radiation^{27, 41, 42, 46–51} and low-temperature argon plasma⁵² has been investigated.

The efficiency of γ -quanta as initiators of the immobilisation of PEG is low. For example it has been possible to immobilise Carbowax 20M to the extent of 90% for an irradiation dose of 24 Mrad,^{49, 51} whereas methylpolysiloxane is 80%–100% cross-linked already after the absorption of 2–10 Mrad.^{28, 29, 50, 53–55} Such results may be regarded as evidence indicating the complexity of the radiation-chemical transformations in the PEG. However, this question has been scarcely investigated.^{56–62} On the basis of the results obtained by capillary gas chromatographic, IR spectroscopic, and ^{13}C NMR methods, it is claimed in a brief communication⁵¹ that hard radiation does not influence appreciably the chemical nature and the permeability of the PEG to diffusion. In our view, this conclusion requires additional confirmation.

Ideas according to which the mechanism of structure formation in polymers under the influence of radiation is of a radical character are most widespread,^{58–60, 63, 64} but one cannot rule out^{43, 60, 63} the possibility of the involvement of ions and radical-ions in cross-linking processes.

The effect of radiation on PEG depends not only on the overall dose absorbed but also on factors such as the average molecular mass of the polymeric stationary phase and the presence in the latter of impurities or specially introduced additives. Thus, for an irradiation dose of 10 Mrad, the degree of immobilisation of the Carbowax 20M and CP-WAX 51 fractions is 10%–14%,^{48, 65} whilst that of the Superox 6 fraction is 25%.⁶⁵ If 5 mass%–10 mass% of cumenyl peroxide is added to CP-WAX 51 under these conditions, the degree of immobilisation of the stationary phase increases to 50%–52%. In the latter case, the polymer is subjected to direct and indirect action of the radiation, the latter consisting in the initiation of the homolysis of the peroxide.

Springston and Dezero⁵² used a low-temperature argon plasma as the initiator of the immobilisation of the PEG of the Superox 0.1 brand. The degree of immobilisation of the stationary phase did not exceed 12% and the capillary columns acquired in addition an adsorption activity.

III. Material initiation

The material initiation of the immobilisation of stationary phases is based on the use of individual compounds capable of decomposing into free radicals in a certain temperature range.

The material initiators of the immobilisation of PEG employed are usually cumenyl peroxide and, more rarely, benzoyl peroxide and aliphatic azo-compounds.

Compared with the nonpolar polysiloxanes, PEG exhibits an appreciably smaller (at least by a factor of 10) capacity for immobilisation under the influence of organic peroxides and azo-compounds, the process being extremely sensitive to experimental conditions. For example, Etler and Vigh⁶⁵ investigated the immobilisation of the PEG of the brand CP-WAX 51, initiated by cumenyl peroxide, on the walls of glass capillaries modified by BaCO_3 crystals. For a ratio of the masses of the stationary phase and cumenyl peroxide of 10:1 and a process temperature of 160–180 °C, the degree of immobilisation of the phase did not exceed 19%. Russo *et al.*⁶⁶ used graphitised lamp black as the modifying agent for the inner surface of the capillaries. For the same content of the initiator at 150 °C, it was possible to

immobilise PEG 20M ($M = 2 \times 10^4$) to the extent of 75%. According to the authors, this entailed grafting the stationary phase to the layer of carbon black adsorbed on the glass. If account is taken of the chemical properties of the surface of the graphitised thermal black^{36, 67} and the inefficiency of the immobilisation of the relatively low-molecular PEG (for example PEG-600 and PEG-1500), it appears unlikely that grafting was the dominant process in the immobilisation of this phase. The degree of immobilisation of the higher-molecular PEG of the brand Superox 4 ($M = 4 \times 10^6$) on the surfaces of capillaries deactivated by tetramethyldiphenyl disilazene (when grafting is impossible in principle) was only 45% under similar conditions.⁶⁸

Glass capillaries with an active (not deactivated) surface have been used in certain experiments.^{69, 70} Thus Yakabe *et al.*⁶⁹ achieved 80% immobilisation of the PEG-20M fraction in the presence of 15% of cumenyl peroxide at a process temperature of 160 °C. Bystricky⁷⁰ required 20%–40% of this initiator in order to achieve the 65%–97% immobilisation of Carbowax 20M at 150 °C.

It is difficult to explain the experimental results obtained in the above studies.^{69, 71} According to Yakabe *et al.*,⁶⁹ when the cumenyl peroxide content is 2%–3% the degree of immobilisation of PEG 20M on glass is 60% whilst according to Buijten *et al.*⁷¹ the degree of immobilisation on PEG of the brand CPTM-WAX 40M ($M = 4 \times 10^4$) on quartz deactivated by PEG 20M is only 3%.⁷¹

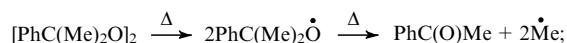
Thus it is evident that the immobilisation of PEG under the influence of cumenyl peroxide is affected also by uncontrollable objective and subjective factors. For example PEG 20M specimens of different origin can differ in the degree of polydispersity and in the amount and nature of the admixture of the polymerisation catalyst.⁷²

According to the results of the studies examined above, the use of higher concentrations of cumenyl peroxide does ultimately lead to the desired result namely the immobilisation of PEG, but according to the view of the majority of the investigators it impairs the efficiency^{66, 69, 73} and the adsorption inertness^{66, 71, 73–75} of the capillary columns. Furthermore, immobilisation under the influence of this initiator alters the polarity of the PEG^{69, 71, 73, 75, 76} and imparts acid properties to the stationary phase.^{68, 69, 73, 77, 78} Martinez de la Gandara *et al.*⁷³ concluded that the classical immobilisation method in which the initiator is introduced into the solution of the phase before depositing it onto the walls of the capillary is partly a source of such problems. The authors developed a two-stage method providing for the deposition of cumenyl peroxide as a separate layer onto a film of the stationary phase. However, this technical procedure did not afford appreciable advantages: an adequate degree of immobilisation (80%–90%) of Carbowax 20M was attained after the addition of 20% of the peroxide, but the immobilised phase manifested acid properties as before. Blomberg and Markides⁷⁹ also used a two-stage method but noted a low reproducibility of the results.

It was noted above that PEG is immobilised under the influence of organic peroxides appreciably less effectively than polysiloxanes. We shall consider in greater detail the causes of this phenomenon. Blum⁸⁰ believes that, in the immobilisation of PEG, an appreciable proportion of the peroxide is consumed on the side reaction involving the oxidation of the terminal hydroxy groups. There is no doubt that this process does occur. However, the number of OH groups in high-molecular PEG is small. For example, the proportion is $\sim 0.17\%$ in Carbowax 20M.⁸¹ Furthermore it is known^{43, 82} that alkyl peroxides are capable of inducing not only the polymerisation but also the depolymerisation of PEG. In addition, the radicals arising in the thermolysis of the peroxide are capable of being incorporated in the chemical structure of the polymer,^{23, 29, 83} which undoubtedly influences the immobilisation process. Finally, the macroradicals formed from the PEG and responsible for this cross-linking are capable of decomposing with dissociation of the polymer chain.^{84–86} Bearing

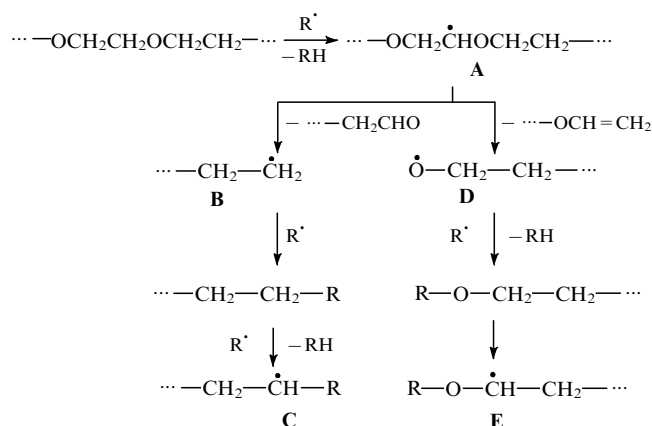
this in mind, one can assume that the immobilisation of PEG under the influence of cumenyl peroxide includes the following stages:

(1) Initiation of the free-radical reaction



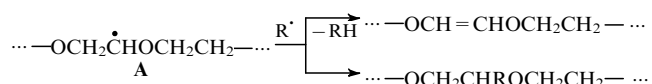
(2) The formation of the macroradicals **A–E** and others as a result of the occurrence of various reactions, for example $\text{S}_{\text{N}}2$ substitution reactions (abstraction of hydrogen), addition reactions, and β -cleavage (Scheme 1):

Scheme 1



R' is any free radical present in the system: methyl, cumenyl, etc., a macroradical.

(3) The recombination and disproportionation of macroradicals, which leads to the termination of the kinetic chain, for example with participation of the radical **A**:



If R' is a macroradical, then recombination leads to the cross-linking of the macrochains and to a gradual development of immobilisation.

One cannot rule out the possibility of the occurrence also of other reactions, in particular those associated with the heterolytic decomposition of cumenyl peroxide and the presence of traces of O_2 , H_2O , etc.

Thus the cause of the comparatively low efficiency of the immobilisation of PEG under the influence of peroxides is apparently that the macroradicals of many types (and especially of type **A**) undergo unimolecular β -decomposition (degradation of the polymer), leading, to a decrease in the degree of polymerisation of the PEG. This effect may be compensated by the high rate of generation of radicals obtained at a high initial peroxide concentration when the competition between radical–radical interactions (second order with respect to the radical) and the decomposition reaction (first order with respect to the radical) does not have an outcome in favour of the latter. There is also the possibility of other ways of solving the problem. For example, the radical immobilisation of PEG is facilitated by the introduction of vinyl groups⁸⁴ into the polymer structure or by employing special active additives (see below).

Comparison of the radiation-induced and chemical initiations of the immobilisation of hydroxyl-containing stationary phases has shown that the efficiency of both procedures is low, but the radiation method has experimental advantages: firstly, the heating of the capillary column before the immobilisation of the stationary phase is eliminated and, secondly, the process initiator (the source of radiation) is outside the column. Consequently the film of the stationary phase is acted upon not thermally and is not

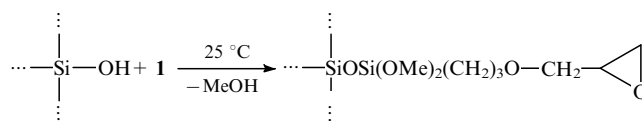
contaminated by the initiator decomposition products as in material initiation.

IV. Composite immobilisation

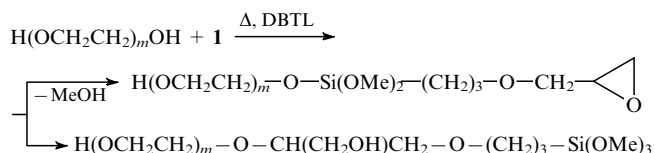
In order to increase the efficiency of the immobilisation of hydroxyl-containing stationary phases, cross-linking and cross-linking-grafting polyfunctional agents are frequently employed. The main function of the former is to form chemical cross-links between the macromolecules of the stationary phase; together with this feature, the latter are capable of grafting the phase to the walls of the column. Incidentally, when the inner surface of the column is modified appropriately, cross-linking agent can also induce the grafting of the phase to the wall of the column. At the same time, the cross-linking-grafting agent can itself act as a modifying agent, generating on the walls of the column an intermediate mono- or poly-molecular layer capable of interacting with the stationary phase. Since cross-linking and cross-linking-grafting agents usually constitute an appreciable proportion of the mass of the immobilised stationary phase, the immobilisation with their participation may be referred to as composite immobilisation. Polyfunctional alkoxy- and acetoxy-silanes are most widely employed as cross-linking-grafting agents: γ -glycidyloxypropyltrimethoxysilane **1**,^{87–90} trimethoxyvinylsilane **2**,⁸⁷ triethoxymethylsilane **3**,^{88,89} and tetraacetoxysilane **4**.⁹¹

Traitler *et al.*⁸⁷ were the first to suggest that alkoxy-silanes (**1** or **2**) be used for the immobilisation of Carbowax 20M. A mixture of cumenyl peroxide and dibutyltin dilaurate (DBTL) served as the process initiator. The silane **1** makes it possible to obtain more thermally stable and adsorption-inert capillary columns. For a mass ratio of the stationary phase and compound **1** of 2 : 1, the degree of immobilisation of Carbowax 20M on the surface of borosilicate glass was 70%–75%, which is lower by 10%–25% than on quartz. According to the authors, this is a result of the catalytic action of the alkali and alkaline earth metals entering into the composition of the glass. Since a strong catalyst is present in sufficient amount (1.34% of DBTL) in the immobilised mixture, we suggest that other causes may also exist. It may be that the hydroxylated surface of the glass ensures more effective grafting of the stationary phase. On the basis of the ideas developed in a number of studies,^{92–95} the immobilisation of PEG with participation of the silane **1** can be represented as follows:

(1) Chemical modification of the column walls.^{92–94}



(2) Chemical modification of the stationary phase.⁹⁵



(3) Structure formation and grafting of the stationary phase to the column walls. This stage is difficult to describe in the form of a scheme, since it is a complex set of inter-related and parallel homolytic and heterolytic reactions.

It follows from the schemes presented that the transesterification of the alkoxy groups of the silane by the silanol groups on the surface of the capillary columns and the aliphatic OH groups of the stationary phase makes an important contribution to the immobilisation of PEG in the presence of the silane **1**. In practice, certain stages of the immobilisation process coincide. Thus, a version of the combination of (2) + (3) stages has been developed,⁸⁷ whilst in other investigations^{88–90} the (1) + (2) + (3)

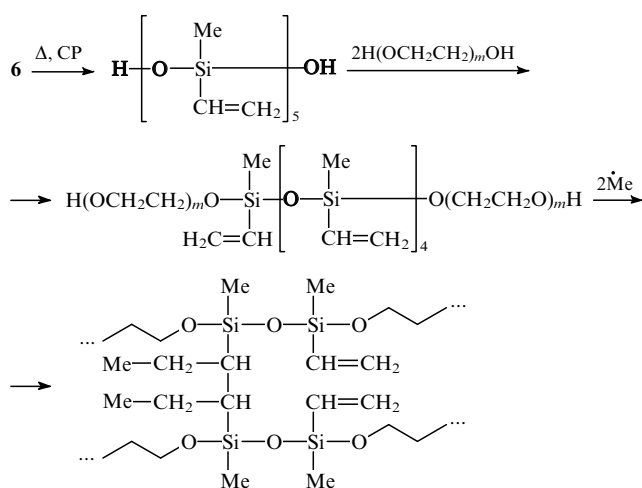
version was devised. It is noteworthy that, as a consequence of the high reactivity of alkoxysilanes, the structures of the immobilised stationary phase is extremely sensitive to the presence of impurities in the reaction medium. Thus at an elevated temperature traces of H_2O and O_2 induce the polymerisation of the silane **1** and also of the products of its interaction with glass and PEG. The polymerisation leads to the formation of siloxane polyethers.

Traitler's idea was developed further in Blum's investigations,^{88,89} devoted to the immobilisation of a series of block copolymers of ethylene and propylene oxides (UCON 50HB 2000, 2800 and 5100, LB 550X, Pluronic P-94, as well as N,N,N',N' -tetrasubstituted ethylenediamines (Sinperonik T/904, T/908). Blum abandoned the use of cumenyl peroxide and DBTL, because the role of the cumenyl peroxide-initiated radical processes in the immobilisation of PEG in the presence of alkoxysilanes is slight, while DBTL may impart an undesirable catalytic activity to the capillary column.

Alkoxy- and acetoxy-silanes and siloxanes have been used successfully also in the immobilisation of other hydroxyl-containing stationary phases, for example α,ω -dihydroxypolysiloxanes.^{91,96–99}

Certain organic compounds containing more than one non-conjugated double bond have found an application as cross-linking agents for PEG and its analogues: 2,4,6,8-tetramethyl-2,4,6,8-tetravinylcyclotetrasiloxane **5**,¹⁰⁰ 2,4,6,8,10-pentamethyl-2,4,6,8,10-pentavinylcyclopentasiloxane **6**,⁷¹ 1,1,3,5,5-pentamethyl-1,3,5-trivinyltrisiloxane **7**,¹⁰⁰ and triallyl isocyanurate **8**.⁶⁹ The detailed mechanism of the cumenyl peroxide-initiated immobilisation of PEG with participation of the above compounds has not been established. The attempt to use NMR spectroscopy for this purpose was unsuccessful as a consequence of the low sensitivity of the method.⁷⁹

Buijten *et al.*⁷¹ proposed a method for the immobilisation of the PEG of the CP™-WAX 40M brand with the aid of methylvinylcyclopentasiloxane. They suggest that the process begins with the opening of the siloxane ring and its condensation with the PEG. The immobilisation proper of the phase is attained as a result of the cumenyl peroxide-initiated structure formation involving the siloxane fragments in the copolymer obtained. The following process mechanism has been put forward:



CP = cumenyl peroxide.

However, this route for the process is possible only in the presence of certain substances — acids, bases, and certain salts — capable of cleaving the siloxane linkage and of catalysing the polycondensation.⁴⁵ Organic peroxides induce structure formation in cyclosiloxanes without ring opening.^{83,101} For this reason, in the presence of cumenyl peroxide the development of radical chain processes is most probable in the system under consideration, whereupon the polymerisation of methylvinylcyclopentasiloxane, its grafting to a PEG macromolecule, as well as structure formation in the PEG and in the copolymer formed take

place simultaneously. The mechanism proposed by the authors can operate as a side process when the stationary liquid phase contains an appreciable amount of an admixture of a polymerisation catalyst or the inner surface of the capillary column is insufficiently deactivated.

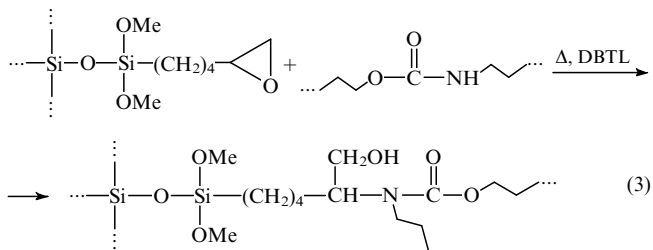
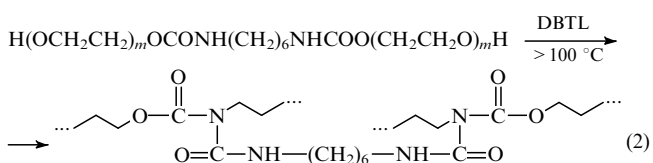
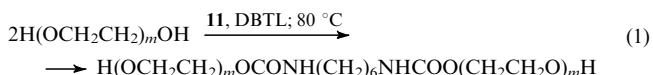
Siloxanes without vinyl groups also possess the properties of cross-linking agents but they are less reactive. Thus, when the cyclosiloxane **6** is replaced by octamethylcyclotetrasiloxane **9**, the degree of immobilisation of CP™-WAX 40M diminishes by a factor of 2.⁷¹

Schomburg *et al.*¹⁰² immobilised Carbowax 20M using acryloylvaline-(*S*)- α -phenylethyl amide **10** containing one vinyl group. However, the latter is not a cross-linking agent. It is a chiral modifying agent which is grafted to the Carbowax 20M macromolecules in the course of the radical immobilisation. As a result, the immobilised phase acquires the property of enantioselectivity. In the study under consideration, the possibility of a deliberate alteration of the selectivity of the stationary phase in the course of immobilisation was first demonstrated. The structural fragments incorporating the immobilised phase are always chosen so that they resemble the sorbates being separated.^{103,104}

Aliphatic and aromatic di- and poly-isocyanates constitute a special group of cross-linking agents: $\text{OCN}(\text{CH}_2)_6\text{NCO}$ **11**, $\text{OCN}(\text{CH}_2)_6\text{N}[\text{CONH}(\text{CH}_2)_6\text{NCO}]_2$ **12**, and $\text{MeCH}_2\text{C}[\text{CH}_2\text{O}-\text{CONHC}_6\text{H}_3(\text{NCO})\text{Me}]_3$ **13**.

The method for the immobilisation of PEG, its analogues, and acid derivatives (Carbowax 20M, Castorwax DD-026, Carbowax 20M-TPA, OV-351, FFAP) under consideration was developed further in the studies of Horka and coworkers.^{105–111}

The immobilisation of hydroxyl-containing stationary phase with participation of isocyanates proceeds in the following manner.^{45,47,112,113} In the presence of the DBTL catalyst or 1,4-diazabicyclo[2,2,2]octane (DABCO), the CO group of the isocyanate reacts with the OH groups of the phase with formation of urethane groups [process (1)]. The latter are extremely reactive and interact with the excess isocyanate and the silane **1** — the agent modifying the inner surface of the capillary column. Allophanate fragments, cross-linking the copolymer [process (2)] arise under these conditions, and the copolymer is also grafted to the walls of the capillary column [process (3)]:



According to the data of Horka and coworkers,^{47,105,106} the immobilisation of PEG with participation of the isocyanates **11–13** makes it possible to obtain stationary phases which are thermally stable up to 305–320 °C. However, these data are inconsistent with the known facts. Thus it has been established^{43,114} that above 200 °C the urethane fragments dissociate *via* a depolymerisation mechanism. There is a possibility of the dissociation of bonds with formation of an olefin and a primary amine.⁶³ The thermal degradation of the allophanate groups

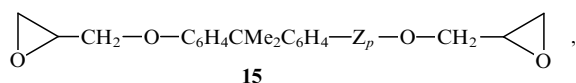
begins already at 120 °C. In the range 300–320 °C, PEG decomposes at an appreciable rate.⁴³ Evidently, in characterising the thermal stability of the stationary phase, it is insufficient to determine the maximum working temperature on attainment of which the properties of the phase are still not significantly impaired. One should also have an idea about the 'lifetime' of the column (or the magnitude of the background flow) at this temperature and about the chemical inertness of the phase in the region of high temperatures.

The immobilisation of acid derivatives of PEG by the method of Horka and coworker^{105–111} is distinguished by the fact that, together with the isocyanate, 3,5-dinitrosalicylic acid (3,5-DNSA) is introduced into the reaction mixture. Apparently the acid is necessary to compensate for the loss of carboxy groups and hence of the specific properties of the phase in the course of immobilisation. Furthermore, if one considers the possible interactions in the PEG–isocyanate–3,5-DNSA system, it becomes evident that the carboxy group is retained only by the part of the acid which does not enter into the structure of the stationary phase. This conclusion is confirmed by data concerning the loss of acid properties after the extraction of the phase by a series of organic solvents.⁴⁷

There have been few studies devoted to the immobilisation of relatively low-molecular PEG ($M < 10^4$). This is evidently associated with the limited stability of films of such stationary phases on the surfaces of glass and quartz and with the narrow range of working temperatures.³⁷ However, low-molecular PEG is characterised by a high functional selectivity.^{36, 37} Thus, on passing from PEG 20M to PEG 600, the McReynolds constants (indices) $y-z$ increase by 60–95 units. In capillary gas chromatography, the requirement for phases with a high functional selectivity has not so far been satisfied,^{115–122} so that the development of methods for the immobilisation of low-molecular glycols appears of very great current interest.

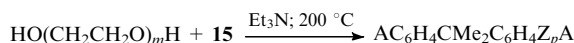
A novel method for the immobilisation of PEG 2500 and PEG 10 000 has been proposed by Sandra *et al.*⁷² The composition comprising PEG and 3-triethoxysilylpropyl isocyanate **14** is immobilised on the walls of a quartz capillary by treatment with water, which is injected in pulses into the flow of carrier gas. The development of the process begins with the hydrolysis of the isocyanate **14**, whereupon a siloxane polyisocyanate is formed¹²³ and its action is subsequently similar to that of the organic isocyanates examined above.

The method of the immobilisation of low-molecular PEG 400 proposed by Mukhina and coworkers^{124, 125} is based on the interaction with the bisphenol A epoxide resin (BE):



$\text{Z} = \text{OCH}_2\text{CH}(\text{OH})\text{CH}_2\text{OC}_6\text{H}_4\text{CMe}_2\text{C}_6\text{H}_4$, $p = 0-3$.

According to the ideas developed in a number of investigations,^{95, 126–130} the stationary phase is in this case immobilised in the following manner. Under the influence of the catalyst (triethylamine), the hydroxy groups of the PEG react with the epoxide groups of BE, which results in the formation of a linear copolymer.



$\text{A} = \text{OCH}_2\text{CH}(\text{OH})\text{CH}_2(\text{OCH}_2\text{CH}_2)_m\text{OH}$.

In the presence of an excess of BE (for the molar ratio PEG:BE < 1), structure formation involving secondary OH groups takes place in the copolymer. There is a possibility of grafting the phase to the surface of glass *via* the both epoxide¹³¹ and hydroxy groups.¹³² Out of the multiplicity of compounds capable of accelerating the interaction of PEG 400 and BE, the

authors gave preference to triethylamine taking into account not only its activity as a catalyst but also its possible influence on the chemical inertness as well as the catalytic and adsorption properties of the stationary phase. As a cross-linking agent, the BE resin also has a series of advantages: firstly, it exhibits a satisfactory adhesion to the surface of glass and quartz, which stabilises the stationary phase film on the walls of the capillary column; secondly, the BE macromolecules contain no functional groups other than the terminal epoxide and aliphatic OH groups and the resin is a polyether like PEG, *i.e.* the characteristics of their thermal and chemical stabilities are comparable;¹³³ thirdly, the loss of hydroxy groups by the PEG on interaction with BE is compensated by the formation of new OH groups.

Thus the use of the agents **1–15** generally promotes an increase in the efficiency of the immobilisation of hydroxyl-containing stationary phases (Table 1). However the problem of increasing the quality of the immobilised phase remains. Thus the copolymer of the PEG of the Superox 4TM brand and the siloxane **7** has basic and acid adsorption centres;⁷⁵ the PEG of the brand CPTTM-WAX 40M, immobilised with the aid of the siloxane **6**, exhibits weak acid properties;⁷¹ Carbowax 20M, immobilised in the presence of the isocyanates **11–13**, is distimety.⁴² Triallyl isocyanurate, used in an amount of 10% relative to the mass of PEG 20M, induces an asymmetry in the chromatographic peaks of all of Grob's test sorbates.⁶⁹ This is probably a consequence of the high functionality of the agents employed.

Regardless of the way in which it is carried out, immobilisation disturbs the molecular order in PEG,^{134, 135} which lowers the degree of crystallinity and the melting point of the stationary phase. This effect is less pronounced in the radiation-induced immobilisation of PEG and is most marked for composite immobilisation. Fernandez-Sanchez *et al.*¹³⁴ established that at 40 °C the degree of crystallinity of PEG of the Superox 20M brand is 83%–86%, while after immobilisation by means of cumenyl peroxide using Bystricky's method⁷⁰ it is 47%–53%. On the other hand, the fraction of the crystalline phase of the polymer immobilised with participation of the silane **1** by the method of Trautler *et al.*⁸⁷ is only 24%–31%. The minimum working temperature of the immobilised high-molecular PEG is reduced in most cases by 20–30 °C.^{49, 51, 65, 70, 71, 77, 134–137} This effect is well illustrated by the temperature dependence of the retention of the sorbate on a column containing PEG 20M before and after immobilisation (Fig. 1). However, the use of large amounts of reagents leads to the opposite result — an increase in the lower limit of the working temperatures owing to the high density of structure formation in the stationary phase.^{87, 107, 110}

It is noteworthy that composite immobilisation leads in most cases to the formation of new phases which may be characterised as statistical copolymers of the initial phases and the cross-linking agents.

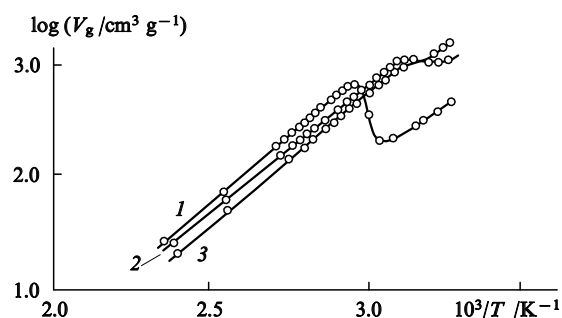


Figure 1. Temperature dependence of the retention of 1-butanol on capillary columns containing PEG 20M before (*1*) and after immobilisation by treatment with cumenyl peroxide (*2*) or a mixture of cumenyl peroxide with γ -glycidyloxypropyltrimethoxysilane (*3*).¹³⁴

Table 1. Immobilisation of PEG and its analogues.

Column material	Column modifying agent	Initiator or catalyst		Cross-linking agent		Immobilisation conditions			Z (%)	SP working temperature range /°C	Ref.
		<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	regime	<i>T</i> /°C	τ /h			
Stationary phase — CP-WAX 51											
B-glass	BaCO ₃	γ - ⁶⁰ Co	(10)	—	—	st	25	—	10	> 40	65
	BaCO ₃	γ - ⁶⁰ Co, CP	(10), 5–10	—	—	"	25	—	50–65	> 40	65
	BaCO ₃	CP	10	—	—	"	180	2	19	—	65
Stationary phase — CP™-WAX 40M											
Quartz	PEG	CP	2	—	—	dn	200	1	3	—	71
Na-glass, quartz	PEG	CP	2	9	4	dn	200	1	40	30–300	71
	—	—	—	ethylene oxide	—	st	280	3	67	30–260	71
	PEG	CP	20	2	4	st	200	1	80–90	30–300	71
Stationary phase — Superox 01											
Quartz	—	plasma Ar	—	—	—	st	25	—	12	—	52
Stationary phase — Superox 4											
Glass	DPS	CP	5	—	—	st	180	1	32	< 280	68
	DPS	CP	10	—	—	"	180	1	45	< 280	68
	DPS	Irganox	10, 10	—	—	"	180	1	100	—	68
	DPS	AtO	10	—	—	"	180	1	0	—	68
Stationary phase — Superox 4™											
Pyrex, quartz	PEG	CP	3	7	10	st, dn	180	3	30	—	75
	PEG	CP	3	7	50	"	180	3	90	—	75
Stationary phase — Superox 6											
B-glass	BaCO ₃	γ - ⁶⁰ Co	(10)	—	—	st	25	—	25	> 40	65
Stationary phase — Carbowax 20M											
Quartz	—	γ - ⁶⁰ Co	(24)	—	—	—	25	—	90	30–280	49, 51
	1	CP, DBTL	1.50, 1.35	1	50	dn	240	24	50–60	80–280	87
B-glass, Na-glass	SE-54	γ - ⁶⁰ Co	(2)	—	—	st	25	—	3	—	48
	SE-54	γ - ⁶⁰ Co	(10)	—	—	"	25	—	14	—	48
	—	CP	20	—	—	dn	150	2	65	< 260	70
	—	CP	40	—	—	"	150	2	97	< 260	70
Pyrex	1	CP, DBTL	1.50, 1.35	1	50	"	240	24	70–75	80–280	87
	PEG	CP	20	—	—	st	130	1	80–90	—	73
Stationary phase — Carbowax 20M											
Simax	1	DBTL	1	11	17	st	145	6	87	60–305	105, 106
	1	DBTL	1	11	25	"	145	6	98	60–305	105, 106
	1	DABCO	1	12	15	"	145	6	97	60–310	107
	1	DABCO	1	13	20	"	145	6	97	60–320	107
Na-glass, quartz	PEG	CP	40	10	100	"	200	—	—	—	102
Stationary phase — Carbowax 20M-TPA (FFAP, OV-351)											
Simax	1	DABCO	1	13 , 3,5-DNSA	20, 10	st	145	5	97–100	60–220	109
Stationary phase — Carbowax 20™											
Pyrex	PEG	CP	3	7	50	st, dn	180	3	50	—	75
Stationary phase — Castrowax DD-026											
Simax	1	DABCO	0.1	13	55	st	145	5	96	80–225	110

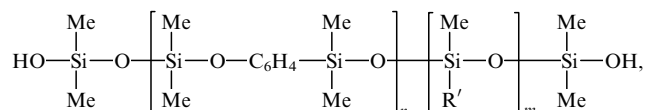
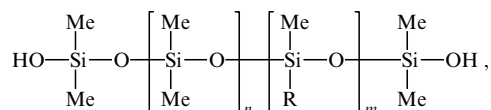
Table 1 (continued).

Column material	Column modifying agent	Initiator or catalyst		Cross-linking agent		Immobilisation conditions			Z (%)	SP working temperature range /°C	Ref.
		<i>I</i>	<i>II</i>	<i>III</i>	<i>IV</i>	regime	<i>T</i> /°C	τ/h			
Stationary phase — PEG 20M											
B-glass	GTB	CP	5	—	—	st	150	1	75	—	66
	GTB	CP	30	—	—	"	150	1	80	—	66
	—	BP	10	—	—	"	200	1	90	40–280	77
Quartz	—	CP	3	3	5	st	160	1	80	—	69
	—	CP	5	3	5	"	160	1	85	—	69
	—	CP	—	—	—	st	160–200	4–6	40–84	< 300	100
Glass	NaCl	BF ₃	—	1	—	st	150	4	—	—	90
Pyrex	—	CP	3	—	—	dn	160	1	50	—	69
	—	CP	15	—	—	dn	160	1	80	—	69
Stationary phase — PEG 2500, PEG-NM 10 000											
Quartz	PEG	H ₂ O	—	14	—	dn	150	0.25	—	—	72
Stationary phase — PEG 400											
Pyrex	—	(C ₂ H ₅) ₃ N	—	15	100	st	200	2	55–61	30–280	124, 125
Stationary phase — acrylic aster of PEG 20M											
Glass	NaCl	AIBN	0.1–1	—	—	st	100	2	—	—	84
Stationary phase — diethyleneglycol adipate											
Pyrex	PEG	CP	20	—	—	st	130	1	60	—	73
Stationary phase — UCON (50HB-2000, 2800, 5100, LB550X)											
Glass	3	CF ₃ COOH	0.5	3	7	st	200	2	50	20–250	88
Stationary phase — Pluronic P-94											
Glass	1	CCl ₃ COOH	4	1	—	st	200	2	20	20–250	88
Stationary phase — Sinperonik T/904, T/908											
Glass	1	Irganox	0.8	1	8	st	200	2	90–100	< 280	89

Note. The following designations have been adopted: *I* — initiator or catalyst; *II* — concentration of initiator or catalyst (mass %) [the irradiation dose (Mrad) is indicated in brackets]; *III* — cross-linking or cross-linking-grafting agent; *IV* — concentration of cross-linking or cross-linking-grafting agent (mass %); SP — stationary phase; st — static immobilisation regime (in a sealed column); dn — dynamic immobilisation regime (in a stream of carrier gas); *Z* — immobilisation efficiency equal to the ratio of the capacity factors of the capillary columns before (*K*) and after (*K'*) extraction of the immobilised stationary phase: $Z = (K/K')100$; DPS — diphenyltetramethylsilazane; Irganox — pentaerythritol tetrakis-3,5-di-*tert*-butylphenyl-β-4-hydroxypropionate; GTB — graphitised thermal black; BP — benzoyl peroxide; AIBN — azobisisobutyronitrile; 3,5-DNSA — 3,5-dinitrosalicylic acid; AtO — azo-*tert*-octane; SE-54 — methylsiloxane containing 5% of phenylpolysiloxane units. Cross-linking and cross-linking-grafting agents: **1–15** — see text. The isocyanates **12** and **13** tend to undergo oligomerisation; the corresponding oligomers are known under the commercial names Desmodur N75 (the number of functional groups is 5–6) and Desmodur L75 (the number of functional groups is 6–7). The main properties of the stationary phases of the commercial brands indicated are quoted in chromatographic handbooks and Company Catalogues.

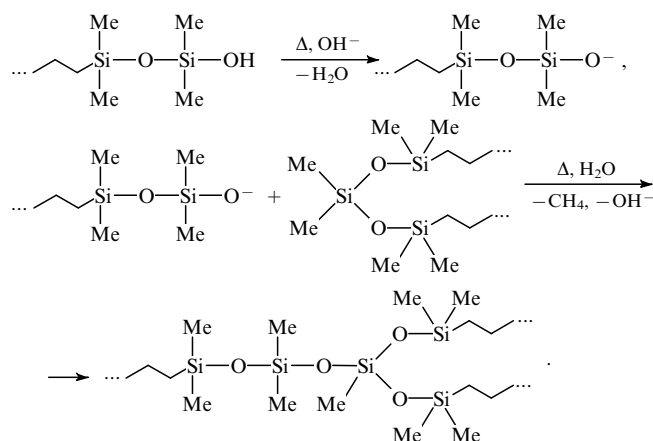
V. Thermal immobilisation

In the majority of methods for the immobilisation of the stationary phase, use is made of the activating effect of thermal energy. Furthermore, in the case of polymeric stationary phases with a specific structure, the thermal energy can function as the principal initiator of the immobilisation process. This was illustrated for the first time in relation to the immobilisation of α,ω-dihydroxypolysiloxanes^{97, 99, 138–140} and α,ω-dihydroxysilarenes.^{141, 142}



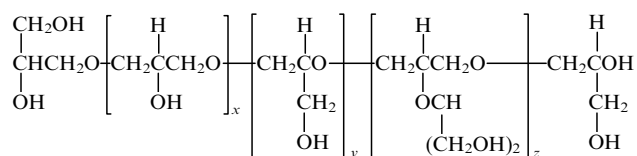
R = Me, Ph, (CH₂)₃CN, (CH₂)₃CF₃; R' = Me, Ph.

On the basis of the analysis of the volatile products formed on thermal immobilisation of α,ω-dihydroxypolysiloxanes, Welsch and Teichmann¹⁴³ proposed the following process mechanism. Under the influence of temperature and catalytically active impurities (traces of O₂, H₂O and the basic catalyst for the polymerisation of the stationary phases), present in the column, siloxide ions are formed and attack the Si–C bond of the polymer and/or the silanised surface of the column. The corresponding hydrocarbon is then evolved and the cross-linking and grafting of the stationary phase take place.



Polycondensation *via* silanol groups makes an appreciably smaller contribution to the immobilisation of α,ω -dihydroxypolysiloxanes than was postulated initially.^{138, 139, 144–149} The application of the thermal method for the immobilisation of polysiloxanes improves significantly the inertness and thermal stability of the capillary column. As a consequence of this, the possibilities of capillary gas chromatography for high-temperature analysis have expanded. Using thermally immobilised α,ω -dihydroxypolysiloxanes, Blum and coworkers^{98, 150, 151} developed methods for the direct gas-chromatographic determination of petroleum porphyrin bases, their metal complexes, and other organic compounds with molecular masses up to 1196 (the traditional applications of gas chromatography involve compounds with molecular masses up to 500).¹⁵² However, on increase in the content of functional groups, the capacity of α,ω -dihydroxypolysiloxanes for immobilisation under the influence of temperature diminishes. Thus the degree of thermal immobilisation of α,ω -dihydroxypolysiloxane containing 60% of cyanopropyl groups does not exceed 40%.¹⁴⁰ For this reason, the polar α,ω -dihydroxypolysiloxanes are usually immobilised with the aid of cross-linking-grafting agents.^{91, 98, 99}

The thermal method has been used by ourselves in the immobilisation of a hydroxyl-containing stationary phase with a polyglycidol (PG) structure.^{153, 154}



It was proposed to use the capacity of polyalcohols for structure formation on heating as a result of dehydration.¹⁵⁵ Evidently the main condition governing the application of this approach in chromatography is an optimum hydroxyl functionality of the initial polymer, ensuring not only its capacity for structure formation but also the permeability of the structured polymer film to sorbate molecules over a sufficiently wide temperature range. The range of working temperatures of the PG-based thermally immobilised phase (PGTM) is from 80 to 300 °C. The chromatographic characteristics of PG change only slightly in the thermal immobilisation process. This makes it possible to postulate that the chemical nature of the bulk of the stationary phase, accessible to sorbate molecules, also hardly changes, *i.e.* an appreciable proportion of the OH groups are retained, although the phases are in fact immobilised *via* these groups. The PGTM-based thermally immobilised phase is characterised by a high resistance to the action of organic solvents and water even at an elevated temperature.

The resistance of immobilised polar phases to the action of solvents is known^{7, 24, 28, 29} to be determined to a large extent by the presence of chemical bonds between the stationary phase and the walls of the capillary column. However, in the case under

consideration the multicentre sorption of the hydroxyl-containing PGTM macromolecules on the dehydrated surface of the glass column is apparently of decisive importance. Among the disadvantages of PGTM one should note the low permeability of this phase to diffusion, which is largely caused by the low segmental mobility of the polymer macromolecules owing to the high density of the hydrogen bonds. When PGTM is used under the conditions of steam chromatography, water loosens the supermolecular structure of the stationary phase films and hence the HETP is reduced by a factor of 2.8, while the minimum working temperature falls by 40–45 °C. On the other hand, the functional selectivity of PGTM increases by only 5%. It is of interest that the corresponding characteristics of PEG 20M under analogous conditions vary in a different way: the selectivity of the phase changes most appreciably (it increases on average by 20%), whereas the efficiency of the separation increases only by a factor of 1.1. By virtue of the high content of the reactive OH groups and the resistance to the action of solvents, PGTM may be used as a matrix for the preparation of new polar immobilised stationary phases *via* their chemical modification *in situ*.¹⁵⁶

Thus the thermal method for the immobilisation of hydroxyl-containing stationary phases makes it possible to obtain the most inert and thermally stable capillary columns and also leads to new possibilities in the synthesis of polar immobilised phases.

VI. Design of hydroxyl-containing stationary phases to be immobilised

Until recently polymeric materials obtained for other purposes have been used as the stationary phases in capillary gas chromatography.^{36, 37} However, it was found that the properties of many stationary phases do not meet the necessary set of requirements most fully formulated by Blomberg.³⁹ According to these requirements, the stationary phases must possess a definite type of selectivity, chemical inertness, thermal stability, reproducibility of properties, an adequate diffusional permeability, and the capacity for immobilisation *in situ*. The experimental data accumulated towards the middle of the 1980s made it possible to proceed to the deliberate synthesis of phases specially designed for capillary gas chromatography.^{115, 116, 120, 157–160} Computer modelling has been used in recent years to determine the composition, structure, and immobilisation conditions for new phases employed in the analysis of specific objects.^{23, 120, 161–164} For example, the stationary phase DB-Dioxin, described by Lautamo *et al.*¹⁶² and Jennings and Nikelly,¹⁶³ represents the application of a computer model of a selective stationary phase for the separation of a series of isomers of polychlorinated dibenzo-*p*-dioxins and dibenzofurans.

The search for phases comparable to PEG in their selectivity but having a wider range of working temperatures and more readily immobilised, is being prosecuted. For this purpose, studies are made on block copolymers of dimethylpolysiloxane and PEG¹⁶⁵ and on copolymers of ethylene glycol and siloxane (brand OV-330 phase).⁷¹ However, polysiloxanes of grafted oligo(ethylene oxide) fragments (PS-OEO) exhibited the best chromatographic characteristics.^{166–169}



$R = (CH_2)_3C_6H_4O(CH_2)_2(OCH_2CH_2)_{2-3}OMe$,
 $m = 0.02–0.05$, $n = 0.45–0.48$.

The composition and structure of the copolymer were optimised taking into account the requirements, listed above, which must be met by the phases: thermal stability, satisfactory adhesion to glass and quartz, and excellent permeability to diffusion are characteristic of the polysiloxane; oligo(ethylene oxide) ensures the required type of selectivity, while the octyl substituent simplifies

the immobilisation by treatment with radical process initiators. This type of 'brush' structure, which successfully combines the advantages of the siloxane skeleton and functional-selective substituents, is characteristic of the majority of new generation stationary phases.^{170–175} Certain characteristics of such phases are presented in Table 2.

Table 2. The capacity factor (k'), the retention index (I), the number of effective theoretical plates (N), and the range of working temperatures of a quartz capillary column (20 m × 200 µm) with different stationary phases.¹⁶⁸

Stationary phase	Dodecanol		Biphenyl		N /tp m ⁻¹	Range of working temperatures /°C
	k'	I	k'	I		
PS–OEO	16.0	1800	15.2	1920	5700	20–280
Carbo-wax 20M	15.4	1756	15.5	1925	5400	60–220
Bondable PEG	17.1	1985	14.2	1740	5600	40–260

It must be emphasised that the advances in the practical realisation of the possibilities of capillary gas chromatography are determined to a large extent by the high quality and diversity of the properties of the capillary columns. The synthesis of new stationary phases, the composition and structural parameters of which have been optimised taking into account the general requirements and characteristics of the objects to be analysed, is therefore one of the principal aspects of the development of capillary gas chromatography.

VII. Conclusion

Hydroxyl-containing stationary liquid phases are nowadays the commonest selective phases in capillary gas chromatography. The polarity of such phases varies within fairly wide limits. The methods for the preparation of immobilised phases examined in the present review make it possible to create the optimal stationary phase of this type for the given variety of separation.

The further development of the methods for the preparation of hydroxyl-containing stationary phases should in our view take place in the following principal directions (1) preparation of hydroxyl-containing chiral phases; (2) increase in the thermal stability of the hydroxyl-containing phases; (3) deliberate alteration of the properties of the hydroxyl-containing phases by dissolving organic and inorganic solvents in them.

In conclusion we may note that the immobilised phases are of interest also for employment in packed columns.¹⁷⁶

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Interaction of hydrocarbons with partial oxidation catalysts

L Ya Margolis, V N Korchak

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Abstract. The interaction of hydrocarbons having different structures with catalysts for their partial oxidation is considered. The activation of the hydrocarbon molecules on the surface can lead to the formation of adsorption complexes or radicals. This process depends on the structure of the hydrocarbons and the energy of the bonds in them, the temperature and nature of the surface of the solid (structure, the valence state of the elements entering into its composition, and the form of oxygen and its mobility). The possible mechanism of the activation of hydrocarbons on different catalytic systems is discussed. The bibliography includes 149 references.

I. Introduction

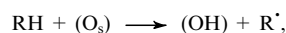
The catalytic oxidation of organic substances is a complex multi-stage process. Numerous studies have been devoted to its mechanism. The interaction of organic substances and solids, in particular catalysts, is known to be accompanied by the formation of intermediate surface compounds which are converted into reaction products on further oxidation. The composition of the products, *i.e.* the direction of the process, are determined to a large extent by the nature of the intermediate compounds and also by the active form of oxygen participating in the oxidation process. The first stage of the catalytic oxidation is the activation of the molecules of organic compounds. Unfortunately, little attention has been devoted to the study of this stage, although in our view it exerts a significant influence on the subsequent oxidation stages.

The interaction of hydrocarbons with the catalyst is accompanied by the formation on its surface of adsorption complexes or radicals. The role of radicals in the oxidation reactions and their influence on the selectivity have been examined in a review.¹ The formation of surface compounds in the interaction of hydrocarbons with various heterogeneous catalysts has been described.² Questions of the interaction of hydrocarbons with partial oxidation catalysts have been examined in a monograph,³ but only the

results published up to 1975 were discussed. It is useful to analyse the current literature data on the oxidation mechanism. Evidently such a task cannot be performed within the framework of a single communication. In the present review, attention is concentrated on the nature of the activation of hydrocarbons and the influence of the chemical properties and structure of the catalysts on the activation.

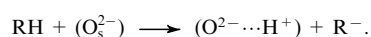
The development of new spectroscopic methods, such as IR Fourier spectroscopy, laser Raman spectroscopy, *etc.*, made it possible to determine the structures of many surface compounds formed in the interaction of hydrocarbons with the catalyst.³ The energies of the bonds in the intermediate compounds formed when hydrocarbons are adsorbed on the active surface centres have been calculated by quantum-chemical methods.⁴ In the calculations of the structures of the surface compounds and of the nature of the bonds between the adsorbed hydrocarbons and the catalysts, many properties of the surfaces of the solids are usually disregarded,^{5, 6} so that an appreciable proportion of the mechanisms of the catalytic reactions and of the activation of hydrocarbons are of a formal character.

The interaction of hydrocarbons with the active centres of the catalysts is accompanied by the deformation^{7–11} and the subsequent dissociation of individual bonds in the reacting molecules. The C–H bond in hydrocarbons may be dissociated homolytically or heterolytically. In the homolytic dissociation, a surface OH group and a free radical are formed on the catalyst surface:

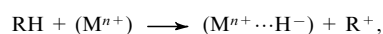


where O_s is surface oxygen.

The heterolytic reaction is accompanied by the binding of a proton on an alkaline surface centre:



The heterolytic dissociation of the hydrocarbon molecule with formation of a hydride on the acid surface centre (Lewis centre) is also possible:



where M^{n+} is the Lewis centre.

In the homolytic dissociation of a C–H bond, the radicals formed on the catalyst surface can be desorbed into the gas phase, initiating the homogeneous propagation of the process, or can remain on the surface and participate in the stages leading to the formation of the reaction products.¹² The characteristics of the

L Ya Margolis, V N Korchak N N Semenov Institute of Chemical Physics, Russian Academy of Sciences, ul. Kosygina 4, 117977 Moscow, Russian Federation. Fax (7-095) 938 21 56. Tel. (7-095) 939 75 46 (L Ya Margolis), (7-095) 939 71 68 (V N Korchak)

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heterogeneous-homogeneous oxidation reactions of hydrocarbons have been described in a review.¹

In considering the dependence of the reactivity of hydrocarbons on their structure, the activation energies (E_a) for the dissociation of various bonds can be compared.⁷ For example:

Bond	E_a /kJ mol ⁻¹	Bond	E_a /kJ mol ⁻¹
CH ₃ –H	456.7	CH ₂ =CHCH ₂ –H	368.7
CH ₃ CH ₂ –H	410.6	C ₆ H ₅ –H	460.9
(CH ₃) ₂ CH–H	398.0		

Alkenes exhibit a higher reactivity than alkanes. Comparative study of the oxidation of various alkenes on a palladium single crystal showed that the allyl C–H bond in the hydrocarbon molecule is less reactive than the vinyl bond.

Saturated hydrocarbons may be activated in two ways:²

(1) cleavage of a C–H bond by electrophiles with formation of a carbonium ion or a carbanion and subsequent dissociation of a C–C bond;

(2) dissociation of a C–C bond in the interaction with a low-valence metal.

The ability to cleave a C–C bond depends on the oxidation state of the transition metal. In redox processes, there is a possibility of the formation of catalytic *ensembles* and the role of the catalyst then consists in transforming one-electron processes into processes involving two and more electrons. Thus the structure of the hydrocarbons and the nature of the bonds in the molecules constitute one of the main factors influencing the way in which they are activated on interaction with catalysts.

Various mechanisms of the activation of butane have been considered in a review.⁷ The dissociation energies of the bonds between hydrogen and the primary, secondary, and tertiary carbon atoms have been compared with the rates of abstraction of one or two hydrogen atoms from the hydrocarbon. Various mechanisms of the activation of hydrocarbons and of the formation in this process of radicals and complexes (carbonium ions and carbanions) have been described in communications^{7–9} devoted to the study of the partial oxidation of alkanes, in particular propane.

The composition of the catalyst exerts a major influence on the activation of hydrocarbons. For example, on the V₂O₅ catalyst one hydrogen atom is abstracted from the CH₃ group of toluene, whereas following the introduction of the PO₄ group into the catalyst a new active centre (V^{δ+}···O^{δ-}···P) is formed on the surface and this time two hydrogen atoms are abstracted simultaneously from the hydrocarbon molecule on this centre. Under these conditions, a surface compound different from that on vanadium pentoxide is formed and a different reaction product is therefore obtained. The activation mechanism depends on the nature of the active surface centres, on which different forms of oxygen may be present. The centres for the adsorption and activation of hydrocarbons consist of cations, acid–base centres, free electrons, and defects and vacancies in the solid. The possible versions of the interaction of hydrocarbons with catalysts will be examined below in relation to olefins (ethene and propene), alkanes (ethane, propane, and butane), and aromatic compounds (benzene and toluene).

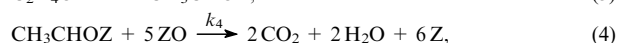
II. Activation of hydrocarbons by the oxygen of the surface

It is very difficult to discover a process in which only the oxygen of the catalyst surface participates. One of the few examples for which it is possible to trace the activation of hydrocarbons by precisely such oxygen is the oxidation of ethene on silver.^{13,14} Ethene is known not to be sorbed on pure silver.

Korchak and Tret'yakov's study¹⁴ was devoted to the kinetics of the oxidation of ethene on silver foil cleaned in an ultrahigh vacuum. The formation of an oxide phase on the surface of silver during the experiment can be virtually completely avoided if the

oxygen pressure is below 10⁻² mm Hg while the catalyst temperature does not exceed 523 K. In order to obtain reproducible kinetic data, the catalyst had to be treated in hydrogen at 773 K to eliminate traces of the oxide phase. Under these conditions, the oxidation of ethene afforded only CO₂ and H₂O.

By observing the above conditions, it was possible to investigate in detail the kinetics of the oxidation of ethene on silver free from a surface oxide phase. At an oxygen pressure of 2 × 10⁻⁴–10⁻² mm Hg and a catalyst temperature of 400–523 K, the principal stages of the mechanism of the extensive oxidation of ethene are described satisfactorily by the following scheme:



where a is the adsorption coefficient and Z a catalyst active centre. Stage (4) represents the overall complete oxidation reaction of acetaldehyde, which proceeds at a high rate and does not limit the overall process.

Korchak and Tret'yakov¹⁴ established that silver free from an oxide layer or oxygen dissolved in the bulk phase is 2 × 10⁴ times more active in the extensive oxidation of ethene than the oxidised form of the catalyst. When the catalyst is saturated with oxygen, the rate of the extensive oxidation falls, which leads to the equalisation of the rates of the extensive and mild oxidation and hence to an increase in the selectivity in the formation of epoxyethane.

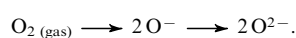
In order to increase the process selectivity, in industry the catalyst is activated in a stream of air. Taking into account the data presented above, one can postulate that the activation takes place as a result of the saturation of the catalyst with oxygen and the formation of an active phase on the surface.

The specific catalytic properties of pure silver can be explained by the fact that the dissociative adsorption of oxygen proceeds at a high rate on this metal. Because of this, extensive coating of the surface by oxygen atoms is achieved, such atoms oxidising ethene rapidly to CO₂ and water.

When oxygen is dissolved in silver, the strength of its bond with the metal diminishes and there is a sharp increase in the activation energy for the dissociative adsorption of oxygen (from 14 to 28 kcal mol⁻¹).¹⁵ As a result, the coating of the surface by atomic oxygen decreases in the course of the reaction, which actually entails a fall in the rate of the extensive oxidation of ethene.

The decrease in the amount of atomically adsorbed oxygen is accompanied by an increase in its molecular adsorption, particularly at elevated O₂ pressures, which should increase the rate of formation of epoxyethane. The principal conclusions reached as a result of the study of the kinetics and mechanism of the oxidation of ethene on pure silver have been confirmed by the results of other investigations. Thus it has been established that the adsorption of ethene on silver becomes possible only after the latter has been treated with oxygen.¹³

The mechanism of the formation of surface oxygen has been described in detail in a series of communications and monographs (see, for example, Margolis³). The oxygen on the surfaces of oxide systems is known to undergo consecutive transformations:



The oxygen ion formed (O⁻) is inserted in the lattice of the solid in the form of O²⁻. The oxygen may dissolve in the near-surface layers of metals.

In the adsorption of oxygen on the surface of silver, the quasi-oxides Ag₂O and Ag₂O₃ are formed, *i.e.* metallic silver is converted into the Ag⁺ cations. The study of the interaction of silver

with oxygen also enabled investigators^{16–18} to reach the following conclusions:

1. Depending on the conditions, the oxygen on the surface of silver is adsorbed in different forms. The dimeric oxide Ag_2O with ionic type of bonding is formed at temperatures below 470 K and this form participates in the extensive oxidation of ethene.

2. If silver is treated with a mixture of ethene with oxygen, weakly bound covalent oxygen appears on the surface of the metal in the form of single atoms, such form corresponding to the structure $\text{Ag}-\text{Ag}-\text{O}$.

It has been suggested that the 'ionic' oxygen creates surface sites for the adsorption of ethene, while the 'covalent' oxygen participates in the formation of epoxyethane. The disposition of oxygen on different faces of the silver lattice depends on the structure of the catalyst surface. This influences the catalyst activity and the selectivity in the ethene oxidation reaction and hence also the structure of the surface compounds.

It has been shown by IR spectroscopy that the adsorption of ethene entails the dissociation of the double bond in the ethene molecule and the formation of various surface compounds.^{19,20} With the aid of improved IR Fourier spectroscopy, strongly bound acetaldehyde and the complex $\text{Ag}\cdot\text{CO}$ have been detected on the $\text{Ag}/\text{Al}_2\text{O}_3$ catalyst.²¹ It has been established^{22–24} that ethene is activated with participation of the atomic surface oxygen. When ethene is oxidised on silver, acetaldehyde, formate, oxalate, and CO_2 are formed in addition to epoxyethane.²⁵ The epoxyethane conversion products have been investigated by IR spectroscopy and NMR and also by an isotope method involving the use of ^{13}C .²⁶

The degree of dispersion of silver on various supports (SiO_2 , Al_2O_3 , TiO_2) is very important for the conversion of ethene into epoxyethane.^{27,28} However, since the heats of adsorption of the reaction components on silver with different degrees of dispersion have not been determined and the coexistence on silver of various adsorbed forms of oxygen has not been confirmed, the question of the influence of the degree of dispersion on the activation of ethene remains open.

The atomic structure of the silver surface (nanoclusters) has been discovered with the aid of a tunnelling microscope and the migration of the metal particles on the surfaces of supports has been observed.²⁹

There is no information in the literature about the influence of the rearrangement of the silver surface on the activation of ethene and the formation of surface complexes. In quantum-mechanical calculations of the energy parameters of the ethene conversion process, simplified models are therefore used³⁰ in which a stationary silver atom bound to oxygen or entering into the composition of the cluster is considered. The calculation has been performed³¹ for the interaction of oxygen, hydrogen, chlorine, hydroxy groups, and ethene with silver clusters on supports. Depending on the mode of coordination to a silver atom, the chemisorbed oxygen (an atomic oxy-radical) can participate in the formation of epoxyethane or can be converted into an inactive form. Additives introduced into the silver influence the ratio of the radical forms of oxygen.

Thus ethene is activated with participation of different forms of oxygen. The oxygen dissolved in the silver lattice influences the process occurring the catalyst surface.

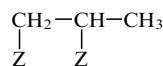
Data concerning the migration of silver atoms on the catalyst surface under the influence of the medium (the formation of clusters of different size, surface diffusion) are not taken into account in the models employed in calculations for the ethene activation process. The mechanisms of the conversion of ethene into epoxyethane are therefore formal in character: although they are in fact used in kinetic analysis, they do not reflect the true reaction mechanism.

III. Activation of hydrocarbons by the oxygen and cations of metal oxides

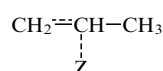
1. Olefins

The most thoroughly investigated stage in the process involving the oxidation of hydrocarbons is their adsorption on oxide systems. Depending on the structure, olefins can be adsorbed in the following forms on the surface of the catalyst:^{32,33}

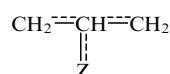
(a) two-centre forms with σ -bonds:



(b) associative π -complex:



(c) dissociative π -allyl complex:



Extensive experimental data on the formation of σ -, π -, and allyl complexes on the surfaces of various oxide systems in the adsorption of propane have been accumulated.^{32–35}

Formal mechanisms have been proposed for the adsorption and the reactions, in which it is postulated that such surface compounds are formed when olefins are activated on the cations of the metal oxide lattices. For example, when propene is adsorbed on MoO_3 it forms a bond with Mo^{6+} , as a result of which a π -complex is formed and the Mo^{6+} ion is simultaneously converted into Mo^{5+} . The structure of molybdenum oxide has been investigated with the aid of an electron microscope and also by X-ray phase analysis and UV and Raman spectroscopy.^{36,37} In the course of the oxidation of propene, MoO_3 is reduced to MoO_2 and MoO . More complex structures — Mo_8O_{20} and Mo_9O_{26} — have also been detected. When MoO_3 was deposited on silica gel, the formation of molybdates was observed.³⁶ The structure of MoO_3 has been investigated in detail^{37,38} and the existence of different forms of oxygen on its various faces has been demonstrated.^{39–42}

Particular attention has been devoted to the $\text{Bi}-\text{Mo}-\text{O}$ system,^{32,33} consisting of three different phases: $\text{Bi}_2\text{O}_3 \cdot 3\text{MoO}_3$ (α -phase), $\text{Bi}_4\text{O}_3 \cdot 2\text{MoO}_3$ (β -phase), and $\text{Bi}_2\text{O}_3 \cdot \text{MoO}_3$ (γ -phase).⁴³ The study of the structures of these phases and of their catalytic activities in the oxidation of propene led investigators to the conclusion that, when propene interacts with the catalyst surface, the abstraction of a hydrogen atom from the methyl group is followed by the formation of π - and σ -complexes. The olefin molecule is activated by a bismuth cation. It has been demonstrated in numerous experiments that the active oxygen necessary for the conversion of these complexes into acrolein originates from MoO_3 . The characteristic features of the transport of the active oxygen in a $\text{Bi}-\text{Mo}-\text{O}$ catalyst have been investigated.⁴²

In order to increase the rate and selectivity of the oxidation of olefins, catalysts with more complex compositions have been used. Several molybdates (multiphase systems) may be present in them, for example $\text{CoMoO}_4 + \text{Bi}_2\text{MoO}_4 + \text{Fe}_2(\text{MoO}_4)_3$.

The mechanism of the action of such complex catalysts has been established with the aid of various methods (IR, UV, EPR, and Mössbauer spectroscopy).^{44,45} The fundamental principle is the separation of the functions of the separate system components. Propene is adsorbed on the $\text{Bi}-\text{Mo}-\text{O}$ component and is activated on bismuth ions, while the oxygen necessary for the conversion of the complexes is supplied by the iron molybdate phase $\text{Fe}_2(\text{MoO}_4)_3$. This phase is converted into the divalent iron molybdate FeMoO_4 .

The propene and oxygen adsorption and activation centres are separated. The study of complex systems showed that, when bismuth molybdate is mixed with the Fe–Co–Mo solid solution, epitaxy of the crystals of one phase on another is observed and the transport of oxygen participating in the oxidation of propene is facilitated.^{46,47} Unfortunately there are no literature data on the adsorption and activation of propene on other complex systems and it is not clear which of the cations ‘abstract’ a hydrogen atom from the olefin molecule.

If an alkene (for example, isobutene) is adsorbed on a complex multiphase catalyst, it is not possible to establish by the thermogrammed desorption (TPD) method which of the phases participates in the process.⁴⁸ The interaction of isobutene with oxygen on the Co–Mo–Bi–Fe catalyst has been investigated by IR Fourier spectroscopy and it has been shown that an anhydride-like compound is formed in the adsorption process. Other forms of the interaction of the olefin with the catalyst have not been observed. Unfortunately, the mechanism of the activation of an alkene on such complex systems could not be elucidated.

A model has been developed for the action of catalysts consisting of several phases (Bi–Mo, Sn–Sb, Mo–Fe), among which oxygen donors and acceptors are present.^{49,50} Oxygen migrates from the donor to the acceptor *via* spill-over. The reaction mechanism on such systems has been called ‘remote control’. It has been suggested that hydrocarbons are adsorbed on the acceptor phase, but there is no experimental confirmation of this. Unfortunately, the elementary mechanism of the activation of alkenes on multicomponent systems still remains unelucidated.

2. Alkanes

The activation of alkanes on oxide catalysts occurs in many cases *via* a heterogeneous-homogeneous mechanism. This applies particularly to the oxidation of methane, which, in contrast to other hydrocarbons, is not adsorbed on the catalyst surface at the reaction temperature. It is activated on impact against the surface, being converted into a methyl radical, which is desorbed and forms a methoxy-compound as a result of a secondary interaction with various forms of oxygen on the surface or with a OH group. The mechanism of the activation of methane, the kinetics of the process, and its energy characteristics have been described in a series of communications (see, for example, Refs 51–57) and will not therefore be considered in the present review.

The oxidation of C₂–C₅ alkanes can proceed *via* two mechanisms — heterogeneous-homogeneous and heterogeneous.⁵³ Ethane, propane, and butane are adsorbed on catalysts and are either oxidised to aldehydes, anhydrides, and acids or are dehydrogenated to alkenes.^{8,9} The alkane oxidation catalysts are molybdenum and vanadium oxides, compounds of the type of molybdates or vanadates, or V–P–O systems.^{7–9,58–60}

The activation of alkanes is ensured by the ability of the catalysts to propagate redox processes and by the presence on their surfaces of atomic oxygen and acid–base centres. The conversion of alkanes into various adsorbed forms — radicals, complexes, and carbonium ions — is possible by virtue of these properties of the catalysts.

A mechanism has been proposed^{61,62} for the activation of ethane on MoO₃ and alkali metal molybdates. The interaction of ethane with atomic oxygen and the Mo⁵⁺ and Mo⁶⁺–O[–] (ethane activation centre) active centres entails the abstraction of a hydrogen atom and the conversion of the hydrocarbon molecule into the C₂H₅· radical. The interaction of C₂H₅· and O[–] leads to the formation of the ethoxide C₂H₅O[–], which is converted into acetaldehyde with participation of a hydroxy group of the catalyst surface. Ethene is formed on decomposition of this ethoxide (oxidative dehydrogenation).

The activity of alkali metal vanadates in the oxidation of ethene depends on the catalyst structure.⁶² The influence of vanadium pentoxide on the activation of ethane has been inves-

tigated and a relation has been demonstrated between characteristics such as the degree of dispersion of the oxide and the yield of acetaldehyde.⁶¹ The oxidation of methane and ethane on iron phosphate has also been studied.⁶³

Numerous studies have been devoted to the oxidative dehydrogenation of propane and the results have been surveyed in reviews.^{8,9} Following adsorption and activation, propane is converted into propene or oxidation products (acrolein, acetaldehyde, *etc.*). These two aspects of the conversion of propane have a common stage — the abstraction of a hydrogen atom from the methyl group of the molecule. According to Michalakos *et al.*,⁶⁴ in the activation of propane a propyl radical is formed and is then converted into propene. The vanadium-containing catalysts Mg–V–O, V–Sb–O, *etc.* are used to effect this process.

Mechanisms for the conversion of propane on Bi–Mo–O, Sn–Sb–O, and other catalytic systems have been proposed in a review.⁹ According to these mechanisms, the oxidation of the intermediate reactive forms, which are the products of the interaction of propane with the catalyst, involves the formation of oxygen-containing surface complexes.

Investigators have devoted much attention to the study of oxidation reactions and oxidative dehydrogenation of butane.^{6,7} It has been established that the mechanism of the activation of butane with participation of different forms of oxygen on the surface of the catalysts is similar to the mechanism of the oxidation of propane.^{65–67}

The oxidation of butane on the V–P–O catalysts leads to the formation of a centre (V⁵⁺ ··· O) on which the hydrocarbon is activated,^{68,69} some of the V⁵⁺ ions being reduced to V⁴⁺. If there are no V⁴⁺ ions in the catalyst, butane is not activated. It has been found^{70–72} that, in the activation of a butane molecule on the V^V = O active centre, two hydrogen atoms are abstracted from it.

On the V–P–O catalyst, butane is converted into oxygen-containing products,⁷³ whilst on other vanadium systems, for example on V–Mg–O, it gives rise to butadiene (oxidative dehydrogenation).⁷⁴

Thus the activation of C₂–C₄ alkanes on various catalysts entails the formation of various surface forms of these compounds (radicals, complexes).

3. Aromatic hydrocarbons

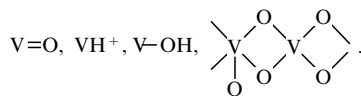
The oxidation reactions of aromatic hydrocarbons may be of two kinds: oxidation of the side chain of alkyl-substituted aromatic compounds without disruption of the structure of the ring and oxidation with degradation of the aromatic ring. Different forms of oxygen — electrophilic and nucleophilic — participate in these processes. Diverse vanadium systems, containing added molybdenum oxide and alkali metals in addition to the vanadium ions, are used as the catalysts.

The catalytic oxidation of aromatic hydrocarbons to maleic and phthalic anhydrides has been studied in fair detail using modern experimental methods. Quantum-mechanical calculations for these systems have also been carried out.⁴ A series of studies have been devoted to the structure, the nature of the surface, and the valence state of the vanadium ion in vanadium catalysts.^{75–78}

Much attention has been devoted to the investigation of supported vanadium catalysts. The role of supports (for example a zeolite, quartz, SiO₂, and aerosil) in the state of the vanadium ion has been investigated resorting to the EPR method. The formation of polyvanadates and oligomers as well as bridges comprising vanadium ions has been observed on silica gel and aluminium oxide.⁷⁷ The structure of vanadium oxide depends on the type of support.⁷⁹ Meta- and deca-vanadates are formed on aluminium oxide, while octahedral vanadium pentoxide is formed on silica gel. The V₂O₅–TiO₂ system merits special attention. Monolayer catalysts are the most active in the partial oxidation of aromatic hydrocarbons.

Bond and Tahir⁸⁰ examined the properties of catalysts obtained by different methods. The state of vanadium ions was

investigated by various spectroscopic methods (IR Fourier spectroscopy, laser Raman spectroscopy, EPR, XPS, NMR). The following types of active centres on the surfaces of vanadium catalysts were established by analysing the data obtained:



The structure of the V_2O_5/TiO_2 catalysts has been investigated by NMR using the ^{129}Xe isotope and it has been shown that vanadium ions form large domains and individual V_2O_5 crystals contain large pores.⁸¹

Analysis of the ^{51}V NMR data obtained in a study of vanadium catalysts deposited on aluminium and titanium oxides showed that the structure of vanadium oxide depends on the degree of coverage of the support and the nature of the latter.⁸² The symmetry of the octahedra in the layers on the outer surface of the support is disturbed to a greater extent than the symmetry of the tetrahedra in the crystal. When vanadium oxide is inserted in titanium oxide, surface defects are formed and the specific surface of the catalyst changes.⁸³ Particularly interesting data have been obtained in a study of the influence of the support (titanium oxide) on the state of the vanadium ion.⁸⁴ In this system, vanadium can exist in the following forms: V^{4+} (forms a solid solution with rutile); V^{5+} (is inserted in the rutile surface and forms a monolayer); VO^{2+} (is formed during the reaction on reduction of V^{5+} in the monolayer); deformed V_2O_5 crystals.

The EPR study of V–Ti catalysts showed that the number of spins and the g -factor depend on the degree of surface coverage of the support by vanadium ions.⁸⁵ Two types of ions were discovered: the tetrahedral V^{4+} and the vanadyl ion. The structure of the active centre of a vanadium catalyst has been described.^{86,87} The vanadium ions on TiO_2 (rutile and anatase) are in different states: an amorphous vanadium layer is formed on anatase, whereas separate regions with partly reduced vanadium ions are produced on rutile.⁸⁸ Analysis of data on the state of vanadium ions on the surface of the catalyst showed⁸⁹ that, depending on the concentration and the method of preparation of the catalyst, mono- or poly-layers are formed and the ratio of the V^{4+} and V^{5+} ions changes.

The wide variety of the possible states of vanadium on TiO_2 led to special interest of investigators in the mechanism of the activation of aromatic hydrocarbons having different structures. A cluster incorporating vanadium ions was chosen as the model. The changes in the energy of the C–H bonds in the methyl group on activation were discovered from the results of a quantum-mechanical calculation for the interaction of toluene with isolated vanadium cluster^{90–92} and it was shown that oxygen plays the role of an adsorption centre if it adjoins the vanadium ion. The approach of the CH_3 group to the cluster results in the deformation of the C–H bonds. The structure of the surface compound and its further transformation into different products depend on the orientation of the toluene molecule relative to the cluster (*via* the ring or the CH_3 group).

The following mechanism of the oxidation of toluene has been proposed on the basis of an IR spectroscopic study: (1) abstraction of a hydrogen atom from the CH_3 group on chemisorption of the hydrocarbon; (2) dissociation of a C–H bond and the formation of a surface complex linked to the metal ion *via* the carbon atom; (3) abstraction of a hydrogen atom from a CH_2 group not linked to the surface.

A comparative study has been made⁹³ of the oxidation of toluene and xylene on the V_2O_5/TiO_2 catalyst and a possible reaction mechanism was discussed.

In a study of the oxidation of benzene to maleic anhydride on vanadium catalysts, especially on vanadium–molybdenum catalytic systems, data were obtained on the phase composition of the catalyst and the state of oxygen on their surfaces and in the bulk phase.³³ Quantum-mechanical calculation for the interaction of

benzene with a vanadium catalyst (a cluster made up of vanadium ions) showed that there is a likelihood of the abstraction of a hydrogen ion from the benzene ring under the influence of the catalyst oxygen and the formation of an intermediate peroxide complex. Depending on the disposition of the benzene molecule on the surface, π - and σ -complexes may be formed.

Thus different forms of oxygen and cations having different valences participate in the activation of hydrocarbons of different classes. The acid–base centres on the catalyst surfaces exert a significant influence on these processes.

IV. The influence of the acid–base properties of catalysts on the activation of hydrocarbons

The catalysts for the partial oxidation of hydrocarbons possess acidic or basic properties. The methods for the determination of these properties, the nature of the surface acid centres, and the link between the type of such centres and the selectivities in various processes have been described in detail in a monograph.⁹⁴ Two types of acid centres are distinguished: Brønsted and Lewis (aprotic). Modern spectroscopic methods have made it possible to discover the surface compounds formed on different acid centres. It has been suggested that the Brønsted centres are bifunctional.^{95–100} They are capable of being proton donors and of altering the basicity of the neighbouring oxygen atoms.

The influence of the acidity of the catalyst surfaces on the oxidation of various organic substances has been examined in a series of publications.^{3,7,96,101} Acetone is formed on oxidation of propene on the Brønsted centres of the MoO_3/Al_2O_3 catalyst.¹⁰¹ Intermediate forms of the type $CH_2-CH^+-CH_3$ (enolate) have been detected by IR spectroscopy on the surface of a tin–molybdenum catalyst. The Lewis centres on oxides can adsorb hydrocarbons in two ways: by abstracting a hydride ion from the alkane with formation of a carbonium ion or from the olefin with formation of a radical-cation.¹⁰²

The interaction of hydrocarbons with Lewis and Brønsted centres has been examined, the mechanism of the activation of propene on bismuth molybdate has been discussed, and the role of the acid centres in the activation of the olefin has been demonstrated.^{9,11,102,103}

The role of the acid centres in the oxidation of propene on the $MoO_3-Sb_2O_4$ system has been investigated by a spectroscopic method and by the method involving the adsorption of pyridine and ammonia.¹⁰⁴ The relation between the degree of conversion of propene on Brønsted centres and between the selectivity and the ratio of the concentrations of the Lewis (N_L) and Brønsted (N_B) centres has been demonstrated. The dissociation of the vinyl C–H bond leads to the formation of an intermediate oxygen-containing propene compound. The intensity of this process depends on N_L and N_B . Detailed quantitative analysis using the adsorption of pyridine and ammonia demonstrated a correlation between the ratio N_B/N_L and the selectivity of the oxidation of propane on molybdenum oxide and on the $MoO_3 + Sb_2O_4$ mixture; the greater this ratio, the higher the selectivity.

Activation in the presence of water vapour on the acid centres of V_2O_5 leads to the dehydration of propene and its dehydrogenation.¹⁰⁵ The activation of propene on copper molybdate results in the formation of an intermediate carbonium ion species.¹⁰³ Acidity influences also the oxidative dehydrogenation of ethane on vanadium oxide deposited on silica gel.¹⁰⁶ It has been shown by the method involving the adsorption of pyridine and ammonia that the higher the degree of acidity, the greater the degree of conversion of ethane.

There are strong acid centres on the $(VO)_2P_2O_4$ catalyst. They consist of V^{5+} ions involved in octahedral coordination and surrounded by the PO_4 group (tetrahedron). The acidity of the catalyst surface influences the oxidation of aromatic compounds.^{107,108} The acid centres also participate in the oxidative dehydrogenation and oxidation of butane.^{108–110} The properties of the acid–base centres may change significantly when additives

are introduced.³ For example, after the addition of Group I elements (K, Na, Li) to MoO₃ deposited on TiO₂ and Al₂O₃, the rates of oxidation of propene and butene on the catalyst change; the introduction of acid (P₂O₅) and basic (Na₂O) additives into SnO₂ alters the mode of oxidation of propene: in the presence of the acid additive, propene is oxidised to acrolein, whereas modification with alkaline additives results in its dehydrogenation to benzene.

The effect of additives promotes the appearance in the vanadium catalyst of new compounds with the vanadium ion. When potassium sulfate is introduced into V₂O₅, vanadyl sulfate containing V⁴⁺ is formed. This is accompanied by a change in the acidity of the catalyst and in the rate of conversion of butadiene. The introduction of acid additives (tellurium and selenium ions) into bismuth molybdate accelerates the formation of acrolein. The addition of phosphorus ions to bismuth molybdate promotes the formation of π -allyl complex from butene. Thus modification of vanadium catalysts alters their acid properties and influences the activation of alkenes.

The structure of the vanadium–molybdenum catalyst for the oxidation of benzene changes when PO₄²⁻ ions are introduced into it: the lattice rearranges and the V–O and Mo–O bonds are disturbed. With increase in the PO₄²⁻ concentration, new compounds (bronzes) appear. These data indicate the influence of the modification on the structure and acidity of the catalyst and hence also on the adsorption of hydrocarbons and their activation.

The study of Blasco *et al.*¹¹² was devoted to the acid–base properties of vanadium catalysts deposited on various supports and to the influence of these properties on the oxidative dehydrogenation of butane. The acidity of the catalysts on different supports was determined from the degree of adsorption of pyridine and ammonia, the concentrations of the acid centres were determined, and it was shown that the selectivity in the conversion of butane depends on the acid properties of the surface. The introduction of additives also alters the acidity of the catalyst and its redox properties and it is therefore difficult to separate the influences of the nature of the support and the additives on the activation of hydrocarbons.

Lewis acid centres capable of activating butane by converting it into a radical have been identified in the V–P–O system.⁸ The oxidative dehydrogenation of ethane on the V/SiO₂ catalyst has been described¹⁰ and the redox reaction mechanism has been examined. It was shown that the activities of the catalysts depend on their acidity.

Thus the acid–base properties of oxide systems influence significantly the activation and conversion of hydrocarbons with different structures, while the alteration of these properties is accompanied by a rearrangement of the structure of the solid and the disturbance of the valence state of certain ions in the catalyst composition. It is therefore difficult to discover the influence of acidity or basicity alone on the mechanism of the activation of hydrocarbons.

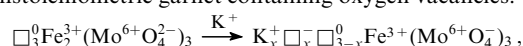
V. The influence of structural defects in the catalysts on the activation of hydrocarbons

The nature of the defects in solids, especially in oxides, has been discussed in numerous communications (see, for example, Tret'yakov¹¹³ and Tomlinson *et al.*¹¹⁴). The conditions in the preparation of the catalysts, the effect of the medium, and impurities alter the structures of solids and influence the type of defects and the distribution of additives which may interact with the basic elements. This may result in the local reconstruction of the initial oxides. Furthermore, clusters may be formed from the structural components and additives.

Defects alter the electronic characteristics of the surface and of the bulk of the solid^{5,6} and thereby influence the activation of the components of the reaction mixtures.^{114,115} The partial oxidation of hydrocarbons is achieved with participation of the oxygen in the oxide lattices. Oxygen vacancies are formed in the course of

this process and oxygen migrates *via* the lattice and interacts with the oxygen from the gas phase.^{30,32} Anionic vacancies influence the abstraction of a hydrogen atom from the propene molecule when the latter is oxidised on various spinels and solid solutions.^{30,33} The structural sensitivity of oxidation reactions has been discussed.^{115,116} Several types of defects in metal oxides have been examined: 'genetic' and impurity defects as well as oxygen vacancies.

Defects and vacancies may arise in complex oxide systems when additives are introduced.¹¹⁷ For example, the modified Co–Mo–Bi–Fe catalyst contains the molybdate Fe₂(MoO₄)₃, which has a garnet-like structure with a vacant dodecahedral sublattice. When alkali elements, especially the potassium ion, the ionic radius of which is optimal for this structure, are introduced, the vacant sublattice is partly filled and the degree of defectiveness of iron molybdate increases. The latter acquires the structure of a nonstoichiometric garnet containing oxygen vacancies:



$\square^0$ — vacancy in the dodecahedral sublattice, $\square^-$ — anionic oxygen vacancy.

Such structural changes influence the mobility of oxygen in the catalyst lattice.

A process involving the appearance of defects in catalysts has been described in a review.¹¹⁷ The adsorption of various substances on catalysts can also induce the appearance of defects in the lattice of the solid. Thus defects are formed after the adsorption of chloride ions on a silver single crystal,¹¹⁸ oxygen from the gas phase being adsorbed on these centres. This type of centre–oxygen associated species is called a 'B defect' and serves as a kind of 'gate' for the permeation of atomic oxygen into the layers of the silver lattice. A model of the structure of silver, on the surface of which chloride ions are sorbed, has been proposed.¹¹⁸

The perovskites ABO₃ have begun to be used recently in oxidative catalysis.^{119–121} Vacancies and defects are formed in the structures of these compounds owing to the nonstoichiometric amounts of the elements A and B. The same vacancies and defects appear when additives are introduced.^{120,121} The properties of the lattice oxygen and adsorbed oxygen have been investigated for the pure and modified lanthanum oxides and the nature of the defects has been established.¹²¹ A calculation has been carried out for a model of the defect and its diffusion from the bulk phase and on the surface.^{122,123} The addition of strontium ions to the perovskite increases the mobility of oxygen and the number of oxygen vacancies.¹²⁴ The interaction of ethene, propene, and isobutene with a defect-containing catalyst, the composition of which is described by the formula Bi_{1-x/3}□_{x/3}Mo_y(V_{1-x}Mo_{x-y}Fe_x)O_y, where □ is a cationic vacancy and $x = 0.13–0.60$, has been investigated.^{124–126} Schemes for the disposition of oxygen around different cations have been proposed and the view has been expressed that the coordinated cation participates in the dissociation of a C–H bond of the hydrocarbon with formation of the allyl group. The rate of oxidation depends on the number of vacancies in the catalyst. Theoretical calculations have been performed for the interaction of hydrocarbons with clusters and structural defects.

The modern experimental methods make it possible to investigate the transformations in a solid, occurring under the influence of the medium, and the structure of the surface compound *in situ*. However, the results of such studies have not been duly employed in establishing the mechanism of the activation of hydrocarbons, which is therefore purely formal.

In considering the questions concerning the influence of the chemical and structural properties of the catalyst on the activation, it is essential to take into account, apart from the factors indicated above, the electronic transitions between the solid and the hydrocarbons being adsorbed. In the electronic theory of catalysis, much attention has been devoted to the establishment of the signs of the charges of the substances adsorbed on metal oxides

and the charge on the surface of the metal.¹²⁷ As a rule, the molecular and atomic oxygen on oxides has a negative charge, while organic substances have a positive charge.^{3,28}

Adsorption on metals entails the formation of dipoles with different directions of the charge relative to the catalyst surface.¹²⁸ According to the electronic theory of catalysis, the activity of the catalyst depends on the position of the Fermi level for the lattice of the solid and electron exchange takes place between the adsorbed molecule of the given substance and the catalyst. The search for the relation between the electronic properties of a solid catalyst, on the one hand, and the charged reacting molecules, on the other, was therefore believed to be a problem of current interest. However, the electronic theory of catalysis was not developed further. The characteristics of the electron exchange process are determined from the change in the electron work function on adsorption and from the electrical conductivity. The change in the electron work function on the V_2O_5/TiO_2 catalysts, pure and modified with potassium ions, has been studied.¹²⁹ The presence of potassium facilitates electron exchange in the solid. The vacancies in oxide lattices may be charged and, when hydrocarbons are adsorbed and interact with oxygen, they may transfer electrons to the surface compounds formed.

The electron exchange between the charged forms of the hydrocarbon and the surface oxygen, observed on various oxides, has been considered in the analysis of the selectivity in the partial oxidation. The catalytic properties of many catalysts are influenced by the charge transfer between the surface and the bulk of the catalyst.^{130–133} This is particularly notable on supported catalysts, the activity of which is related to the electrical conductivity.^{131,132} The electronic characteristics of the catalysts influence the rate of interaction of hydrocarbons with surface oxygen but do not alter the type of activation.

Thus analysis of the activation of hydrocarbon molecules on partial oxidation of catalysts has shown that this is a complex process which includes diverse interactions depending on the structure and energy parameters of the molecules being adsorbed and also on the characteristics of the catalyst surface (the form of oxygen, the valence state of ions, vacancies, and defects).

VI. The selectivity of the partial oxidation and activation of hydrocarbons

The principal characteristics of the partial oxidation are the rate and selectivity of the reaction.^{134–138}

The partial oxidation processes are almost always accompanied by extensive oxidation. There are two mechanisms of the extensive oxidation of hydrocarbons: the consecutive mechanism, where the partial oxidation product is converted into CO_2 and water, and the parallel mechanism where CO_2 and water are formed from the hydrocarbon *via* other intermediate species (surface compounds, radicals). The selectivity of the oxidation depends on the process mechanism.¹³⁹

The extensive oxidation of hydrocarbons of different classes on the $MgCr_2O_4$ catalyst typical for this process has been studied.¹⁴⁰ The spectroscopic investigation showed that hydrocarbons react with chromium ions functioning as active centres. The weakest C–H bond is then ruptured and C–O bond is formed, while further oxidation leads to the formation of carboxylates and carbonates.

The activation of hydrocarbon molecules on partial oxidation catalysts is the first and probably the rate-determining stage of the process. Further reactions of the surface forms produced with participation of oxygen determine the type and structure of the oxidation products. In the elucidation of the activation mechanism, one of the main questions is that of the role in this process of the structure and energy of the bonds in the hydrocarbon molecule and also the question of the form of oxygen capable of participating in the formation of the partial oxidation product. Comparative study of hydrocarbons of several classes makes it possible to establish the influence of their structure on the activation.

Among all the alkenes, only ethene is converted into epoxyethane on a silver catalyst. The attempt to obtain epoxypropane on this catalyst proved unsuccessful: propene is activated by involvement of the methyl group, from which a hydrogen atom is abstracted and this results in the formation of the allyl group.^{140,141} Ethene is activated as a consequence of the rupture of the double bond by oxygen, which leads to the formation of a complex preceding the formation of epoxyethane.

Aldehydes and acids or alkenes appear as a result of the activation of alkanes (oxidative dehydrogenation). For example, two hydrogen atoms may be split off from the hydrocarbon molecule on activation of butane. The products of this reaction are maleic anhydride, maleic aldehyde, or butadiene. Still more significant differences are observed in the activation of aromatic hydrocarbons. One hydrogen atom is split off in this case from the ring (benzene is formed), two hydrogen atoms are split off from the side chain (alkyl-substituted aromatic hydrocarbons are formed), or the ring is ruptured. In a study devoted to the selective oxidation of light alkanes,¹⁴² the view has been expressed that the choice of catalytic systems for these reactions must be determined by the structure of the active centres and their redox and acid–base properties. Particular attention was devoted in this investigation to the reaction products, their stability, and the strength of the bond with the solid (ease of desorption). The adsorption mechanism and the mechanism of the insertion of oxygen in oxide catalysts were examined.

The interaction of hydrocarbons with the surface of an oxide catalyst is accompanied by its reduction, *i.e.* by a change in the valence state of the cations. This process influences the mode of activation of the hydrocarbon molecules. In a number of instances, the rate of activation and its mechanism are determined by the redox properties of the catalyst. The lack of capacity for reduction (for example, in the vanadium–phosphorus catalyst) prevents the formation of oxygen-containing products from butane and the process proceeds on other surface centres (for example, acid centres). Oxidative dehydrogenation then takes place. The rates and selectivities of the oxidation of various hydrocarbons on the same catalysts may differ as a consequence of the formation of various intermediate forms. For example, on bismuth molybdate propene gives rise to an allyl complex, whilst butene produces a π -complex with elimination of two hydrogen atoms.

The V–Mo–Ti catalytic system is the most active in the oxidation of aromatic hydrocarbons, while propene is oxidised on it with a low selectivity.¹⁴³

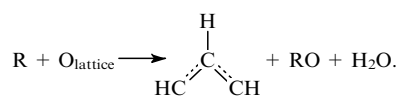
Oxidative dehydrogenation takes place preferentially on the $Mg_2(VO_4)_2$ catalyst. On other vanadium systems, the rates of partial oxidation and oxidative dehydrogenation depend on the ratio of V^{4+} and V^{5+} (see Refs 55, 64). As a consequence of the removal of oxygen from the lattice of the catalyst in the interaction of its surface with a hydrocarbon, vacancies (defects) arise and electron exchange processes take place within the lattice.

The influence of the nucleophilicity and electrophilicity of oxygen on the mechanism of the oxidation of hydrocarbons has been examined in numerous studies.^{4,33,137–140} The abilities of Bi–Mo–O and V_2O_5 to oxidise hydrocarbons of different classes have been compared on the basis of the analysis of the interaction of electrophilic oxygen with the C–C and C–H bonds in the hydrocarbon molecule. For example, bismuth molybdate is incapable of oxidising aromatic hydrocarbons, while V_2O_5 cannot oxidise olefins. The diversity of the mechanisms of the activation of hydrocarbons on different catalytic systems is determined not only by the state of the organic molecule and oxygen but also by the properties of the catalyst surface. We have already considered the influence of the structure and redox properties of the solid on the activation of hydrocarbons. However, the characteristic features of the acid centres of the catalyst are no less important.^{134,136}

In the activation of hydrocarbons on the surfaces of catalysts, the complexes or radicals formed interact with oxygen almost simultaneously with the dissociation of the C–H bond. The lattice

oxygen of the oxide or the atomic oxygen adsorbed on the metal surface are known to participate in the partial oxidation reaction. The molecular oxygen adsorbed from the gas phase participates in the extensive oxidation. The structure of the surface and the valence state of the ions influence the bond energy of the oxygen in the lattice and its mobility. Numerous studies, in which the mechanism of the interaction of the adsorbed hydrocarbon with different forms of oxygen is discussed, have been devoted to these questions (see, for example, Refs 3, 7, and 31). In essence, the activation step involves the adsorption of a hydrocarbon molecule and its interaction with oxygen. The selectivity in the formation of the reaction products depends on the structure of the oxygen--hydrocarbon complex which has appeared and also on its mobility and reactivity.

It has been suggested that the mechanism of the partial oxidation is determined by the interaction of the mobile activated hydrocarbon complex or radical with the stationary lattice oxygen:¹³⁶



At a low temperature there is a possibility of the formation of peroxides (as a result of the interaction with O_2^-) and their subsequent decomposition with formation of oxygen-containing products.

On extensive oxidation, the activated mobile oxygen interacts with the stationary hydrocarbon complex:



The mobile oxygen may consist of an adsorbed atom or molecule. The continuation of the reaction in the gas phase is possible (a homogeneous-heterogeneous mechanism).¹

Sokolovsky¹⁴¹ carried out a kinetic analysis and proposed models for the extensive oxidation of hydrocarbons. The selectivity and the partial oxidation of hydrocarbons are determined not only by the structure of the molecules of hydrocarbons of different classes and the C-H bond energies but also by the valence state of the components of the catalyst surface. One of the stages in the activation of hydrocarbons consists of redox reactions in the catalyst. The cations in the lattice of the solid undergo a change in their valence state as a result of the adsorption of hydrocarbons. There is also a corresponding change in the mode of oxidation. For example, in vanadium catalysts, oxygen bridges may be formed on the vanadium ions. These are readily reduced when the hydrocarbon is adsorbed, as a result of which oxygen is removed and a C-O bond is formed. The reaction products contain oxygen.

The acid-base properties of the catalyst as well as the redox reactions influence the conversion of hydrocarbons and the process selectivity. When the reaction is carried out on complex oxide systems (for example, $\text{MoO}_3\text{-Sb}_2\text{O}_4$),¹⁰⁴ a relation is observed between the ratio of the number of Brønsted and Lewis centres and the selectivity in the conversion of propene into acrolein. On the other hand, a change in the ratio of the molybdenum and antimony oxides alters the concentration of the oxidation-reduction centres on the surface and influences the migration of oxygen *via* the lattice. The combined operation of these factors promotes the dissociation of oxygen, the enhancement of oxygen spill-over between the phases, and the adsorption of the protons split off from the propene molecule. Such is the complex mechanism of the influence on the activation of the hydrocarbon by various processes occurring on the catalyst surface.

The oxidation kinetics have been considered in a large number of publications, both review publications¹³⁸ and those devoted to the investigation of individual catalytic reactions in the extensive and partial oxidation of hydrocarbons. Apart from the dependences of the reaction rate and selectivity on the pressure, temper-

ature, and contact time, models of the process, corresponding to the observed parameters, are presented in these communications.

In order to choose a model, it is essential to elucidate which stage of the oxidation process determines its rate. Almost all investigators believe that this stage is the activation of the hydrocarbon on the catalyst surface with formation of various surface compounds. Formal schemes, which do not always correspond to the true reaction mechanism, have been proposed in many investigations.

The foundations for the construction of a kinetic model of the methane oxidative condensation reaction on the $\text{PbO}/\text{Al}_2\text{O}_3$ catalyst have been described.¹⁴⁴ Ethene, ethane, and extensive oxidation products are formed in this process from methane. The reaction proceeds *via* a heterogeneous-homogeneous mechanism. Characteristic features of the process at different temperatures, oxygen pressures, and for other parameters have been investigated. The proposed model includes the formation of the methyl radical from methane, its dimerisation to ethane, and the reaction with oxygen to form a peroxide. The dependence of the limiting selectivity and of the rate of formation of the products on various parameters has been established on the basis of this model and it has also been shown that the process proceeds *via* a redox mechanism. It is postulated that ethane is activated and the extensive oxidation products are formed on different centres.

Albonetti *et al.*⁸ investigated the kinetics of the oxidation of ethane and ethene. Kinetic analysis showed that this reaction has a redox mechanism. The rate constants for the formation of methyl radicals and the extensive oxidation products were found, equations were proposed for the rates of formation of different products, and the limiting selectivities were established.

A similar approach to the elucidation of the mechanisms of catalytic partial oxidation processes, based on a profound kinetic analysis and the establishment of a relation between the physicochemical properties of the catalysts and the selectivity of the oxidation process, has also been used in other studies.^{143, 144} A two-centre model has been proposed for the oxide catalyst as well as kinetic models for the partial oxidation of olefins (propene, isobutene) and unsaturated aldehydes. It is postulated that the hydrocarbon and oxygen are adsorbed on centres of different types and that the interaction between them occurs as a result of the diffusion of oxygen from its adsorption centres to the reaction centres, which function simultaneously as the hydrocarbon adsorption centres.

Kinetic analysis of the two-centre model and the active surfaces of oxide catalysts has been carried out.¹⁴⁵⁻¹⁴⁹ Apart from a detailed mechanism of the transfer of oxygen from its adsorption centres to the reaction centres, it proved possible to describe the principal kinetic features of the oxidation of propene, isobutene, and methacrolein to acrolein, methacrolein, and methacrylic acid respectively under stationary conditions.

VII. Conclusion

The activation of hydrocarbons on the surfaces of catalysts is the first and rate-determining stage of their partial and extensive oxidation. The hydrocarbons are converted into active radicals or complexes, which form different surface compounds, affording different oxidation products.

The way in which the hydrocarbon interacts with the surface of the solid depends on the structure of the organic molecule (bond energy) and the nature of the catalyst surface (structure, valence state of its constituent ions, and the forms of oxygen and its mobility).

In the structure of the catalyst there are defects, which can also serve as activation centres. Electron exchange takes place between the solid and the adsorbed hydrocarbon. The interaction of the hydrocarbon with oxide systems is accompanied by redox processes in the solid involving a change in the valence state of the lattice cations. Brønsted and Lewis acid centres also participate in the activation of the hydrocarbon. The mode of oxidation of

hydrocarbons, namely to oxygen-containing products or to hydrocarbons with a different structure (oxidative dehydrogenation), depends on the activation mechanism.

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